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CONTENTS

EDITORIAL

Consumer medicine information

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From a consumer perspective, the saying 'we don't know what we don't know' is particularly apt when it comes to information about medicines. Consumers may be prescribed medicines about which they know little or nothing. These medicines can have significant health repercussions that the patient would not necessarily know to ask about. Consumer Medicines Information (CMI) is intended to inform patients, but it is just one component of effective medical care. In 2016 a media controversy over an asthma medicine which has been associated infrequently with adverse effects in children highlighted the responsibility that doctors and pharmacists share to ensure patients are properly informed.[1]

Doctors and pharmacists are responsible for advising patients about the benefits and risks of their medicines particularly when a new medicine is prescribed. However, despite that expectation and the availability of CMI on the internet and sometimes in leaflets, it is not unusual for consumers to be dispensed a medicine without the advice they need to ensure its safe and effective use. Patients with several conditions who are taking multiple medicines will have a greater need for detailed information.

The CMI produced by pharmaceutical companies in paper form or online is by and large comprehensive and understandable. However, CMI can tend to emphasise potential harms rather than benefits and it does not include information about off-label indications. There may also be limited information about interactions with other medicines, including complementary medicines.

There are at least four Australian websites which give links to CMI.[2-5] CMI leaflets were inserted into medicine packs but many companies have since stopped this practice, because of concerns about keeping leaflets up to date and difficulties fitting a legible leaflet inside a medicine pack. However this can have negative consequences when neither the doctor nor the pharmacist provides adequate information and the consumer does not know about, nor knows how to access, the internet-based CMI that has superseded paper-based information. The late Sally Crossing AM, Convenor of Cancer Voices Australia, who initiated the campaign for a return to CMI leaflets, said: 'We should not have to know to ask for CMIs, especially when sick, … or be expected to muddle through the internet, when another fail-safe solution is available.'[6]

Payment for provision of CMI by pharmacists was specified as part of the dispensing fee in the Fourth Community Pharmacy Agreement of 2005. More recent pharmacy agreements do not mention CMI. Provision of CMI in written or verbal form is recommended practice for pharmacists although no longer specifically included in the dispensing fee.

The CMI guide on the Australian Government Health Department's website was published in 2000. While it describes what CMI is meant to do, the guide does not specify who should be directly responsible for telling consumers about CMI, or providing access to it.

The Therapeutic Goods Administration states:[4]

> CMI documents may not be available for every product. Sponsors are required to provide CMIs prior to new prescription medicines and specified over-the-counter (OTC) medicines being released to the market. Products that have been registered but not yet released to the market will not have accompanying CMI documents.
>
> For medicines that do have CMIs, TGA regulations require that the CMI be made available to consumers either in the pack or in another manner that will enable the information to be given to the person to whom the medicines are administered or otherwise dispensed.

The issue of access to CMI has prompted a campaign to return CMI leaflets to medicine packaging. The national CMI guide promulgated under the Quality Use of Medicines strategy in 2000 was meant to ensure medicine information was 'designed to inform consumers about prescription and pharmacist-only medicines' in a reader-friendly and standardised way.[7] Seventeen years on, we have an unsafe and less effective situation where CMI leaflets are no longer inserted in packages, and patients are not getting the information they need.

Despite the existence of CMI, uncertainty remains about who should be ensuring it gets to the patient. While discussion with the prescribing doctor usually takes place, it is not easy for a patient to recall all the details needed for safe and effective use of a medicine. Doctors and pharmacists can help consumers by talking about CMI, especially if a medicine is being used for an off-label indication.

An Australian study concluded that doctors and pharmacists are still a preferred source of CMI, despite its increasing availability on the internet.[8]

The study suggested patients may benefit from the clarification of who is responsible for providing CMI. Few respondents preferred the internet as a source of medicine information. An earlier, smaller study found that fewer than half of participants had received written medicine information.[9]

We need to be better informed health consumers. The Australian Commission on Safety and Quality in Health Care estimates that about 60% of adults have low health literacy. If we are serious about the Quality Use of Medicines, we require that CMI is not only known about but can be easily read and understood.

Adequate health literacy, often dependent on simple advice from a GP or pharmacist, not only benefits the individual's health but also reduces the risks to the system of waste and costly medication misadventure.

Medicines Australia hosted a stakeholder's meeting on 3 August 2016 to discuss CMI and options to address these major problems. Participants at that meeting agreed to do more work on both the format and content of CMI and the process by which people can access CMI and other information on medicines.

Conflict of interest: none declared

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LETTERS

Letters to the Editor

Treating patients on new anticoagulant drugs

Aust Prescr 2017;40:46–7
http://dx.doi.org/10.18773/austprescr.2017.021

I agree with the authors of the new oral anticoagulants article that the drugs should be viewed 'as useful arrows in the prescriber's quiver of oral anticoagulants' rather than to replace warfarin.[1] However a previous *Australian Prescriber* comment[2] did not adequately address the practical aspects of reversal of the newer anticoagulants.

Significant concerns have been raised about how the manufacturer of dabigatran may have withheld data in the RE-LY trial,[3] with the possibility that issues about the bleeding risk were far greater than were acknowledged. This was particularly in light of the drug's 'fickle pharmacokinetics' resulting in highly variable plasma concentrations[4] and differences in how the different drug regulators managed this issue.[5]

Trials involving dabigatran versus warfarin may have underestimated major bleeding rates,[6] and possibly the risk of gastrointestinal bleeding related to dabigatran and rivaroxaban compared to warfarin[7] despite their touted safety profile.

There was also controversy with the ROCKET-AF trial of rivaroxaban,[8] where serious allegations that a defective point-of-care device was used in the warfarin arm. This could have potentially affected the trial results and emphasises the importance of post-marketing trials to authenticate company-sponsored trials used to support the drug's approval.

Even idarucizumab, the monoclonal antibody antidote to dabigatran (both from Boehringer Ingelheim), comes with a certain caveat not widely known – the median time to bleeding cessation was 11.4 hours for those with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent.[9] Hopefully, whatever a 'life-threatening bleed' is, 12 hours delay (before bleeding stops) is consistent with meaningful life.

Although the effect of reversal is up to 24 hours, 'subsequent increases in dabigatran concentrations that occurred 12 hours after the administration of idarucizumab in six patients and 24 hours after the administration of idarucizumab in 16 patients were also evident by increases in the clotting times and may reflect the redistribution of extravascular dabigatran into the intravascular compartment'.[9] Therefore the anticoagulation effect of dabigatran, taking 2–4 days post cessation to be safe from significant bleeding or major surgery, may still relapse 24 hours after the last dose of idarucizumab.

Conversely, warfarin can be reversed by vitamin K, prothrombin complex concentrate or fresh frozen plasma within 15 minutes to six hours.[10]

Clinicians and patients should be informed of these facts before embarking on therapy involving the newer anticoagulants.

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Paul Chin and Matthew Doogue, the authors of the article, comment:

Dr Goh raises important concerns about the reversal of anticoagulation with the new oral anticoagulants in the setting of bleeding, particularly in relation to dabigatran.

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.

Dabigatran therapy was found to be non-inferior to warfarin in terms of major bleeding risk and mortality in the randomised controlled trials that preceded the availability of the reversal agent, idarucizumab.[1-3] It is possible that idarucizumab will improve the safety of dabigatran to the extent that it is superior to the safety of warfarin, for example by rapid reversal before acute surgery or in the event of a major gastrointestinal haemorrhage.

The durability of anticoagulation reversal is a concern with both the new anticoagulants and warfarin. For warfarin, laboratory coagulation monitoring is important following the use of reversal agents, as its long half-life (around 40 hours) may outlast the half-lives of the reversal agents.[4] The use of INR and associated threshold values requiring action are routinely used in monitoring of patients on warfarin.[5] However, it remains to be established which laboratory tests and what thresholds should be used to monitor patients treated with the new anticoagulants in the setting of bleeding requiring anticoagulation reversal. For dabigatran, the thrombin clotting time and the measurement of plasma dabigatran concentrations are expected to be particularly informative for clinical decision making.[6,7]

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LETTERS

Treating dental patients on new anticoagulant drugs

Aust Prescr 2017;40:48
http://dx.doi.org/10.18773/austprescr.2017.022

I just have two questions on the use of anticoagulants on dental patients.[1] First, in the paragraph on managing risk it says:

> Before undertaking any treatment, dentists must obtain a thorough medical history from the patient. This includes the name, dose and prescriber of all drugs.

