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EDITORIAL

Australian Prescriber: a new chapter

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Australian Prescriber is back! The news has been received warmly—as would be expected, considering the swell of support last year when the future of the journal was uncertain following the closure of the previous publisher, NPS MedicineWise.[1] *Australian Prescriber* is a respected, independent and accessible journal of therapeutics that has supported health professionals in Australia to make informed prescribing decisions for almost 50 years.[2] That there would be a future for *Australian Prescriber* was never in doubt considering its reputation and popularity, and that the National Medicines Policy[3] continues to advocate for 'access to up-to-date, reliable and good quality information for the Australian health system'.[4]

The new publisher, Therapeutic Guidelines Ltd, is an independent not-for-profit organisation. It is well respected in Australia for producing Therapeutic Guidelines, a point-of-care clinical decision support database covering over 2500 diagnoses.

Much like *Australian Prescriber*, Therapeutic Guidelines Ltd has been a stalwart of the healthcare community in Australia for over 45 years. The first edition of the Antibiotic guidelines was published in 1978 by a multidisciplinary team based at the Royal Melbourne Hospital. The first few editions were free. In 1984, publication of the guidelines was transferred to the Victorian Medical Postgraduate Foundation, now Health Education Australia Ltd (HEAL), which introduced a fee to ensure future viability. New titles began to be added in the late 1980s, each written by an appropriate expert group, and today, Therapeutic Guidelines covers 21 clinical areas. The guidelines moved home one last time when the not-for-profit publisher Therapeutic Guidelines Ltd was incorporated in 1996. The organisation has been successful because it was created by healthcare professionals to support healthcare professionals, a principle that continues to this day.

The opportunity to take on *Australian Prescriber* was unexpected but welcome, and Therapeutic Guidelines Ltd is delighted to have won the competitive tender. The missions, values, stakeholders and expertise of the two publications align. *Australian Prescriber* is a natural fit for Therapeutic Guidelines Ltd, with the opportunity to collaborate across publications an added bonus.

The Editorial Executive Committee of *Australian Prescriber* has reconvened so readers can expect the same high-quality topical and relevant articles every two months, and the popular biweekly podcast series will restart in September. Collaboration with professional colleges and societies to develop an engaging content strategy, and to enable article accreditation for continuing professional development, will be central to ensuring the journal prospers. ◀

Conflicts of interest: Leigh-Anne Claase is Chief Executive Officer of Therapeutic Guidelines Ltd.

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This article is peer-reviewed

Letter to the Editor

Sex hormones and risk of coronary artery disease in women

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We challenge the implication of the article on coronary artery disease in women,[1] based on the Zhao analyses of 2834 postmenopausal women,[2] that oestradiol is cardioprotective and explains women's lower rates of cardiovascular disease, compared with men, before menopause.

We undertook an analyses of the large-scale UK Biobank, involving 57,204 women with detectable oestradiol concentrations.[3] In both pre- and post-menopausal women, in unadjusted analyses, the hazard ratio (HR) (95% confidence interval) per unit higher in log-transformed oestradiol for myocardial infarction was 0.73 (0.58; 0.92), indicating that higher oestradiol was associated with a lower risk of myocardial infarction. However, after adjusting for age, this HR became 0.94 (0.75; 1.17) and the association was no longer apparent. After further adjusting for classical cardiovascular disease risk factors, the HR was 1.05 (0.83; 1.31). Furthermore, results were similar in subgroup analyses defined by age, menopausal status, socioeconomic status, contraceptive pill use and the use of hormone replacement therapy. Zhao and colleagues undertook their analyses in postmenopausal women alone, thus not allowing for the vital comparison between women pre and post menopause.

Indeed, we did observe the rates of myocardial infarction were higher with increased age, and that oestradiol concentrations were lower with increased age, although this was not necessarily a consequence of the menopause. The presumed cardioprotective effects of oestradiol seem to be largely confounded by age and further by other cardiovascular risk factors, and menopause itself does not seem to be a causal factor for coronary heart disease risk.[4]

The article also states that higher concentrations of androgens contribute to a higher risk of cardiovascular disease in women based on findings from Zhao et al.[2] However, there is conflicting evidence within this domain. Islam and colleagues, in an analysis of the SHOW (Sex Hormones in Older Women) sub-study of the ASPREE trial,[5] showed that higher quarters of testosterone (Q3 vs Q1 and Q4 vs Q1) were associated with a lower risk of major adverse cardiovascular events. Sievers and colleagues also demonstrated that low baseline testosterone in women 70 years and older was associated with increased cardiovascular disease events.[6] Studies have also demonstrated no associations with testosterone and cardiovascular disease events[7] or cardiovascular mortality[8] in women.

We therefore propose that the associations of oestrogen and testosterone with coronary artery disease in women are not so clear cut in light of the numerous conflicting findings.

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

LETTERS

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Natalie Montarello and Wai Ping (Alicia) Chan, the authors of the article, comment:

We agree that menopause as a cause of cardiovascular disease is not clear-cut with multiple studies showing conflicting results. However, it has been shown consistently that women develop cardiovascular disease 7 to 10 years later than men,[1] and that early age at menopause is associated with increased risk of cardiovascular disease.[2] The increased risk here is clearly not solely attributed to oestrogen depletion, as you have pointed out in the UK Biobank Study on the effect of oestradiol on cardiovascular disease, but a combination of factors including age and the transition period into menopause.

Postmenopausal women have higher total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride concentrations and lower high-density lipoprotein cholesterol (HDL-C) concentrations. LDL-C and apolipoprotein B concentrations, the more 'atherogenic' components of the lipid profile, have been shown to be associated with menopause and not age alone.[3] Similarly, weight gain and loss of skeletal mass have been attributed to ovarian ageing, rather than chronological ageing alone.[4] Postmenopausal women are also more insulin-resistant, have higher blood pressure and central obesity,[5] contributing to the development of metabolic syndrome. It is therefore possible that oestrogen depletion worsens the cardiovascular risk-factor profile, which leads indirectly to increased cardiovascular disease during the menopause transition.

Finally, in relation to androgens and cardiovascular disease in women, high and low concentrations have both been associated with cardiovascular disease, and there are even some studies that show no association. The increased events of cardiovascular disease in women with polycystic ovarian syndrome have been attributed to the increased adiposity and, possibly, an interaction with hyperandrogenism,[6] although the mechanism has yet to be elucidated. The role of hyperandrogenism is likely to be due to the negative interaction with cardiovascular risk factors, as above.

We acknowledge and are aware of the complex interaction of sex hormones and cardiovascular disease in women. However, we chose not to discuss these as the paper was aimed at providing an overview of the approach and management of coronary artery disease in women.

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ARTICLE

Prescribing and peritoneal dialysis

SUMMARY

Peritoneal dialysis is a home-based therapy for patients with end-stage kidney disease. It is less efficient in removing solutes and fluid than haemodialysis but offers more flexibility and independence.

Peritoneal transport characteristics affect the dialysis prescription. The timing of drug administration is independent of the dialysis process except for the administration of intraperitoneal antibiotics. Dose reductions should follow current recommendations for patients with kidney disease.