Does the author really mean that the prescriber should be noted for each drug? I am wondering whether this is an error and perhaps was meant to be duration, or purpose? If not, for what reason should the prescriber be noted? This would be difficult information for many patients to provide accurately and difficult to substantiate for long-term therapy.

Second, there is no mention of the use of post-extraction tranexamic acid mouth rinse in this article. Despite strong support for its use after dental extractions in patients on warfarin, there are mixed opinions within the dental profession on the role of this mouthwash for patients on direct-acting oral anticoagulants.

Certainly, there is no evidence that it actually works and the absence of a proprietary product makes it difficult to support. However, many dental practitioners use it with the new oral anticoagulants just in case. A statement in the article on its role would have been helpful.

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REFERENCE

1. Daly C. Treating patients on new anticoagulant drugs. Aust Prescr 2016;39:205-7. http://dx.doi.org/10.18773/austprescr.2016.085

Christopher Daly, the author of the article, comments:

It should be standard practice for dentists to record the name of the patient's GP and any specialist physicians as they may need to be contacted to discuss the patient's medical status or medicines. It also provides a medicolegal record in the patient's notes. When listing the medicines, it is necessary to record the prescriber as it is not uncommon for patients to be prescribed drugs from both their GP and specialists. During a dental visit, it should be standard practice to review and update the patient's medical status as well as prescription and over-the-counter medicines.

For patients on warfarin, randomised controlled trials have shown that tranexamic acid mouthwash prevents bleeding after dental extractions.[1–3] No such trials have been reported for the new anticoagulants. The dental management guideline for patients taking new anticoagulant drugs does not advise using tranexamic acid mouthwash as there is insufficient evidence to show any additional benefit over local measures (haemostatic plugs, suturing and compression).[4]

Whereas warfarin inhibits synthesis of coagulation factors II, VII, IX and X, the new anticoagulants directly inhibit one specific factor – either thrombin (dabigatran) or factor Xa (apixaban and rivaroxaban). Thus, the clotting cascade beyond factor X is irreversibly turned off while these drugs are in the circulation. In the absence of evidence-based data of efficacy and on the basis of the pharmacological effects of the new anticoagulants, tranexamic acid mouthwash is not recommended as a post-extraction measure.

Christopher Daly
Chair (former)
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Correcting iron deficiency

Aust Prescr 2017;40:49
http://dx.doi.org/10.18773/austprescr.2017.023

My colleagues and I recently noted that the article on correcting iron deficiency did not include up-to-date information on intravenous iron replacement therapy in Australian hospitals.[1]

Iron polymaltose has been used for decades and in the last five years there have been additional clinical studies across several Victorian hospitals looking into the safety and rapid administration of high doses.[2-6] This information was omitted from the article despite the new data on safety and adaptation of the rapid infusion protocol for iron replacement using the safe and cheaper alternative to the newer product ferric carboxymaltose.

Many tertiary centres provide medication administration infusion services, which include iron polymaltose for management of iron deficiency anaemia. Using iron polymaltose negates the inconvenience of using ferric carboxymaltose on numerous occasions for doses over 1000 mg. This is common as the average dose for iron replacement is approximately 1200–1300 mg.

Patients who would benefit from ferric carboxymaltose are those with renal or heart failure who do not require doses over 1000 mg, and patients with mild–moderate iron deficiency requiring doses of 1000 mg or less with poor oral drug adherence or intolerance to oral supplements. These people can be treated with a single dose of ferric carboxymaltose.

Omission of this information for your readers does not provide them with a comprehensive update on current practice in the management of iron deficiency anaemia.

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Iouri Banakh has previously received a grant provided by the Society of Hospital Pharmacists of Australia and sponsored by Sanofi.

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Jonathan Baird-Gunning and Jonathan Bromley, the authors of the article, comment:

As stated in our article, we agree that iron polymaltose is the preferred preparation for hospital inpatients due to its low cost and ability to be given at doses greater than 1 g in a single infusion.

We note the recent studies in Victoria assessing the safety of administering this preparation as a rapid infusion – 75 minutes for doses less than 1500 mg and 100 minutes for 1500–2000 mg have been proposed. This appears to have a similar safety profile to the standard slow infusion protocol.[1] The potential benefit in an ambulatory setting could be for those requiring higher infusion doses, especially in rural settings where travel time needs to be considered in addition to infusion cost and nursing time. Ferric carboxymaltose requires only a 15-minute infusion, however as we highlighted the total dose cannot exceed 1 g.

It must be stressed that the product information does not currently support the rapid protocol for iron polymaltose and clinicians would need to discuss this approach with their drug and therapeutics committees if they wish to consider these changes.

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LETTERS

Oral supplements and iron deficiency

Aust Prescr 2017;40:50
http://dx.doi.org/10.18773/austprescr.2017.024

I wonder if the authors of the article on iron deficiency could clarify when oral iron supplements should be taken.[1] The article advises taking them without food, but the iron supplement packs (and AusDi) advise taking them with food.

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REFERENCE

1. Baird-Gunning J, Bromley J. Correcting iron deficiency. Aust Prescr 2016;39:193-9. http://dx.doi.org/10.18773/austprescr.2016.069

Jonathan Baird-Gunning and Jonathan Bromley, the authors of the article, comment:

Iron supplements can be taken with or without food, however their absorption can be reduced when taken with food as outlined in our article. Gastrointestinal adverse effects from oral iron are common and are often the reason for poor compliance. Taking the iron with or soon after food may reduce these effects and in turn potentially improve compliance.

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ARTICLE

Managing the drug treatment of rheumatoid arthritis

SUMMARY

Rheumatoid arthritis is an inflammatory condition affecting synovial joints. Without treatment, the underlying inflammatory process leads to joint destruction, pain, deformity, disability and accelerated cardiovascular disease.

Disease-modifying antirheumatic drugs will attenuate the inflammation. Their benefits are seen at all stages of the disease, however the best outcomes are achieved when they are used shortly after the onset. Patients with suspected rheumatoid arthritis should be referred promptly.

Disease-modifying antirheumatic drugs are often used in combination and can have serious adverse effects. Their safe use requires ongoing monitoring to identify potential adverse events.

The risk of infection is increased and vaccination is best given before starting disease-modifying antirheumatic drugs.

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Keywords
disease-modifying antirheumatic drugs (DMARDs), immunosuppression, rheumatoid arthritis

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Introduction

Rheumatoid arthritis is a chronic autoimmune condition that classically presents as a symmetrical polyarthritis of proximal small synovial joints. It has a prevalence of 0.46% in the Australasian region, and affects women more frequently than men.[1] The onset is usually between 35 and 60 years, however the majority of the disease burden in Australia is in people over 65 years.[2]

The cause of rheumatoid arthritis remains unknown, although our understanding of the pathological processes has advanced greatly in the last 20 years. Many pro-inflammatory cytokines are involved and some of these are therapeutic targets for the development of new drugs.[3]

Optimal management of rheumatoid arthritis requires an understanding of the therapeutic goals, the options available to attain them and the associated potential complications. Drugs are only one part of the management of the patient.

The significance of inflammation

The cytokine milieu in rheumatoid arthritis influences a multitude of physiological processes. These include promoting the influx of immune effector cells into the joint synovium, and activation of osteoclasts, chondrocytes and fibroblasts.[3] There is a positive feedback loop that reinforces the inflammatory process. Unabated, this process results in joint pain and destruction, ultimately causing deformity and disability.

Chronic inflammation also contributes to an increased risk of myocardial infarction, stroke and death. A Canadian population-based prospective cohort study reported an absolute increase in cardiovascular events of 5.7 per 1000 person-years (95% confidence interval 4.9–6.4) in patients with rheumatoid arthritis compared to those without.[4] The use of disease-modifying antirheumatic drugs (DMARDs) to attenuate the inflammatory process has been shown to prevent joint erosions and reduce pain, cardiovascular morbidity and mortality.[3,5]

Nomenclature

The development of targeted monoclonal antibodies and small-molecule kinase inhibitors has widened the therapeutic options in rheumatoid arthritis. Each drug has a proven ability to modify the disease process to varying extents. However, the increase in drugs has thwarted our simple terminology of DMARDs, as the term no longer refers solely to synthetic chemical entities. A new nomenclature has been proposed[6] and applied to the drugs registered in Australia for the treatment of rheumatoid arthritis (see Box).