Fluid overload is common in patients undergoing peritoneal dialysis. Residual kidney function can ameliorate this problem and needs to be preserved. Dialysis solutions with high glucose concentrations contribute to adverse metabolic effects.

Peritoneal dialysis-related catheter complications and infections may require patients to transition to haemodialysis. Antifungal prophylaxis needs to be co-administered for the duration of antibiotic courses for any indication to reduce the risk of fungal peritonitis.

Close communication with the patient's supervising dialysis unit is required.

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Keywords
dialysis solutions, end-stage kidney disease, kidney failure, peritoneal dialysis

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Introduction

Peritoneal dialysis is a home-based treatment modality for end-stage kidney disease. Like haemodialysis, it aids solute and water clearance. Haemodialysis achieves this in four to five hours three times per week, whereas peritoneal dialysis takes longer.[1] However, the health-related quality of life of patients undergoing peritoneal dialysis is comparable to that of patients having haemodialysis.[2]

The elimination of uraemic toxins and excess water is important for successful peritoneal dialysis. However, increasing emphasis is placed on the patient's symptoms, burden of therapy, nutrition and quality of life.[3,4] Shared decision-making can facilitate sufficient treatment and enable patients to achieve their life goals. While patients receive specialist management from dialysis units, primary healthcare providers are essential for ongoing care.

Adult patients usually have comorbidities and polypharmacy is almost universal.[5] Prescribing generally follows the principles applied to other patients with end-stage kidney disease.[6] Doses of renally cleared drugs are reduced or their intervals extended, and prescribing resources should be consulted. Therapeutic drug monitoring is available for selected drugs with a narrow therapeutic index.[7]

Peritoneal dialysis principles

In peritoneal dialysis, a dialysis solution (dialysate) is instilled into the peritoneal cavity via a catheter tunnelled through the abdominal wall. In an exchange, the solution is left to dwell for several hours and then replaced with fresh dialysate.

The peritoneal membrane allows movement of solutes and water between the vascular and peritoneal space. Its transport characteristics are assessed through an equilibration test and can be classified as low, low-average, high-average or high.[8] Patients who are low transporters require longer dwell times, while high transporters usually need shorter dwells. Transport characteristics can change over time, and the process often fails eventually.

Dialysates

Dialysis solutions generate the diffusion and osmotic gradients required for solute and water transport. Their glucose contents are high (1.5%, 2.5% and 4.25%) and contribute to hyperglycaemia, hyperinsulinaemia and dyslipidaemia.[9] Solutions with higher glucose concentrations remove more fluid, but their use should be minimised.[10]

Glucose-sparing dialysates contain icodextrin, a starch-derived polymer. However, it is metabolised to maltose which is absorbed and causes falsely elevated blood glucose concentrations in monitors that are not specific for measuring glucose.[11]

More physiological dialysis solutions contain bicarbonate instead of lactate as a buffer. Their neutral pH can reduce inflow pain and preserve residual kidney function.[1,3] Dialysates containing amino acids may be adjuncts in the treatment of malnutrition.[12] However, higher costs limit their use.

Treatment modalities

Peritoneal dialysis can be performed either continuously or intermittently. In continuous ambulatory peritoneal dialysis, the dialysate is exchanged manually about every four hours during the day with a longer dwell overnight. In automated peritoneal dialysis, a cycler performs shorter exchanges while the patient is asleep, but a day dwell may be included. Medicines are given irrespective of when peritoneal dialysis is performed, as its effect on drug clearance is not clinically relevant.[6]

Home therapy

Peritoneal dialysis is performed by patients or carers in the community. They are trained in aseptic techniques, when to adjust therapy and how to troubleshoot.[13] A clean environment and appropriate storage of consumables are prerequisites. The supervising dialysis unit provides support and should be contacted early when problems arise.

Compared to undergoing haemodialysis in a healthcare facility, patients performing peritoneal dialysis need appropriate cognitive capacity and manual dexterity. However, the benefits include relative independence and flexibility regarding the location and timing of treatment.

Showering and swimming are permissible with an intact catheter exit site. Before strenuous exercise, the dialysate should be drained and the catheter extension line secured.[14]

Fluid management

The patient's hydration needs to be assessed regularly to achieve a normal volume status.[10] The supervising dialysis unit provides the patient with an action plan in relation to changes from an ideal dry weight. Fluid intake should match losses, and dietary salt intake generally needs to be restricted.[9]

While dehydration may be characterised by muscle cramping and hypotension, fluid overload is more common. Overload can be addressed with oral fluid restriction, additional exchanges with icodextrin or temporary use of higher glucose dialysate. Loop diuretics can be very effective in larger doses (e.g. up to 250 mg oral furosemide daily).[10]

Residual kidney function

In end-stage kidney disease, residual kidney function is associated with better patient outcomes.[4] It declines more slowly with peritoneal dialysis than with haemodialysis but nevertheless diminishes over time.[9] Additional measures to preserve residual kidney function include good control of blood pressure (especially with ACE inhibitors or angiotensin receptor antagonists), use of diuretics and glucose-sparing dialysates. Nephrotoxic drugs and volume depletion should be avoided.

Residual kidney function can be measured with a 24-hour urine volume and creatinine clearance.[10]

Complications

Non-infectious and infectious complications of peritoneal dialysis can lead to treatment failure. Close attention needs to be given to their prevention and effective management.

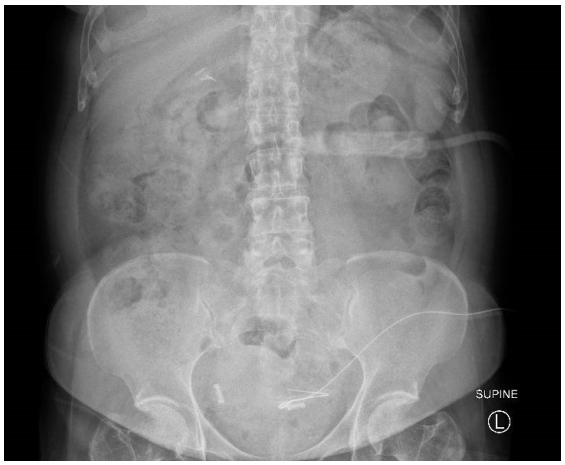
When prescribing an antibiotic for any indication, patients also need to be given antifungal prophylaxis for the duration of the antibiotic therapy to prevent fungal peritonitis.[15] Nystatin (tablets or capsules) 500,000 units orally four times a day is suitable. Fluconazole 200 mg taken orally every 48 hours is an alternative but is associated with drug interactions and prolongation of the QT interval on the ECG.[16]

Constipation can lead to catheter malfunction including displacement of its tip, and peritonitis.[17] Daily soft bowel motions can be achieved with sufficient dietary fibre intake as well as laxatives. Stool softeners and osmotic agents are preferred over stimulant laxatives.[18] Enemas with a high sodium and phosphate content should be avoided.

Catheter malfunction

Exchanges of dialysate are best achieved with the catheter tip located in the pelvis. This can be confirmed by abdominal radiographs (see Fig.).