A systematic review and meta-analysis found that corticosteroids reduce demonstrated radiographic erosions.[7] While this effect defines corticosteroids as DMARDs, their toxicity profile makes routine long-term use undesirable. Other infrequently used DMARD therapies include azathioprine, ciclosporine and gold salts.

Box **Disease-modifying antirheumatic drugs**

Synthetic DMARDs

Conventional

- methotrexate
- sulfasalazine
- leflunomide
- hydroxychloroquine
- corticosteroids

Targeted

- Janus kinase inhibitors
  - tofacitinib

Biologic DMARDs

Tumour necrosis factor antagonists

- adalimumab
- golimumab
- certolizumab pegol
- infliximab*
- etanercept

IL-1 receptor antagonist

- anakinra

IL-6 receptor antagonist

- tocilizumab

Anti-CD20 monoclonal antibody

- rituximab

CTLA-4-Ig fusion protein

- abatacept

DMARDs disease-modifying anti-rheumatic drugs
IL interleukin
CTLA cytotoxic lymphocyte-associated antigen
* also available as a biosimilar

The importance of early treatment

Remission is unlikely to occur without intervention.[8] Bone erosions are detectable in 25% of people within three months of onset[9] and in 70% by three years.[10] Delaying treatment beyond three months causes more joint destruction and a higher chance of requiring persistent DMARDs to maintain remission.[11] Early DMARD therapy during this 'window of opportunity' (that is within three months of onset) will more readily induce remission and delay progression.[9]

Methotrexate monotherapy

Methotrexate is the backbone of rheumatoid arthritis treatment. Monotherapy consistently reduces radiographic progression and improves quality of life.[12] Approximately 40% of patients will respond to monotherapy.[13] Limited comparative data suggest that other conventional DMARD monotherapies are as effective as methotrexate.[14] However, its demonstrated long-term benefits, cost, acceptable safety profile and synergy with other DMARDs make methotrexate the recommended first choice for monotherapy in the guidelines of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[15,16]

Combination therapies

Combining DMARDs is frequently used as a first-line strategy, particularly for those with poor prognostic factors. A systematic review and network meta-analysis compared methotrexate monotherapy to methotrexate in combination with other DMARDs for patients with rheumatoid arthritis who were treatment-naïve or had an inadequate response to methotrexate alone.[13] The combination of methotrexate with sulfasalazine and hydroxychloroquine, so called 'triple therapy', has greater efficacy than monotherapy in both early rheumatoid arthritis and non-responders, but higher toxicity.[13] Combining methotrexate with biologic DMARDs has also demonstrated superior outcomes compared to methotrexate monotherapy in those with an inadequate response.[13]

The optimal combination of DMARDs and timing of combination therapy is debated. Unless methotrexate is poorly tolerated it should always be continued when starting other DMARDs.

Choosing the right treatment

The choice of treatment for a patient is influenced by the duration and severity of disease, previous treatments and regulatory restrictions. There are also patient-specific factors such as comorbidities, patient preference, family planning, and financial and social circumstances.

Pre-treatment evaluation

Before starting DMARDs, all patients should have baseline blood tests including full blood examination, serum creatinine and liver enzymes. Abnormalities may alter the choice of therapy and dosing (e.g. methotrexate is renally excreted). All patients should be screened for hepatitis B virus, hepatitis C virus and tuberculosis as there is a risk of reactivation of latent infections or worsening of active infection.

Other important considerations include congestive heart failure, malignancy, lymphoproliferative disease, multiple sclerosis, chronic obstructive pulmonary disease, bronchiectasis and interstitial lung disease. Further evaluation is required before treatment.

Pregnancy, contraception and lactation

The management of rheumatoid arthritis before, during and after pregnancy can be challenging. Although many women will have an improvement in

disease activity during pregnancy, remission is rare.[17] Poor pregnancy outcomes occur more commonly with high disease activity and include miscarriage, prematurity and pre-eclampsia.[17] With the exception of sulfasalazine and hydroxychloroquine, all DMARDs are considered either unsafe or of uncertain safety during pregnancy.[18] Counselling on effective methods of contraception is essential to prevent unplanned pregnancy while taking teratogenic drugs.[17] Planned pregnancy is preferable and allows time for appropriate treatment changes to be made while optimising disease control. Certain DMARDs (e.g. leflunomide, methotrexate) must be stopped at least 3–6 months before conception.[18]

During lactation the immunosuppressive effects of some DMARDs may affect the infant because of drug excretion into breast milk. Information on drugs and lactation can be found at the United States National Institute of Health Lactmed website (https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) or via local medicines information services.

Treating to target

The aim for every patient is to achieve a target of remission or low disease activity, as this leads to better outcomes.[16] Disease activity is quantified by validated tools, such as the disease activity score based on a 28-joint count (DAS28), the clinical disease activity index (CDAI) and the simplified disease activity index (SDAI).[16] A score is calculated from patient-reported pain and function, serum markers of inflammation (e.g. C-reactive protein or erythrocyte sedimentation rate) and physical joint examination. A score of moderate to high disease activity is an indication for more intense therapy with combination DMARDs until the target score (or lower) is achieved. While the optimal scores for defining low disease activity and remission continue to be refined, the treat-to-target approach is recommended by the ACR and EULAR guidelines.[15,16] These provide a practical summary of evidence-based treatment algorithms, although they do not completely reflect the Australian regulatory restrictions. The Australian restrictions can be reviewed at the Australian Government Department of Human Services website (www.humanservices.gov.au/health-professionals/enablers/rheumatoid-arthritis).

Monitoring

Monitoring treatment with DMARDs is important to ensure their safe and effective use. The potential adverse effects of methotrexate include mouth ulcers, gastrointestinal discomfort, hepatotoxicity, myelosuppression, reversible alopecia and pneumonitis. The development of adverse drug reactions should prompt review for incorrect dosing, drug interactions or new renal impairment. Supplementation with folic acid can improve the gastrointestinal symptoms and reduce the risk of liver function abnormalities.[19] Although an optimal folic acid regimen has not been identified, 5–10 mg orally once a week, preferably not on the same day as methotrexate, is generally recommended.

Details regarding adverse drug reactions and the monitoring of DMARDs can be found in the Table,[20,21] or in previous *Australian Prescriber* articles.[22-27] Patient medicine information handouts are also available from the Australian Rheumatology Association website (www.rheumatology.org.au).

Infection

Patients with rheumatoid arthritis have an increased incidence of infection compared to the general population, in particular those with higher disease severity, corticosteroid use and other comorbidities.[28] Combination DMARD regimens, especially those that include a biologic drug, are associated with a markedly increased risk of serious infections.[29] This risk is highest in the first six months of therapy.[29] These infections are of concern, in particular reactivation of tuberculosis.[30] The risk of reactivation of latent tuberculosis is high with DMARD use, particularly with biologic DMARDs and tofacitinib.[15] Vigilance for infection is important, as its signs and symptoms may be atypical in immunosuppressed patients. In particular the febrile response may be blunted due to cytokine blockade. Patients should be advised to seek medical attention if they have localising symptoms of infection, an unexplained illness or a fever.

The management of minor infection requires ongoing clinical review until it resolves, with early consideration of antimicrobial therapy. Herpes zoster is more common in people taking tofacitinib and biologic drugs and may have multi-dermatomal presentations.[31] Early antiviral treatment is required. The continuation of DMARDs with recurrent minor infections should be discussed with the treating rheumatologist.

Serious infections requiring hospitalisation or intravenous antibiotics usually lead to the discontinuation of most DMARDs, especially tumour necrosis factor antagonists. Long-term corticosteroids, if part of the current therapy, should be continued and possibly increased during infection due to the likelihood of adrenal suppression and the risk of an Addisonian crisis if they are stopped. Resumption of other DMARDs may be

considered after recovery, but must be done with informed consent and close monitoring. Repeated infections, irrespective of severity, may also lead to DMARD discontinuation.

Disease flares

The definition of a 'flare' in rheumatoid arthritis poses a challenge, as patient and physician reports of flare do not always correlate with an increase in disease activity.[32] Flares defined by increased disease activity are associated with increased pain, functional deterioration and radiographic progression.[33] These flares often occur when the dose of DMARD is reduced.