Fig. **Abdominal X-ray showing peritoneal dialysis catheter**



Abdominal X-ray showing the tip of the peritoneal dialysis catheter (radiopaque line) correctly positioned in the pelvis. The cylindrical shape projected over the mid-abdomen is the connector of the extension line. The bowel is faecally loaded.

Image courtesy of Department of Radiology, John Hunter Hospital, Newcastle, NSW

Peritoneal dialysis catheters can remain in place for years, but their patency may diminish over time or during episodes of peritonitis. Fibrin strands in the effluent can be reduced by adding heparin to the dialysate (500 units/L). Unblocking a catheter with irrigation or a fibrinolytic drug should occur under the guidance of the supervising dialysis unit.[12]

Infections

Peritoneal dialysis-related infections are a major contributor to patient morbidity and treatment failure. Their prevention requires good hand hygiene and aseptic technique during exchanges.

The catheter exit site should be cleaned at least twice a week and after it becomes soiled or wet.[19] Suitable antiseptics include chlorhexidine 2% or povidone-iodine 10%. Drainage of the peritoneal fluid and antibiotic prophylaxis are recommended before colonoscopy and invasive gynaecological procedures.

All contaminations and episodes of infection need to be discussed with the dialysis unit. When infections are suspected, samples should be collected for culture and sensitivities before starting empirical antibiotics. Skin commensals, such as coagulase-negative staphylococci and corynebacteria, can be pathogenic.[19]

Fungal infections as well as those caused by methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* are more difficult to treat and require specialist input. Severe, unresolving or recurrent infections are indications for catheter removal.

Catheter-related infections

Infections involving the catheter are a major risk factor for peritonitis. They require early treatment.[19] Exit-site infections are associated with local inflammation and purulent discharge from which skin swabs should be taken.[19] They often respond to treatment with oral antibiotics for a minimum duration of two weeks (with antifungal prophylaxis). Topical anti-infectives may also be applied daily during exit-site care. Antibacterial honey is an alternative to mupirocin ointment except in patients with diabetes, in whom it appears to be ineffective.[20]

Tunnel infections present with inflammation along the catheter tract, and a collection may be evident. These are treated with oral, intravenous or intraperitoneal antibiotics. Surgical drainage may be needed.

Peritonitis

Risk factors for peritonitis include constipation, enteritis, gastrointestinal bleeding, persistent hypokalaemia, and gastric acid suppression especially with H_2 antagonists.[16]

Peritoneal dialysis-related peritonitis is diagnosed when two of the following are present:

- abdominal pain or cloudy effluent (mild cloudiness can be detected by an inability to read a printed sheet of paper through the effluent bag)
- effluent leukocyte count greater than 100/microlitre with more than 50% polymorphonuclear cells
- positive effluent culture.[16]

In addition to skin and environmental organisms, enteric pathogens from a surgical cause may be responsible. When peritonitis occurs, the exchange technique needs to be re-assessed.

Unlike other causes, peritoneal dialysis-related peritonitis frequently has a more subtle presentation. It can often be managed outside hospital. Empirical treatment covers Gram-positive and Gram-negative organisms and often consists of intraperitoneal cefazolin 15 mg/kg or vancomycin 15 mg/kg, with gentamicin 0.6 mg/kg. These can be mixed into one dialysate bag and left to dwell in the patient for six hours once a day. Treatment is adjusted when the organism is identified and continued for 14 days. The exceptions are intermittent vancomycin dosing based on serum concentrations, and the treatment of organisms such as *Staphylococcus aureus*, *Enterococcus* and *Pseudomonas* for 21 days.[16]

Close liaison with the dialysis unit is required. If the patient has features of systemic sepsis, intravenous antibiotics are added. Insufficient improvement after five days of therapy or the presence of fungal peritonitis requires surgical removal of the peritoneal dialysis catheter and transition to haemodialysis.

Diabetes mellitus

Hyperglycaemia increases the risk of catheter-related infections and contributes to fluid retention. Glucose-lowering therapies may need to be increased when dialysis solutions with high glucose concentrations are used regularly.[19] In end-stage kidney disease, the use of metformin is not recommended and insulin effects are more pronounced.[10] Glycaemic targets should be individualised.[9]

Conclusion

Peritoneal dialysis enables patients to undergo kidney replacement therapy outside of healthcare facilities and can be adjusted to suit individual needs. While

SELF-TEST QUESTIONS

True or false?

1. If antibiotics are given for a chest infection in a patient undergoing peritoneal dialysis, an antifungal drug should always be co-prescribed.

2. H_2 antagonists are a risk factor of peritonitis in patients having peritoneal dialysis.

Answers on page 19

the technique is simple, adverse metabolic effects from glucose-containing dialysis solutions need to be minimised. Complications may require patients to transition to haemodialysis, with infections being a particular threat. Polypharmacy is common and judicious prescribing is required. With appropriate support, patients can live with kidney failure and enjoy a good quality of life. <

Conflicts of interest: none to declare

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ARTICLE

Treatments for atopic dermatitis

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Keywords
atopic dermatitis, calcineurin inhibitors, corticosteroids, immunosuppression, Janus kinase inhibitors, phototherapy

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SUMMARY

Atopic dermatitis usually develops in childhood, but can occur in adults. Management involves drug and non-drug treatments to clear the skin.

Not all patients with atopic dermatitis have allergies. Most patients have trigger factors that can be avoided.

All patients should use soap substitutes and bath oils. Moisturisers are important for improving the condition of the skin.

Topical corticosteroids are the main drug treatment. The choice of corticosteroid depends largely on the site of the atopic dermatitis.

Topical calcineurin inhibitors can be considered for sensitive sites such as the face where potent topical corticosteroids are potentially harmful.

Adjunctive treatments given during flares of dermatitis include bleach baths and wet dressings. Antihistamines may help to relieve itch.

Phototherapy may be considered by a specialist for adults if there is inadequate response to treatment.

Severe cases of atopic dermatitis may require systemic treatment. Immunosuppressants, such as ciclosporin, have been used and now dupilumab and upadacitinib are available for severe chronic atopic dermatitis.

Introduction

Atopic dermatitis is a common, multifactorial skin condition that is often managed by GPs. It affects all ages and is heterogeneous in appearance. While there is usually a flexural predominance, it can be localised to the face or hands, or be generalised. Patients complain of itch as well as the rash.

Management of atopic dermatitis is similar in adults and children. It requires a combination of drug and non-drug therapy. Corticosteroids are the mainstay of drug therapy, but biological drugs are now available.

Non-drug treatment

The aim is to manage aggravating factors and improve the condition of the skin. All patients should be instructed to use soap substitutes or bath oils long term.

Avoiding triggers

It is usually possible to identify factors that trigger a flare of atopic dermatitis. Some triggers can be avoided.

Heat

Most patients report that their skin flares in response to heat. Hot baths or showers, bedding, warm clothing or exercise can all be triggers. Patients should be educated to avoid overheating and use cool compresses when their skin is hot or itchy.

Irritants

Soaps, detergents, rough fabrics, seams, clothing labels and exfoliants may all aggravate atopic dermatitis.

Allergens

Not all patients with atopic dermatitis have allergies, but allergens can play a role in some patients. Fragrance is the most common cause of contact allergy, followed by preservatives in consumer products, for example methylisothiazolinone. Patients should always use fragrance-free products. Do not use products containing essential oils (e.g. lavender oil), or food ingredients (e.g. oatmeal, goats' milk, nut oils, pawpaw); these have a high risk for causing sensitisation and consequent food allergy. Sensitisation to contact allergens is more common in atopic individuals due to their impaired skin barrier, but can also occur in those without a known history of atopy. Dietary restrictions are to be minimised, particularly in infants, without input from specialists. Animal dander, house dust mite,[1] pollens and grasses are other potential allergens to recognise

and avoid. Skin prick and RAST testing are of limited diagnostic yield in most cases of eczema.

Moisturiser

Moisturiser is the cornerstone of the management of atopic dermatitis. A genetic tendency to dry skin, caused by filaggrin mutations, underlies most cases. Keeping the skin well moisturised ensures the skin barrier remains intact, prevents penetration of pathogens and allergens, and minimises itch. Patients should moisturise at least daily, but more often if their skin is particularly dry, or during flares.

Moisturisers should be tailored to the sites affected and patient preference. For example, a greasy moisturiser containing liquid paraffin may be suitable around the mouth of a dribbly infant but on the face of an adolescent it may cause acne. Lighter moisturisers may be preferable for hairy areas where folliculitis is more common.

The latest advances in moisturisers specifically for atopic dermatitis include the addition of ceramides which help to repair the deficient skin barrier and restore water permeability.[2-5] Some also contain prebiotics and probiotics to assist in homeostasis of the skin flora and minimise the predominance of *Staphylococcus aureus*. These eczema-specific moisturisers should in theory be more efficacious than standard moisturisers, however it is usually acceptable for a patient to use any bland moisturiser rather than nothing at all.

Drug treatment

The goal of drug treatment is to clear the atopic dermatitis completely. Undertreatment is likely to lead to recurrence.

Topical corticosteroids

Topical corticosteroids are the most important pharmacotherapy for atopic dermatitis. However, the correct selections of strength, quantity and duration of use remain major problems for both GPs and patients alike.

Patients should be counselled that topical corticosteroids are effective and safe when used correctly and should not be avoided or used sparingly. One of the common reasons for treatment failure is underuse due to steroid phobia. Patients are often concerned about the risk of skin thinning, becoming reliant on a corticosteroid, or that corticosteroids make things worse in the long term. They should be counselled that if the correct strength is prescribed for the site, then there is unlikely to be any concern with using a corticosteroid until the skin is clear. This can take weeks to months depending on the severity and chronicity of the atopic dermatitis. Treatment can be repeated on and off, for years if necessary. There is no need to taper topical steroids. They can be stopped when the skin is clear, or reduced to twice a week as maintenance in recurrence-prone areas.

Face

Only the weakest topical corticosteroids, hydrocortisone 0.5% or 1%, are relatively safe on the face and eyelids. If they are effective, they can be used twice a day until the skin is clear. Higher potency topical corticosteroids should be avoided as they commonly cause periorificial dermatitis, a form of steroid-induced rosacea. Other adverse effects such as telangiectasia, acne and erythema can also occur when moderate- and high-potency topical corticosteroids are applied to the face for prolonged periods. Cataracts and glaucoma are the main risks of long-term use of potent topical corticosteroids on the eyelids. If hydrocortisone is ineffective after two to four weeks, then non-steroid options such as a calcineurin inhibitor, or crisaborole should be considered.

Body and limbs

The body and limbs are more tolerant of topical corticosteroids than the face, with few adverse effects. Patients should be reassured that skin thinning is rare and, if seen, reversible. Suitable strengths include methylprednisolone aceponate 0.1%, or mometasone furoate 0.1%. These are used once daily until the skin is clear, then as needed. Ensure patients have a prescription for at least one to two months supply. An authority prescription may be needed to obtain adequate supply through the Pharmaceutical Benefits Scheme (PBS).

Hands and feet

The thick skin of the palms and soles requires a high-potency topical corticosteroid to achieve clearance of atopic dermatitis. Betamethasone dipropionate 0.05% is the standard strength for these sites. Apply twice a day until clear. These sites take longer to clear than other areas – four weeks is usual.

Calcineurin inhibitors

Pimecrolimus and tacrolimus are useful topical anti-inflammatory drugs for the treatment of atopic dermatitis. They are particularly used on the face and eyelids when mild topical corticosteroids are ineffective and where potent topical corticosteroids are not desirable.

Pimecrolimus 1% cream is available on the PBS (authority prescription) for specified patients over six months of age. It is used twice daily until the skin is clear. It can then be reduced to twice a week as maintenance therapy.

Tacrolimus is only available in Australia on a private prescription, compounded as either

cream or ointment in strengths of 0.03% or 0.1%. Tacrolimus 0.03% is equivalent to pimecrolimus 1%.

The main adverse effect of calcineurin inhibitors is a stinging or burning sensation on initial use. This normally subsides after a few days and is not harmful. Discomfort can be minimised by keeping the drug in the fridge and applying moisturiser first.

Crisaborole

Crisaborole 2% cream is approved for mild to moderate atopic dermatitis in patients over the age of two years. It is a phosphodiesterase-4 inhibitor which works by reducing cytokines including tumour necrosis factor alpha.

In clinical trials, 30% of patients were clear or almost clear after 28 days of crisaborole, compared to 18–25% with placebo (vehicle-only).[6] There are no trials comparing its efficacy to topical corticosteroids. The main adverse effect of crisaborole is stinging (4%), followed by flare of atopic dermatitis, pain and skin infection. Apart from the limited efficacy of crisaborole for atopic dermatitis, cost may limit use, with 60 g crisaborole costing approximately $145 on private prescription.

Adjunctive treatments

Bleach baths, oral antihistamines and wet dressings are all potentially helpful adjunctive therapies when patients have a flare of atopic dermatitis. See Box for useful resources that include patient handouts and videos.

Bleach baths

Patients with broken skin, weeping, crusting or sores should be instructed to have bleach baths. Plain, fragrance-free household bleach is added to the bath (¼ cup (62.5 mL) to a child's half-full bath, ½ cup (125 mL) to a full adult bath) for two to five minutes before getting out and patting dry. Oral antibiotics are generally not required unless the patient is systemically unwell or has failed to respond to bleach baths.

Antihistamines

Antihistamines can provide some relief from itch when given regularly. Less-sedating drugs, for example cetirizine or loratadine, are given during the day. Sedating antihistamines, for example promethazine or cyproheptadine, are given at night if sleep disturbance is a problem. Sedating antihistamines should not be used in children under the age of two years. Less-sedating antihistamines are considered to be relatively safe from the age of six months.

Wet dressings

Soaked clothing, tubular bandages or cloths held in place with crepe bandages can be used overnight or for periods of around four hours. They give relief from itch and aid penetration of moisturiser and topical corticosteroids.