Objective assessment of disease activity is essential to determine if treatment intensification is required. This should include a joint assessment, a patient- and physician-reported disease severity measure, and measures of inflammation such as C-reactive protein or erythrocyte sedimentation rate. Increases in disease activity should trigger an urgent review by a rheumatologist.

Pain may be managed with paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs). Opioid analgesia may cause adverse drug reactions without additional benefit and is best avoided.[34]

Glucocorticoids may be considered for disease flares. They are given either orally at low dose (e.g. prednisolone 10–15 mg daily), intramuscularly or intra-articularly. Intramuscular injections (e.g. methylprednisolone acetate) have the benefit of sustained activity without the inconvenience of daily oral dosing or a requirement for tapering the dose.

Vaccination

When indicated, vaccination for pneumococcus, influenza, hepatitis A and B and human papillomavirus is recommended irrespective of DMARD choice.[15] Live vaccines should be avoided in people taking DMARDs, although varicella zoster may be considered in those who are not on biologic DMARDs.[15] Vaccines may be given any time during therapy, however the best time is before treatment as DMARDs may attenuate the immune response. We recommend consulting the Australian Immunisation Handbook for further details.[35]

Complementary medicines

Despite widespread use of complementary medicines there remains a lack of evidence of their benefit. No complementary medicines have demonstrated disease-modifying effects. Meta-analyses of the published data suggest that omega-3 polyunsaturated fatty acids are effective at improving pain and reducing NSAID use. The optimal dose is yet to be determined (reported range 1.7–9.6 g daily).[36] Evening primrose oil, borage seed oil, *Tripterygium wilfordii* Hook F (thunder god vine) and blackcurrant seed oil may improve some symptoms of rheumatoid arthritis.[36,37] Adverse effects have been reported, making the harm–benefit profile unfavourable.[37]

The advent of biosimilars

A biosimilar is a biologic drug that is similar, but not identical, to a registered original biologic drug. The differences may theoretically result in altered efficacy and increased immunogenicity, therefore strict regulation is essential. The Australian Therapeutic Goods Administration requires multiple criteria to be fulfilled before a biosimilar can be registered.[38] Considering the current expense of biologic drugs for rheumatoid arthritis in Australia, a cheaper and effective biosimilar is an attractive option. Even if it is deemed to be equivalent to the original product, the safety and efficacy of switching between products is uncertain.

Conclusion

The advances in rheumatoid arthritis therapy over the last 20 years have markedly changed the way the disease is managed and have improved outcomes. Understanding the therapeutic goals and the options available to achieve them, pre-treatment evaluation, and the ongoing monitoring for complications of the disease and its treatment, will ensure the best outcomes for patients. Further advances in biotechnology are likely to lead to even more changes in the therapeutic landscape of rheumatoid arthritis. ≺

Tom Wilsdon attended Editorial Executive Committee meetings as the clinical pharmacology registrar for Australian Prescriber *in 2016. He is a member of the South Australian Formulary Committee.*

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Table **Disease-modifying antirheumatic drugs and monitoring in rheumatoid arthritis**

Drug	Adverse drug reaction	Monitoring	Action
For all DMARDs	Myelosuppression Hepatotoxicity	Routine unless otherwise specified: FBE, EUC, LFTs at baseline, 2–4 weekly for 3–6 months and every 6–12 weeks thereafter. This regimen is influenced by comorbidities and changes to therapy.	Abnormalities in blood monitoring may lead to dose adjustments, treatment interruption or cessation.
	Malignancy	Age-related cancer screening programs and self-reported symptoms	
	Infection	Self-reported fever (>38 °C), localising symptoms or unexplained illness. Fever may not always be present due to DMARD-induced alterations in cytokine profile. Maintain a high index of suspicion, particularly for reactivation of latent tuberculosis or hepatitis B infection.	
Methotrexate	Alopecia	Self-reported hair loss	Usually reversible after stopping drug
	Mouth ulcers	Self-reported mouth ulcers Inspection of oral mucosa	Folic acid supplementation (not on day of methotrexate)
	Pneumonitis	Symptoms of cough or dyspnoea Routine respiratory examination	CXR, PFTs and urgent specialist review
	Abnormal LFTs Cirrhosis	LFTs as per routine for all DMARDs	Continue folic acid supplementation. If AST or ALT <2 x ULN, repeat LFTs in a month. If normalising, continue. If persistent elevation, reduce dose. If AST or ALT >2 x ULN, interrupt treatment and discuss with rheumatologist.
Sulfasalazine	Haemolytic anaemia	Symptoms of anaemia	Stop treatment and seek specialist advice.
	Abnormal LFTs	LFTs as per routine for all DMARDs	If AST or ALT <2 x ULN, repeat LFTs in a month. If normalising, continue. If persistent elevation, reduce dose. If AST or ALT >2 x ULN, interrupt treatment and discuss with rheumatologist.
Corticosteroids	Adrenal suppression (more likely with courses >3 weeks and prednisolone doses ≥7.5 mg)	No specific monitoring required	Do not stop abruptly. Consider increasing the dose during intercurrent acute illness.
	Diabetes	Blood glucose and HbA1c monitoring	If continued use is necessary, consider escalation of hypoglycaemic treatment.
	Hypertension	Blood pressure checks each visit	If continued use is necessary, consider antihypertensive drugs.
	Osteoporosis (when used at doses of prednisolone ≥7.5 mg for ≥3 months)	Bone mineral density assessment at baseline, repeat at 3 months Self-reported skeletal pain suggesting fracture	If continued use is necessary, strongly consider starting a bisphosphonate.
	Psychosis Mania Delirium Depression Insomnia	Vigilance for new or worsened mental health or sleep disturbance	Cease, or use the lowest possible dose. Seek specialist advice. Discuss with rheumatologist.

Table **Disease-modifying antirheumatic drugs and monitoring in rheumatoid arthritis (continued)**

Drug	Adverse drug reaction	Monitoring	Action
Hydroxychloroquine	Photosensitivity	Self-reported sensitivity	Sun protection strategies
	Haemolytic anaemia	Symptoms of anaemia	Stop treatment and seek specialist advice.
	Blue–grey skin discolouration	Self-reported skin discolouration and examination of sun-exposed sites	Stop treatment immediately and seek specialist advice. Sun protection strategies
	Corneal deposits Retinal toxicity	Baseline ophthalmological assessment, then repeat at 5 years with annual review thereafter if therapy ongoing.[20] Annual review is recommended from initiation of therapy in high-risk patients (age >70 years, macular disease, renal disease, liver disease, higher than recommended dose).[20] Self-reported visual disturbance	Stop drug and seek specialist advice.
Leflunomide	Alopecia	Self-reported hair loss	Usually reversible. Reduce dose or stop drug.
	Hypertension	Blood pressure assessment on each visit	Reduce dose and/or add antihypertensive.
	Pneumonitis	Symptoms of cough or dyspnoea Routine respiratory examination	CXR, PFTs and seek specialist review.
	Peripheral neuropathy	Self-reported paraesthesia or weakness	Stop drug, consider NCS and EMG if not resolving, seek specialist advice.
	Hepatotoxicity	LFTs every 2–4 weeks for 3 months, then every 3 months ongoing	If AST or ALT <2 x ULN, continue and repeat LFTs in a month. If AST or ALT 2–3 x ULN, reduce dose and repeat LFTs in 2–4 weeks. Continue if normalising. If persistent elevation, discuss with rheumatologist. If AST or ALT >3 x ULN, stop drug and repeat LFTs in 2–4 weeks. If elevated, discontinue, consider washout and discuss with rheumatologist. **Note:** For any severe reactions to leflunomide consider cholestyramine washout (8 g 3 times a day for 11 days)
Tofacitinib	Abnormal LFTs	LFT frequency determined by other DMARDs used	If AST or ALT 1–2 x ULN, seek specialist advice. If AST or ALT >2 x ULN, seek urgent advice.
	Myelosuppression	FBE after 3–4 weeks, then every 3 months	Seek specialist advice, stop drug if severe.
	Dyslipidaemia	Lipid profile 8 weeks after starting and then guided by results	Modify lifestyle and diet, consider lipid-lowering therapy.
	Reactivated tuberculosis	Ideally detected pre-treatment, but may present during treatment as pulmonary or disseminated disease	Stop treatment immediately and seek specialist advice.
	Herpes zoster	Patient-reported rash or pain	Start antiviral treatment within 72 hours of rash onset. If recurrent, discuss with rheumatologist.
Abatacept	COPD exacerbation	Symptoms of COPD exacerbation	Treat exacerbation and discuss with rheumatologist.
	Hypertension	Blood pressure	Modify lifestyle, consider antihypertensive.
	Injection site reactions	Visualisation of injection site	Rotation of injection sites, antihistamines, topical cold packs, topical corticosteroids
	Anaphylaxis	–	See *Australian Prescriber* wallchart[21]
Rituximab	Infusion reactions	–	Stop or slow the rate of infusion, treat symptoms.
	Anaphylaxis	–	See *Australian Prescriber* wallchart[21]
	Myelosuppression	FBE before each treatment	If severe, delay treatment.

Table **Disease-modifying antirheumatic drugs and monitoring in rheumatoid arthritis (continued)**

Drug	Adverse drug reaction	Monitoring	Action
Anakinra	Myelosuppression (especially neutropaenia)	FBE frequency determined by other DMARDs used. Neutropaenia may be delayed and prolonged.	Discontinue and discuss with rheumatologist.
	Injection site reactions	Visualisation of injection sites	Rotation of injection sites, antihistamines, topical cold packs, topical corticosteroids
	Infection	As per routine monitoring for all DMARDs	Arrange follow-up visit, consider antimicrobial, remain vigilant for deterioration and the need for hospitalisation, stop if serious infection.
	Anaphylaxis	–	See *Australian Prescriber* wallchart[21]
TNF inhibitors	Injection site reactions	Visualisation of injection sites	Rotation of injection sites, antihistamines, topical cold packs, topical corticosteroids
	Drug-induced lupus	Self-reported rash, fever or arthralgia	Assess urine for evidence of glomerulonephritis. Assess serum lupus antibody profile and complement levels. Seek urgent advice from rheumatologist.
	Demyelinating syndrome	Self-reported neurological symptoms	Consider MRI, seek specialist advice.
	Malignancy	Participation in age-appropriate screening programs	Stop treatment immediately and seek specialist advice.
	Infection	As per routine monitoring for all DMARDs	Arrange follow-up visit, consider antimicrobial, remain vigilant for deterioration and the need for hospitalisation, stop if serious infection.
	Reactivated tuberculosis	Ideally detected pre-treatment, but may present during as pulmonary or disseminated disease without fever	Stop treatment immediately and seek specialist advice.
	Herpes zoster	Self-reported rash or pain	Start antiviral treatment within 72 hours of rash onset. If recurrent, discuss with rheumatologist.
Tocilizumab	Hypertension	Blood pressure checks each visit	Modify lifestyle modification, consider antihypertensive.
	Myelosuppression	FBE at baseline, then every 4–8 weeks	Interrupt treatment and discuss with rheumatologist.
	Dyslipidaemia	Lipid profile at baseline. Repeat after 4–8 weeks of treatment, then as per relevant guidelines	Modify lifestyle modification, consider lipid-lowering therapy.
	Gastrointestinal perforation	Self-reported abdominal pain	Stop therapy and discuss with rheumatologist.
	Infection	As per routine monitoring for all DMARDs **Note:** CRP is an unreliable marker for infection during tocilizumab therapy due to IL-6 blockade	Minor infection – interrupt treatment until recovered. Serious infection – stop treatment.
	Abnormal LFTs	LFTs at baseline and every 4–8 weeks for 6 months, then every 3 months	If AST or ALT >1–3 x ULN, reduce dose, or stop until normal. If AST or ALT >3 x ULN, stop until >1–3 x ULN then reduce dose. If AST or ALT >5 x ULN, discontinue treatment.

ALT	alanine aminotransferase	EMG	electromyography	MRI	magnetic resonance imaging
AST	aspartate aminotransferase	EUC	electrolytes, urea, creatinine	NCS	nerve conduction study
COPD	chronic obstructive pulmonary disease	FBE	full blood examination	PFTs	pulmonary function tests
CRP	C-reactive protein	HbA1c	glycated haemoglobin	TNF	tumour necrosis factor
CXR	chest x-ray	IL-6	Interleukin-6	ULN	upper limit of normal
DMARDs	disease-modifying antirheumatic drugs	LFTs	liver function tests		

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ARTICLE

Managing acute pulmonary oedema

SUMMARY

Acute pulmonary oedema has a high mortality. It requires emergency management and usually admission to hospital.

The goals of therapy are to improve oxygenation, maintain an adequate blood pressure for perfusion of vital organs, and reduce excess extracellular fluid. The underlying cause must be addressed.

There is a lack of high-quality evidence to guide the treatment of acute pulmonary oedema. The strongest evidence is for nitrates and non-invasive ventilation.

Diuretics are indicated for patients with fluid overload. Furosemide (frusemide) should be given by slow intravenous injection.

Routine use of morphine is not recommended because of its adverse effects. Oxygen should only be administered in cases of hypoxaemia.

Inotropic drugs should only be started when there is hypotension and evidence of reduced organ perfusion. In these cases, dobutamine is usually first-line treatment.

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Introduction

Acute pulmonary oedema is a medical emergency which requires immediate management.[1] It is characterised by dyspnoea and hypoxia secondary to fluid accumulation in the lungs which impairs gas exchange and lung compliance.[2]

The one-year mortality rate for patients admitted to hospital with acute pulmonary oedema is up to 40%.[3] The most common causes of acute pulmonary oedema include myocardial ischaemia, arrhythmias (e.g. atrial fibrillation), acute valvular dysfunction and fluid overload. Other causes include pulmonary embolus, anaemia and renal artery stenosis.[1,4] Non-adherence to treatment and adverse drug effects can also precipitate pulmonary oedema.

There are no current Australian data on the incidence of acute pulmonary oedema or heart failure. However, self-reported data from 2011–12 estimated that 96 700 adults had heart failure, with two-thirds of these being at least 65 years old.[5] Most patients with chronic heart failure will have at least one episode of acute pulmonary oedema that requires treatment in hospital.[6]

There are several different clinical guidelines for the management of acute pulmonary oedema.[7-15] However, these are based predominantly on low-quality evidence and expert opinion. The goals of treatment are to provide symptomatic relief, improve oxygenation, maintain cardiac output and perfusion of vital organs, and reduce excess extracellular fluid. Any underlying cause should be identified when starting treatment.

The drugs used in treatment include nitrates, diuretics, morphine and inotropes. Some patients will require ventilatory support. A working algorithm for the management of acute pulmonary oedema in the pre-hospital setting is outlined in the Figure.

Nitrates

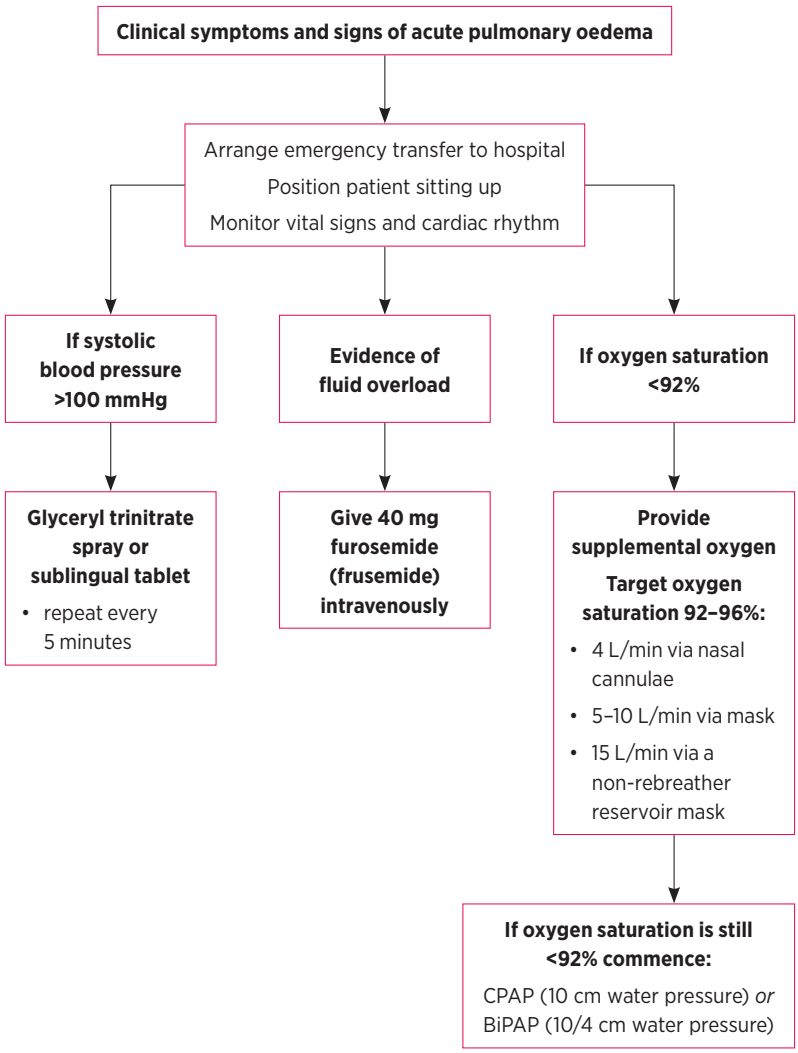
Despite the widespread use of nitrates in acute pulmonary oedema, there is a lack of high-quality evidence to support this practice. When nitrates have been compared to furosemide (frusemide) and morphine, or furosemide alone, there has been no difference in efficacy for outcomes such as the need for mechanical ventilation, change in blood pressure or heart rate, and myocardial infarction.[16]