Second-line treatments

Patients should be reviewed several weeks after having a flare of atopic dermatitis to check for response to treatment. If there is no response or response is inadequate based on skin appearance, symptoms of itch, poor sleep, or impact on school, work, family functioning or mental health, then further treatment and specialist referral are required.

Oral prednisolone has been used to treat flares of atopic dermatitis. While this may result in short-term improvement, many patients will require recurrent courses of prednisolone due to the long-term genetic tendency to atopic dermatitis. However, prednisolone, rather than topical corticosteroids, is the source of corticosteroid adverse effects, and it should be avoided if possible. There are safer, more effective options than prednisolone to consider in patients requiring more than topical corticosteroid treatment.

Phototherapy

Phototherapy with narrowband ultraviolet B (UVB) results in significant improvement in most patients with atopic dermatitis. A history of exacerbation with sun exposure, melanoma, or very fair skin (skin phototype 1) are contraindications. Lack of access to services in rural areas and not being able to attend due to work commitments are barriers to treatment. Phototherapy is generally not administered to children until they are able to comply with safety measures such as wearing goggles and standing unaided in the light cabinet.[7]

Immunosuppression

Ciclosporin is PBS-listed for treating severe atopic dermatitis. This is a medium-term treatment option (up to two years) due to the significant risk of renal impairment, hypertension and the potential for serious infections.

Drugs that have been used off label for atopic dermatitis include methotrexate, mycophenolate mofetil and azathioprine. Immunosuppressive drugs have largely been superseded by newer advanced therapies.

Box **Useful resources for adjunctive treatment**

Eczema. Kids Health Information Fact sheet. Royal Children's Hospital Melbourne.

Formula for an eczema bath. Royal Children's Hospital Melbourne.

Eczema wet-dressings video. Sydney Children's Hospitals Network.

Dupilumab

Dupilumab is a monoclonal antibody that blocks the binding of interleukins 4 and 13, which are key drivers of atopic dermatitis. It is an immunomodulator, not an immunosuppressant.

Dupilumab must be prescribed by a dermatologist or immunologist and is given as a fortnightly subcutaneous injection, for indefinite use. It is administered in conjunction with topical treatments.

The key trials of dupilumab report that two-thirds of patients will achieve a greater than 75% reduction in severity by 16 weeks and this is maintained out to 52 weeks.[8] Registry data suggest that real-world experience is in fact better than this, with 70–89% of patients achieving 75% skin clearance by week 52.[9,10]

Patients treated with dupilumab should use lubricant eye drops to avoid conjunctivitis, which is seen in around one-third of patients. They may complain of red, itchy, watery or gritty eyes. This is usually allergic conjunctivitis, or blepharitis, which can be exacerbated by dupilumab. It is generally mild to moderate and temporary. General practitioners should advise patients to increase the frequency of lubricant eye drops, add in topical and oral antihistamines, and treat their eyelids with tacrolimus ointment. A referral to an ophthalmologist may be required if symptoms persist.

Dupilumab is PBS-listed for severe chronic atopic dermatitis with an Eczema Area and Severity Index (EASI score) of 20 or more, or severe involvement of the hands or face. Patients currently must be aged 12 years or older (although it has recently been approved by the Therapeutic Goods Administration for children aged 6–12 years with expected PBS listing to follow) and have failed four weeks of appropriate topical corticosteroids or calcineurin inhibitor therapy.

Upadacitinib

Upadacitinib is a selective Janus kinase 1 (JAK 1) inhibitor, which blocks downstream signalling of multiple cytokines. It is therefore immunosuppressive. Oral upadacitinib has a rapid onset of action, with 70–80% of patients achieving 75% reduction in the severity of atopic dermatitis by 16 weeks.[11]

JAK inhibitors can cause cytopenias and elevation of lipid levels, so blood-test monitoring is required. The most common adverse effect of upadacitinib is acne. Infections, particularly herpes simplex and zoster, are also increased. Patients with suspected infections should be assessed and managed promptly. Consider empiric antiviral drugs if zoster or herpes simplex is suspected. The patients should be advised to withhold upadacitinib until they have fully recovered.

Patients should be fully vaccinated before starting treatment. Live vaccines are contraindicated during treatment.

The PBS criteria for upadacitinib are the same as for dupilumab.

Conclusion

The management of atopic dermatitis combines drug and non-drug therapy. Topical corticosteroids are still the main drug treatment, but other options, such as topical calcineurin inhibitors, may be used at some sites. Immunomodulating and immunosuppressive drugs may be required for severe cases of atopic dermatitis. ◀

Conflicts of interest: Gayle Ross has been a paid speaker and on medical advisory boards for Abbvie, Leo Pharma, Sanofi Genzyme, Lilly, Johnson & Johnson and Ego Pharmaceuticals.

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Testing for COVID-19: a 2023 update

SUMMARY

Nucleic acid amplification tests (NAATs), including polymerase chain reaction (PCR) assays, are more sensitive for the detection of SARS-CoV-2 than rapid antigen tests (RATS), and are the gold standard for diagnosis of acute COVID-19. However NAATs can remain positive for weeks following infection due to low-level shedding of non-viable viral fragments.

RATs (in particular self-testing) are the mainstay of COVID-19 diagnosis due to their convenience, speed and high specificity. The sensitivity of RATs is highest within seven days of symptom onset. A negative RAT result may warrant a NAAT or repeat RAT for confirmation.

The presence of spike antibodies is consistent with either vaccination or infection. Nucleocapsid antibodies suggest a previous infection. Serological tests measuring neutralising antibodies that infer immunity are not readily available.

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Introduction

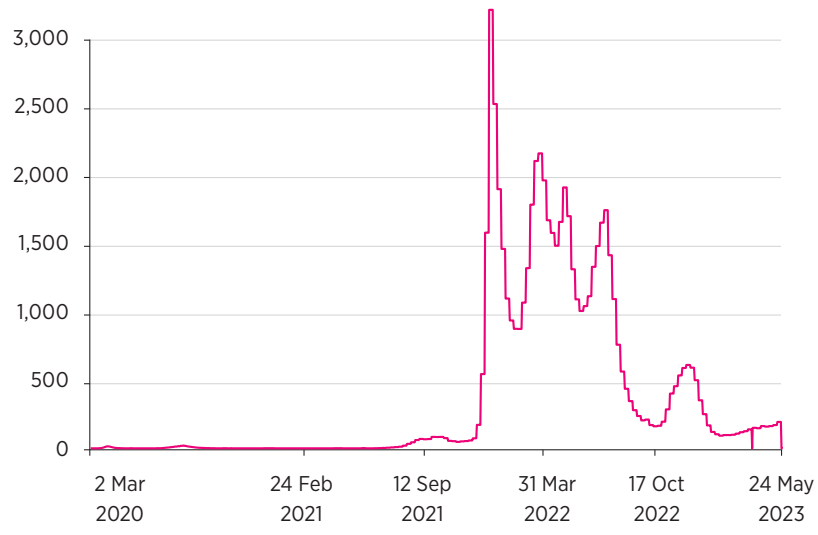
Much has changed since the October 2020 *Australian Prescriber* article on diagnostic tests for SARS-CoV-2.[1] In the first two years of the COVID-19 pandemic, case numbers and mortality were low due to border closures, lockdowns and intensive test, trace, isolate and quarantine policies.[2] Vaccines were developed, tested and manufactured in record time and were rolled out in 2021. With the opening of borders and emergence of new variants of concern, Australia now has widespread community transmission in a relatively well-vaccinated population. Notified cases exceed 11.2 million, with more than 20,300 deaths, the majority of which have occurred since 1 January 2022 (Fig. 1).[2,3] The mortality rates in the highly vaccinated Australian population have remained relatively low in comparison to those in other developed countries.[3]