The mechanism of nitrate action is smooth muscle relaxation, causing venodilatation and consequent preload reduction at low doses.[13] Higher doses cause arteriolar dilatation, resulting in reduced afterload and blood pressure. Specifically in the coronary arteries, this dilatation results in increased coronary blood flow.[9] These actions collectively improve oxygenation and reduce the workload of the heart.[13]

In general practice nitrates can be given sublingually. Hospitals may use infusions as intravenous administration is preferred due to the speed of onset and the ability to titrate the dose (Table 1).[8,13]

Nitrates are associated with hypotension and therefore blood pressure monitoring is essential to ensure the systolic blood pressure is maintained above 90 mmHg.[8,13] They should not be given if the

Fig. **Pre-hospital management of acute pulmonary oedema**



CPAP continuous positive airway pressure
BiPAP bi-level positive airway pressure
Source: References 1, 2, 8, 11 and 13

Table 1 **Recommended nitrate dose regimens**

Presentation and administration	Dose	Frequency	Maximum dose
Glyceryl trinitrate spray	400 microgram (2 puffs)	repeat every 5 min	1200 microgram
Glyceryl trinitrate sublingual tablet	300–600 microgram	repeat every 5 min	1800 microgram
Glyceryl trinitrate intravenous infusion*	5–10 microgram per min	double every 5 min	200 microgram per min

* first line in acute pulmonary oedema
Source: References 8 and 13

systolic blood pressure is less than 90 mmHg or the patient has severe aortic stenosis, as these patients are preload dependent.[2,8,17] If the patient has recently taken a phosphodiesterase inhibitor, such as sildenafil, nitrates are contraindicated. Nitrates are generally well tolerated with the most common adverse effect being headaches. Other adverse effects include reflex tachycardia and paradoxical bradycardia.[13] Nitrates are also associated with tachyphylaxis, with tolerance developing within 16–24 hours of continuous administration.[9]

Diuretics

There is a lack of controlled studies showing that diuretics are of benefit in acute pulmonary oedema. However, diuretics are indicated for patients with evidence of fluid overload.[13] Loop diuretics such as furosemide reduce preload and should be withheld or used judiciously in patients who may have intravascular volume depletion.[9,13]

Intravenous administration is preferred, with the dose of furosemide ranging from 40–80 mg (Table 2).[1,2,8,13] The higher doses in the range are used for patients already taking oral diuretics or with chronic kidney disease. An initial bolus can be given slowly intravenously and repeated 20 minutes later if required.[8] After the bolus, a continuous intravenous infusion may be considered, commencing at a rate of 5–10 mg per hour.[1] A small randomised controlled trial did not find any difference in outcomes between bolus and continuous infusion.[18] Higher doses have been associated with greater improvement in dyspnoea. They are also associated with worsening of renal function and increased admissions to intensive care, but this association is likely to reflect more severe disease.[18] In hospital, insertion of an indwelling catheter helps to monitor urine output.

Morphine

Morphine has been part of the traditional treatment for acute pulmonary oedema as it can reduce dyspnoea.[1,19] This effect was presumed to be secondary to venodilatation, resulting in venous pooling and preload reduction.[1,7,19] However, this mechanism of action is now being questioned.[19] Morphine also reduces sympathetic nervous activity and can reduce the anxiety and distress associated with dyspnoea.[1,18]

The adverse effects of morphine include respiratory and central nervous system depression, reduced cardiac output and hypotension. Morphine used for acute pulmonary oedema has been associated with adverse events such as significantly increased rates of mechanical ventilation, intensive care admissions and mortality.[20] In the absence of high-quality randomised

trial data, the best current evidence suggests that morphine may cause harm. Morphine is therefore no longer recommended for routine use in acute pulmonary oedema.[19] It may be beneficial if there is ongoing chest pain resistant to nitrates.[20] Low doses of morphine (1–2.5 mg) can be useful to facilitate the tolerance of non-invasive ventilation but the patient needs to be monitored for sedation.[8]

Ventilatory support

The first step in improving ventilation for patients with acute pulmonary oedema is to ensure that they are positioned sitting up.[1] This reduces the ventilation–perfusion mismatch and assists with their work of breathing.

Oxygen is not routinely recommended for patients without hypoxaemia as hyperoxaemia may cause vasoconstriction, reduce cardiac output and increase short-term mortality.[21] There is a risk that prescribing oxygen for a breathless patient in the absence of hypoxaemia may mask clinical deterioration and hence delay appropriate treatment.[11] Supplemental oxygen and assisted ventilation should only be used if the oxygen saturation is less than 92%.[11]

If required, oxygen should be administered to achieve a target oxygen saturation of 92–96%. Depending on the clinical scenario, oxygen titration can occur using a number of oxygen delivery devices. These include up to 4 L/minute via nasal cannulae, 5–10 L/minute via mask, 15 L/minute via a non-rebreather reservoir mask or high-flow nasal cannulae with fraction of inspired oxygen greater than 35%. For patients with chronic obstructive pulmonary disease, the target oxygen saturation is 88–92% and the use of a Venturi mask with inspired oxygen set at 28% is recommended.[11]

If the patient has respiratory distress, acidosis or hypoxia, despite supplemental oxygen, non-invasive ventilation is indicated.[2] There is no significant clinical benefit of bi-level positive airway pressure ventilation (BiPAP) over continuous positive airway pressure ventilation (CPAP), so the modality chosen should be guided by local availability.[22,23] Non-invasive ventilation should be commenced at 100% oxygen with recommended initial settings of 10 cm of water pressure for CPAP and 10/4 cm water pressure (inspiratory positive airway pressure/expiratory positive airway pressure) for BiPAP.[8] Contraindications to non-invasive ventilation include hypotension, possible pneumothorax, vomiting, an altered level of consciousness or non-compliance.[7]

If, despite non-invasive ventilation, there is persistent hypercapnia, hypoxaemia or acidosis, then intubation should be considered.[7] Other indications for intubation include signs of physical exhaustion, a decreasing level of consciousness or cardiogenic shock. Endotracheal intubation is only indicated in a very limited number of cases and carries inherent risks and challenges. The rapid sequence induction needs to be modified to account for the haemodynamic compromise of the patient. After intubation constant suctioning is usually required and ventilation can be very challenging.[7,19] Additionally, positive pressure ventilation is likely to potentiate any hypotension.

Inotropes

Intravenous inotropic drugs are indicated in acute pulmonary oedema when there is hypotension and evidence of reduced organ perfusion.[12,14,15,19] Their use is limited to this clinical situation in critically ill patients as they are associated with a longer length of hospital stay and increased mortality.[19] In cases of impaired left ventricular function and hypotension, first-line therapy is an intravenous infusion of dobutamine.[12,19,24] As well as its positive inotropic actions, dobutamine has peripheral vasodilatory effects that can result in worsening hypotension, which may require

Table 2 **Recommended doses of furosemide (frusemide)**

Presentation and administration	Dose	Frequency
Slow intravenous bolus	4 mg/min	repeat after 20 min if necessary
• normal renal function	40–80 mg	
• renal insufficiency or severe heart failure	up to 160–200 mg	
• chronic loop diuretic users	initial intravenous dose equal to maintenance oral dose,* titrate to response	
Intravenous infusion	5–10 mg per hour	continuous

* The oral bioavailability of furosemide (frusemide) is approximately half that of the intravenous formulation.
Source: References 1, 2, 8 and 13

management with a vasopressor. Dobutamine can cause arrhythmias and is contraindicated if the patient has ventricular arrhythmias or rapid atrial fibrillation.