Variants of concern

Variants of concern are assigned by the World Health Organization when an emerging viral lineage displays increased transmissibility, immune (including vaccine) evasion, resistance to antiviral therapy and/or increased disease severity.[4] Since the emergence of SARS-CoV-2 in December 2019, five viral lineages have been classified as variants of concern: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529).[4]

The Omicron variant emerged in late November 2021, replacing Delta to become the dominant strain globally.[5] Omicron evolved to have increased transmissibility and immune evasion, but does not seem to be more virulent.[5] In 2022 there were several waves associated with the emergence of Omicron sublineages in Australia; initially BA.1, followed by BA.2 and its descendants BA.5 and BA.2.75.[6,7] More recently, recombinant sublineages arising from the exchange of genetic material between strains have emerged and expanded; these include XBB, XBF, XBC, and others.[7,8] The WHO is currently reviewing its classification system for emerging variants to better reflect the current landscape dominated by Omicron descendants.[4]

Fig. 1 **Daily COVID-19 incidence per million population in Australia, March 2020 to May 2023** [3]



Reproduced from reference 3

Diagnostic tests

In 2020–21, nucleic acid amplification tests (NAATs) were the main method for diagnosing COVID-19. They remain the most sensitive and specific gold-standard tests.[9] In late 2021, rapid antigen tests (RATs) became available in Australia. Their wide availability, convenience and speed of providing results has led to them becoming the dominant testing method in Australia. Viral culture testing is not available outside specialist reference laboratories and is not routinely performed. There is no readily available test to determine infectivity.

Nucleic acid amplification tests

NAATs detect the genetic material of pathogens in clinical specimens. The most widely used tests are polymerase chain reactions (PCRs). These tests have been authorised for use in laboratories and in point-of-care settings.

Laboratory-based nucleic acid amplification tests

For laboratory-based tests, SARS-CoV-2 nucleic acid (RNA) is extracted and transcribed to DNA, followed by amplification and detection. The recommended specimen is obtained through a single swab of the throat and bilateral deep nasal passages (or nasopharynx). The specimen can either be collected by healthcare workers or can be self-collected. Saliva is a less-sensitive specimen.[10]

There are many assays directed against a variety of different viral gene targets. Most commercial assays are high throughput and include at least two targets. In many jurisdictions, systems have been developed that enable results to be communicated directly to the patient, such as by SMS.

Point-of-care nucleic acid amplification tests

For point-of-care tests, the clinical specimen can be placed directly into a point-of-care NAAT kit. The test kit performs both nucleic acid extraction and amplification and can provide results in approximately one hour. These low-throughput kits are suitable for use outside the main laboratory, such as in emergency departments or remote clinics, but generally require a trained operator. Point-of-care NAATs are performed under the supervision of healthcare professionals according to the clinical governance requirements outlined by the National Pathology Accreditation Advisory Council.[11]

Cycle threshold

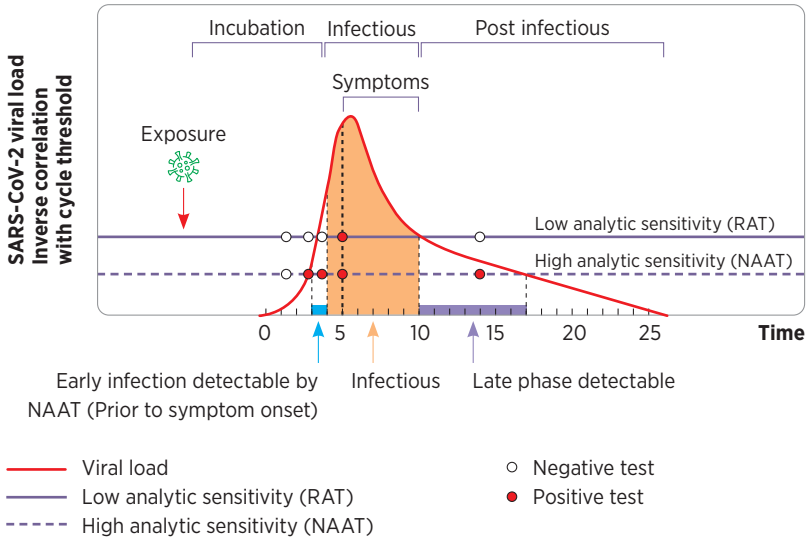
The cycle threshold (Ct) value is the number of amplification cycles before the virus is detected in a PCR. The Ct values from different assays are not directly comparable with each other. A lower Ct value is associated with a larger amount of viral material in a specimen, that is, the Ct value and viral load are inversely related. In acute infection, the viral load usually peaks at around the time of symptom onset, and gradually falls thereafter.[12] A high Ct value may represent very early-stage infection, in which case repeat testing 24–48 hours later would reveal a fall in the Ct value (Fig. 2).[13]

Following SARS-CoV-2 infection, low amounts of SARS-CoV-2 RNA with high Ct values (e.g. more than 35 cycles) can be detected for several months.[14] Studies using viral culture methods have shown that this represents non-infectious shedding of nonviable viral fragments.[15] In some cases, the Ct values can inform decisions about infection control and isolation, alongside testing history and the clinical context. Immunosuppressed individuals may have persistent viral shedding with low Ct values and may have prolonged viral culture positivity and therefore infectivity.[16] Ct values are not included in pathology reports because they vary by assay,[17] although the laboratory may include a comment indicating low-level detection.

Indications

The main indication for a NAAT is to resolve possible false-negative RAT results and, less commonly, suspected false-positive results. For example, in a symptomatic individual with a negative RAT result, a NAAT is indicated to rule out COVID-19. This is particularly important for symptomatic individuals in high-risk settings, including healthcare workers, patients, visitors and carers.

Fig. 2 **Changes in the SARS-CoV-2 viral load over time** [13]



Adapted from reference 13, with permission from BMJ Publishing Group Ltd

Rapid antigen tests

Since January 2022, more than half of all notified cases have been detected using a RAT (Fig. 3).[7] These lateral flow immunoassays detect the presence of viral protein (usually the nucleocapsid protein) in a clinical specimen. The sensitivity is greatest during the symptomatic period, and it is recommended that the tests are performed within seven days of symptom onset.[18] RATs available in Australia have high specificity, and have the benefit of providing results within 15–30 minutes. Specimen collection and testing and the interpretation of some RAT results can be done unsupervised at home (self-tests), while others require supervision by a healthcare practitioner or trained staff member (point-of-care tests). RATs are less sensitive than NAATs, so if there are symptoms compatible with COVID-19, a negative RAT result should be followed by a NAAT. If a NAAT is unavailable, serial RATs should be performed. Consistent with their lower sensitivity, prolonged positivity is less of a problem with RATs than for NAATs (Fig. 2).

Postmarketing evaluations are undertaken by or on behalf of the Therapeutic Goods Administration (TGA), and where claimed performance criteria are not met, the TGA registration is withdrawn. To our knowledge, six registrations have been withdrawn at the time of writing.[19] There is currently no evidence to suggest decreased performance associated with emerging variants, but this requires ongoing monitoring.[19]

Rapid antigen self-tests

The TGA approved the use of RAT self-tests for SARS-CoV-2 from November 2021 in Australia, and at the time of writing, there are 73 approved test kits.[20] Each test uses a different methodology (e.g. some use nasal or oral swabs and others use saliva). In June 2022, the first self-administered NAAT was approved.[21] For TGA approval, self-tests must have a minimum clinical sensitivity of 80% for specimens collected within seven days of symptom onset and clinical specificity of at least 98% compared to laboratory NAATs. A summary of tests approved for use in Australia is available on the TGA website, including a rating of the clinical sensitivity of each test:

- 'acceptable' if greater than 80%
- 'high sensitivity' if greater than 90%
- 'very high sensitivity' if greater than 95%.

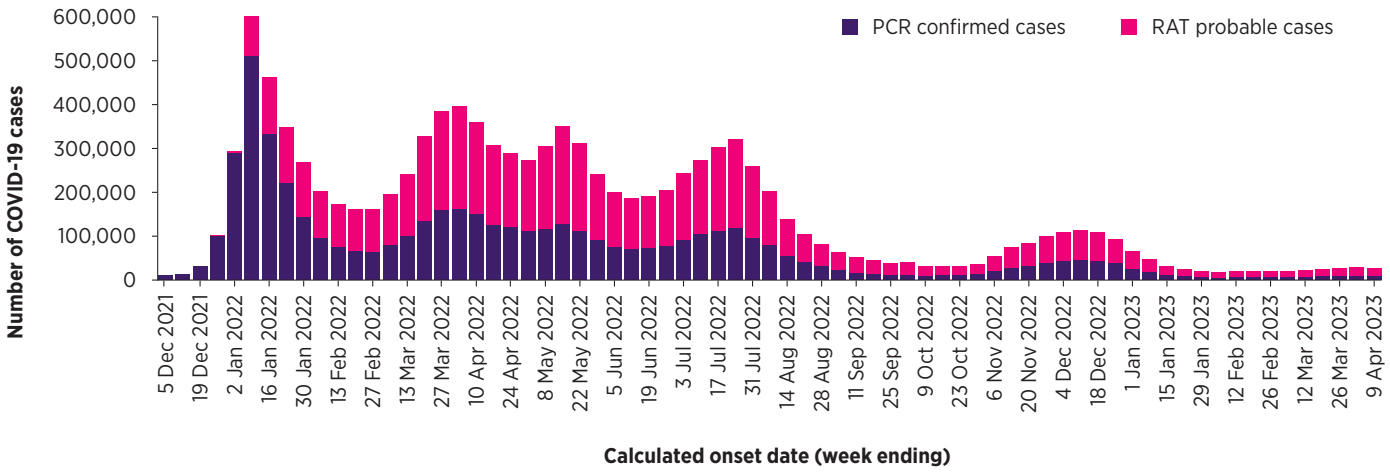
Following a positive RAT self-test result, reporting requirements vary by jurisdiction and can be checked on the relevant state or territory government websites.

If a false self-test result is suspected, the correct methodology for the test including specimen collection, inoculation of the buffer and cartridge, and correct incubation time should be reviewed with the patient, with an interpreter if needed. Specimen collection and testing (e.g. point-of-care RAT or NAAT) by a trained professional should be done if there are concerns.

Point-of-care tests

Similar to point-of-care NAATs, point-of-care RATs are performed under the supervision of healthcare professionals according to the clinical governance requirements outlined by the National Pathology Accreditation Advisory Council.[11] Trained staff are responsible for sample collection and testing, the

Fig. 3 **COVID-19 notifications by rapid antigen tests (probable cases) and nucleic acid amplification (PCR confirmed) tests in Australia** [7]



Source: NNDSS extract from 19 April 2023 for cases with an illness onset from 29 November 2021 to 9 April 2023.
Reproduced from reference 7

interpretation of results and the provision of clinical advice if needed. There are currently 51 different point-of-care RATs approved by the TGA.

Serology

The targets for SARS-CoV-2 serological assays include antigens within the spike and nucleocapsid proteins. Antibodies against SARS-CoV-2 can be detected using indirect immunofluorescence assays, enzyme-linked immunosorbent immunoassays and chemiluminescent microparticle immunoassays. IgG appears early and is usually detectable by day 14 after symptom onset, at approximately the same time as IgM.[22] The detection of IgG is more specific and useful than the detection of IgA and IgM.

All vaccines in use in Australia generate antibodies against the spike protein, and the detection of spike antibodies may be due to either vaccination or infection. Nucleocapsid antibodies indicate prior SARS-CoV-2 infection.

Neutralising antibodies confer immunity to SARS-CoV-2, but these are difficult to measure. Testing for these is not readily available outside specialist reference laboratories.[23]

National seroprevalence studies using a convenience sample of blood bank donors indicate that at least 71% of Australian adults were estimated to have had COVID-19 by December 2022, which is twice as high as case notifications would suggest.[24] This nucleocapsid antibody-based snapshot is likely an underestimate, given the assay sensitivity of approximately 84%.[24] Spike antibody prevalence was 99.6%, suggesting that almost the entire Australian population has been vaccinated and/or has had COVID-19 infection.[24]

Uses and limitations of SARS-CoV-2 serology

The detection of spike antibodies can demonstrate a response to vaccination. However, routine post-vaccination testing is not recommended as there are currently no serological correlates of immunity.

Serology is not recommended for the diagnosis of acute infection.[25] The detection of nucleocapsid antibodies can be used to confirm previous infection with COVID-19 (e.g. if a NAAT or RAT was not performed at the time of acute illness or if a false-negative RAT result was suspected). It is important to note that nucleocapsid antibodies wane over time. There is no role for the use of less-sensitive IgG and IgM lateral flow assays, and some jurisdictions have prohibited their use.

Genomics

Genomic sequencing has played a key role in public health management since the beginning of the pandemic. It was through metagenomic sequencing (i.e. sequencing all nucleic acids in a clinical specimen) that a novel coronavirus was identified as the cause of pneumonia in cases with unknown aetiology in Wuhan, China, in December 2019.[26] Rapid sharing of sequence data enabled the development of sensitive and specific NAATs. In 2020–21, a large proportion of notified cases across Australia had a specimen sequenced, with real-time interjurisdictional data sharing, which enabled tracking and tracing of the virus and investigation of the source of cases with no obvious exposure or transmission link.[27,28] As the virus has evolved, genomic surveillance has identified variants of concern and has been used to monitor resistance to pharmacotherapies.[5,8,16] With widespread community transmission, a sampling strategy has been developed to target international arrivals, hospitalised patients with severe illness, outbreaks, immunosuppressed individuals with prolonged infection, and reinfections.[29]

Genomic sequencing can be performed using specimens collected for PCR tests. This is rarely indicated for individual patient management but may assist in differentiating relapse from reinfection, or in the detection of mutations associated with resistance to pharmacotherapies. At the individual patient level, it is most relevant for immunocompromised patients in hospitals.