Another inotrope that may increase cardiac output and improve peripheral perfusion is milrinone. It should only be used for the short-term management of severe heart failure that has not responded to other treatments. Milrinone may increase mortality in acute exacerbations of chronic heart failure. It can be considered in patients with chronic beta blockade.[19]

Follow-up

The underlying cause of the patient's acute pulmonary oedema should be treated. This includes reviewing their medicines to see if any drugs, such as non-steroidal anti-inflammatory drugs, verapamil or diltiazem, could have contributed to the problem. Additional monitoring including daily weights, and measurements of serum electrolytes and renal function is also recommended.[15]

Once the patient with cardiogenic acute pulmonary oedema has been stabilised the goal of therapy is to improve long-term outcomes. If an echocardiogram shows a preserved left ventricular ejection fraction, the focus is to treat any associated conditions. This includes the management of hypertension with antihypertensive drugs, reduction of pulmonary congestion and peripheral oedema with diuretics, and rate control for atrial fibrillation. If there is evidence of a reduced ejection fraction and chronic heart failure then an ACE inhibitor, beta blocker and mineralocorticoid receptor antagonist should be considered.[2]

ACE inhibitors are best started at 24–48 hours after admission, provided the patient is haemodynamically stable.[2] They should be used cautiously in patients with hypotension or renal impairment, with close monitoring of blood pressure and renal function.[7,9] Beta blockers, such as bisoprolol, are commenced at low dose once the patient is euvolaemic, before discharge from hospital. Mineralocorticoid receptor antagonist drugs, such as spironolactone, are best started soon after discharge with careful monitoring of blood pressure, serum potassium and renal function.[2]

Conclusion

Guidelines have highlighted that there is a lack of evidence to support the currently used therapies. Additionally there are concerns regarding the efficacy and safety of these treatments for acute pulmonary oedema. There has therefore been a shift over the last few years to favour nitrates and non-invasive ventilation as first-line management. However, opioids and diuretics may have a role in some patients. <

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Morphine reduces the need for mechanical ventilation in patients with acute pulmonary oedema
2. Nitrates should not be given to patients with acute pulmonary oedema if their systolic blood pressure is below 90 mmHg

Answers on page 83

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ARTICLE

Managing hepatitis C in general practice

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SUMMARY

All people with risk factors for hepatitis C should have a serological screening test for anti-hepatitis C antibodies.

A positive screening test should be followed by a test for hepatitis C RNA to confirm the diagnosis. The hepatitis C genotype and viral load should then be determined.

The severity of fibrosis should be assessed by clinical and laboratory assessment and the use of non-invasive serum scores. Transient elastography is particularly recommended when serum scores do not clearly exclude cirrhosis. Patients with a high likelihood of cirrhosis should be managed in a specialist setting.

Patients with chronic hepatitis C should be treated with oral direct-acting antivirals. The treatment regimen and duration should be selected according to hepatitis C genotype, viral load, previous treatment experience and the presence or absence of cirrhosis.

Adherence to the antiviral regimen is essential. To establish whether treatment was successful, patients should be tested for hepatitis C RNA 12 weeks after completing treatment.

Introduction

All oral, direct-acting antiviral treatments for chronic hepatitis C are highly effective and well tolerated. Approximately 95% of patients will be cured with a short course of treatment. These new treatments are available on the Pharmaceutical Benefits Scheme (PBS), and have a very wide prescriber base that includes GPs. Australia therefore has the potential to markedly reduce the number of people living with hepatitis C in the next 10–15 years. New cases will become rare, and rates of hepatitis C-related advanced liver disease, liver failure, liver cancer and liver transplantation will decrease.[1]

This outcome can only be achieved if all people with chronic hepatitis C are diagnosed, assessed, treated and followed up appropriately. It is essential that all medical practitioners, particularly those in primary care, have the skills to diagnose patients with hepatitis C and either manage them with specialist support as needed, or refer them for specialist care (see Box).

The majority of patients do not have severe liver injury and can be managed safely and effectively in the community. However, those with cirrhosis or complex comorbidities and those who have relapsed or failed to respond to previous interferon-free treatment should be managed by an appropriate specialist. Australian consensus recommendations for the treatment of hepatitis C are available, and provide guidance in many areas of hepatitis C care.[2,3]

Screening, diagnosis and assessment

It is estimated that 82% of the 227 000 people living with hepatitis C in Australia have been diagnosed.[4] However, many of these people have either not been informed of their diagnosis or are not aware of the implications of chronic viral hepatitis. Before 2016, fewer than one in four Australians with chronic hepatitis C had been treated and approximately one in five were undiagnosed. Because hepatitis C is a major cause of chronic liver disease, cirrhosis and liver cancer, it is essential that all people with chronic infection are identified so that treatment can be provided.

Box When to refer patients with hepatitis C to a specialist or liver clinic

- Cirrhosis *
- Hepatitis B co-infection
- HIV co-infection †
- Complex comorbidities and medication requirements
- Chronic kidney disease (eGFR <50 mL/min/1.73 m^2)
- Under 18 years of age
- Failure of treatment with all-oral therapy (sustained virologic response not achieved)
- Ongoing evidence of liver disease despite achieving sustained virologic response
- Preference not to treat hepatitis C in primary care

eGFR estimated glomerular filtration rate

* In rural or remote settings, access to a specialist should not be a barrier to treatment, but the patient should be discussed with a specialist and a management plan including specialist review should be developed.

† Or refer to a GP experienced in the management of hepatitis C/HIV co-infection.

Anyone at risk of contracting a blood-borne infection should be tested for hepatitis C, as should anyone with evidence of chronic liver disease or abnormal liver enzymes.[2] Injecting drug users should be a major focus for testing as they represent approximately 80% of infected people. Other important groups include migrants from high-prevalence countries or regions such as Egypt, Pakistan, Mediterranean and eastern European countries, Africa and Asia.

Patients should be screened using a serological test for anti-hepatitis C antibodies. If screening is positive, diagnosis requires confirmation of infection using a polymerase chain reaction (PCR)-based assay to detect hepatitis C RNA. If viral RNA is present, genotype and viral load testing should be performed to determine the appropriate treatment regimen and duration. The Figure shows a simplified schema for the management of patients with chronic hepatitis C.[3] Patients who have antibodies to hepatitis C but test negative for viral RNA (confirmed on two occasions at least one month apart) do not have chronic hepatitis C. They may have spontaneously cleared infection, been previously successfully treated, or have a false positive antibody result.

All patients should be assessed for liver disease and comorbidities. Having a history of excessive alcohol intake, being overweight or obese, and having type 2 diabetes or other liver disease significantly increase the chance that an individual has advanced fibrosis or cirrhosis. Laboratory testing should include assessment of renal function, blood glucose, other blood-borne infections such as HIV and hepatitis B, liver enzymes and full blood count. An elevated aspartate aminotransferase (AST) and low platelet count are suggestive of advanced fibrosis or cirrhosis.