Other winter viruses

Throughout 2020–21, other respiratory viruses, particularly influenza A and B, disappeared from circulation altogether. Respiratory syncytial virus was still present but had unexpected, unseasonal peaks of activity. The winter of 2022 saw the re-emergence of influenza A with an early and sharp rise in case numbers and deaths.[30]

Twelve combination RATs that include influenza A and B have been registered by the TGA for self-testing. With additional circulating viral respiratory pathogens, multiplex NAATs for common respiratory viruses including influenza A and B, respiratory syncytial virus and SARS-CoV-2 were recommended for the winter of 2022.[31] This is referred to as a 'respiratory virus panel' and is the recommended method for diagnosing these other respiratory viruses. Some panels also include human metapneumovirus, parainfluenza virus, rhinovirus, adenovirus and bacterial pathogens as part of respiratory NAATs. It is not uncommon for multiple respiratory viruses including SARS-CoV-2 to be detected at one time, particularly in infants and small children.

Conclusions

While NAATs remain the gold standard for SARS-CoV-2 detection, RATs and self-testing are currently the main method for diagnosing COVID-19. RATs are most

sensitive when used within seven days of symptom onset. Serial RATs, or NAATs in high-risk settings, are indicated for symptomatic individuals with an initial negative RAT result. There is no readily available serological test that infers immunity. The detection of nucleocapsid antibodies can confirm previous infection, and the presence of spike antibodies can be due to either infection or vaccination. The development, refinement and implementation of diagnostic tests for COVID-19 have been a major achievement and critical to the relatively well-managed pandemic in Australia. The involvement of patients in their own diagnostic testing, public health notification and management (primarily isolation) has represented a paradigm shift. This will form the basis of future development in the management of infectious diseases and outbreaks. <

Conflicts of interest: none declared

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NEW DRUGS

New drugs

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Treosulfan

Approved indication: acute myeloid leukaemia and myelodysplastic syndrome in adults, and malignant and non-malignant haematological diseases in children

Trecondi (Link Medical Products)
vials containing 5 g powder for reconstitution

Before haematopoietic stem cell transplantation (HSCT), patients with haematological disorders routinely receive conditioning with radiation or chemotherapy regimens, such as busulfan with fludarabine. However, these regimens are associated with a high incidence of adverse events. The alkylating drug treosulfan, which has strong myelotoxic and immunosuppressive properties, may have less toxicity. The drug is indicated with fludarabine as part of conditioning treatment before allogeneic HSCT for acute myeloid leukaemia or myelodysplastic syndrome in adults who are at high risk of adverse effects from standard conditioning therapies. Treosulfan is also indicated, with or without thiotepa, in children older than one month of age with malignant or non-malignant haematological diseases.

The dose of treosulfan is adapted to the patient's body surface area and is given as a two-hour intravenous infusion on three consecutive days before HSCT. The drug is spontaneously converted to its active form in the body with a terminal half-life of about two hours, and 25–40% of the dose is excreted unchanged in the urine. In addition to patients with severe renal or hepatic impairment, treosulfan is contraindicated in patients with severe cardiac or lung impairment, active non-controlled infectious diseases, and DNA breakage repair disorders such as Fanconi anaemia. Live attenuated vaccines are also contraindicated during treatment. All concomitantly used drugs must be dosed two hours before or eight hours after the intravenous infusion of treosulfan. Drugs with a narrow therapeutic index (e.g. digoxin) that are substrates for cytochrome P450 (CYP) 3A4, CYP2C19 or P-glycoprotein should not be given during treatment with treosulfan. Interactions with high-dose chemotherapy have not been observed.

Treosulfan is an irritant and a human carcinogen. Care must be taken when handling the drug to avoid extravasation and contact with skin and mucous membranes.

In an open-label, multicentre, randomised controlled phase III trial, adults (18–70 years of age) with acute myeloid leukaemia or myelodysplastic syndrome received treosulfan (220 patients) or busulfan (240 patients) with fludarabine before HSCT. Two years later, the event-free survival rate was 64% in the treosulfan arm and 50% in the busulfan arm. There were no statistically significant differences between the treatment arms in terms of disease recurrence, progression after HSCT or platelet recovery after HSCT. The two-year overall survival (71% vs 56%), transplantation-related mortality (12% vs 28%) and non-relapse mortality (11% vs 23%) were all improved in the treosulfan arm compared with the busulfan arm. Graft failure occurred in eight patients in the busulfan arm.[1]

A prospective, multicentre, non-randomised phase II trial studied 65 children (28 days to 17 years of age) with acute lymphoblastic leukaemia, acute myeloid leukaemia, myelodysplastic syndrome or juvenile myelomonocytic leukaemia. They received a combined regimen of treosulfan, fludarabine and thiotepa before HSCT. Three years later, the cumulative incidence of non-relapse mortality was 3.1%. The three-year Kaplan–Meier estimate of relapse- or progression-free survival was 74% and that of overall survival was 83%. Eleven patients (17%) died in the trial due to relapse or progression (eight patients) and transplantation-related causes (three patients).[2]

Myelosuppression with pancytopenia is a desired therapeutic effect of conditioning regimens and, therefore, blood counts should be monitored frequently until recovery. The risk of infection is increased during severe neutropenia. Oral mucositis is a very common adverse effect and so mucositis prophylaxis is recommended.

During the phase III trial in adults, drug-related serious adverse events were reported in six patients (3%) in the treosulfan arm and eight patients in the busulfan arm (3%). The most common of these included infections (four patients in each arm) and hepatobiliary disorders (three patients in the busulfan arm). Adverse reactions did not result in any dose reductions or treatment discontinuation. Fifty-two patients (24%) in the treosulfan arm and 82 patients (34%) in the busulfan arm died. The most common causes of death were relapse and transplantation-related causes (including infection and graft-versus-host disease).[1]

The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

During the phase II trial in children, treatment-emergent adverse events were reported in 97% (63/65) of the patients. The most common severe adverse events included oral mucositis (43%), infections and infestations (43%), nausea and vomiting (34%), and diarrhoea (15%).[2] Seizures might occur in infants 1–3 months of age. Dermatitis in the nappy area may occur in small children due to the excretion of treosulfan in urine.

Ovarian suppression and amenorrhoea with menopausal symptoms are common in pre-menopausal patients receiving treosulfan. The treatment can impair fertility in both men and women. Patients are advised to use effective contraceptive options during and for six months after stopping treatment.

Treosulfan was relatively well tolerated in the trials involving patients with haematological diseases. The low mortality and manageable adverse effects associated with treosulfan make it a suitable option for conditioning regimens in preparation for HSCT in both adults and children.

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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ANSWERS TO SELF-TEST QUESTIONS

1 True 2 True

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