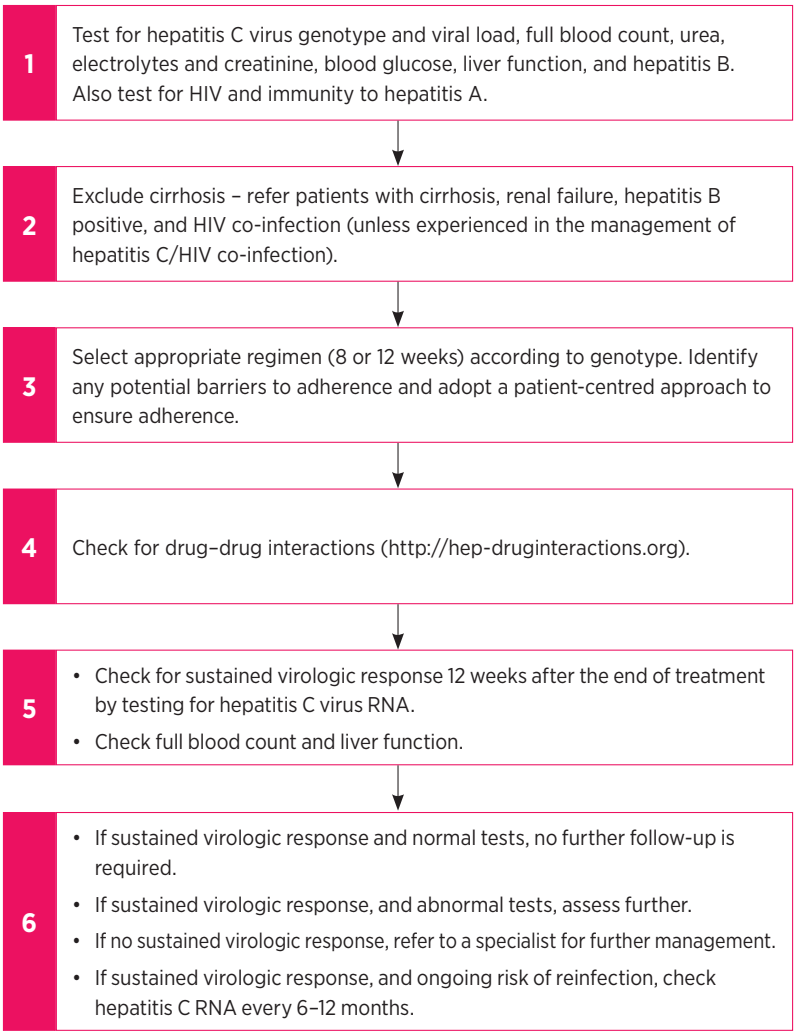
Fibrosis assessment is essential before starting antiviral treatment as the results can change after treatment and people at risk of long-term complications such as hepatocellular carcinoma can be missed. Many people with a low risk of advanced fibrosis, such as younger patients with a short duration of infection or people without a history of excessive alcohol intake or metabolic risk factors, can be assessed using simple validated serum-based scores such as the APRI score (AST to Platelet Ratio Index)[5] and Hepascore.[6] A low score excludes cirrhosis, and patients with a high score (e.g. an APRI score ≥1) have an increased likelihood of cirrhosis and should be assessed further.

Patients requiring more accurate assessment of liver fibrosis than can be determined by serum markers may benefit from transient elastography (Fibroscan).[7] Fixed machines in liver clinics, or portable machines in community settings, offer rapid, accurate and non-invasive assessment of fibrosis. Access to transient elastography is increasing and can generally be arranged through the local health district or other providers. As with serum markers, a low score is very accurate for excluding cirrhosis, but a median liver stiffness of at least 12.5 kPa is associated with a significantly higher chance of cirrhosis. These patients require specialist review and long-term surveillance for hepatocellular carcinoma and other liver disease complications.

Antiviral treatment of hepatitis C

Multiple oral regimens are currently available on the PBS. They may be prescribed by a medical practitioner experienced in the treatment of chronic hepatitis C infection, or in consultation with a gastroenterologist, hepatologist or infectious diseases physician.

Fig. **Essential steps in treating hepatitis C in primary care**



Source: Reference 3

As this therapeutic area is evolving rapidly, it is important that prescribers keep abreast of changes or maintain close links with specialists, to ensure patients are given the most appropriate treatments. It is anticipated that, in the next 12 months, new treatments will be approved that are equally effective across all hepatitis C genotypes. It will therefore become less important to know what genotype the patient has before treatment. In the meantime, it is essential that the hepatitis C genotype is determined, as not all currently approved regimens are effective or available for all genotypes.

Table 1 shows treatment regimens currently approved and available on the PBS. Additional regimens are approved but not recommended as they provide inferior efficacy or tolerability. It should be noted that a short, eight-week course of sofosbuvir/ledipasvir fixed-dose combination is appropriate for treatment-naïve patients with genotype 1 infection, no cirrhosis and a viral load less than 6 x 10^6 IU/mL. Most other patients require 12 weeks of treatment, while some patients with cirrhosis and previous treatment failure (who will generally be under specialist care) require 24 weeks of treatment.

Key features of the currently available regimens are shown in Table 2. Each antiviral drug must be used in combination with at least one additional antiviral drug to avoid drug resistance. These antivirals are directed at discrete intracellular targets of hepatitis C including the NS5B polymerase involved in replication (sofosbuvir, dasabuvir), the NS3/4A protease involved in protein production (grazoprevir, paritaprevir), and the NS5A domain involved in assembly and release (daclatasvir, ledipasvir, elbasvir, ombitasvir and velpatasvir). Some regimens include ribavirin.

Table 1 **PBS-listed oral treatments for chronic hepatitis C**

Daily drug regimen	Brand name	Genotype	Treatment duration (depending on patient characteristics)			
			No cirrhosis		Cirrhosis *	
			Treatment-naïve	Treatment-experienced †	Treatment-naïve	Treatment-experienced †
Sofosbuvir 400 mg/ledipasvir 90 mg fixed-dose combination	Harvoni	1a or 1b	8 weeks ‡ or 12 weeks	12 weeks	12 weeks	24 weeks
Sofosbuvir 400 mg + daclatasvir 60 mg (± ribavirin) §	Sovaldi + Daklinza	1a or 1b	12 weeks	12 weeks or 24 weeks	12 weeks (+ ribavirin) or 24 weeks (no ribavirin)	12 weeks (+ ribavirin) or 24 weeks (no ribavirin)
Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg fixed-dose combination + dasabuvir 250 mg twice daily (± ribavirin) §	Viekira Pak or Viekira Pak-RBV	1a only	12 weeks (+ ribavirin)	12 weeks (+ ribavirin)	12 weeks (+ ribavirin)	12 weeks or 24 weeks (+ ribavirin)
		1b only	12 weeks	12 weeks	12 weeks	12 weeks
Elbasvir 50 mg/grazoprevir 100 mg fixed-dose combination (± ribavirin) §	Zepatier	1a or 1b, 4	12 weeks	16 weeks (± ribavirin)	12 weeks	16 weeks (± ribavirin)
Sofosbuvir 400 mg + ribavirin §	Sovaldi	2	12 weeks	12 weeks	12 weeks	12 weeks
Sofosbuvir 400 mg + daclatasvir 60 mg (± ribavirin) §	Sovaldi + Daklinza	3	12 weeks	12 weeks	12 or 24 weeks (± ribavirin)	12 or 24 weeks (± ribavirin)
Sofosbuvir 400 mg/velpatasvir 100 mg fixed-dose combination # (± ribavirin) § ¶	Epclusa	1–6	12 weeks	12 weeks	12 weeks	12 weeks

PBS Pharmaceutical Benefits Scheme

* Patients with cirrhosis should be managed in a specialist setting. An interferon-free regimen is not currently available for patients with genotype 6.

† Treatment-experienced usually refers to failure to clear virus on pegylated interferon plus ribavirin.

‡ Eight weeks may be considered if hepatitis C RNA is less than 6 × 10^6 IU/mL.

§ Ribavirin dosing is weight-based. Recommended dose is 1000 mg daily for people weighing less than 75 kg and 1200 mg daily for people weighing at least 75 kg.

Currently (March 2017) recommended by the Pharmaceutical Benefits Advisory Committee for PBS listing.

¶ Adding ribavirin is recommended in all patients with decompensated cirrhosis and can be considered in patients with compensated cirrhosis who have genotype 3 infection.

Table 2 **Current hepatitis C antiviral treatments**

Drug	Mechanism of action	Genotype coverage	Key drug interactions and recommendations	Contraindications and warnings *
Sofosbuvir	NS5B RNA polymerase inhibitor (chain terminator)	Pan-genotypic, must be used in combination with another drug.	Phenytoin should not be co-prescribed. Not recommended with amiodarone as symptomatic bradycardia has been reported.	Sofosbuvir concentrations increase in renal impairment. Dose adjustment not necessary in mild and moderate impairment. Safety has not been established when eGFR <30 mL/min/1.73 m^2. If these drugs are the only option, closer monitoring for adverse effects is advised.
Sofosbuvir/ ledipasvir	NS5A inhibitor + polymerase inhibitor	Approved only for genotype 1 (effective also in genotypes 4, 6).	Phenytoin should not be co-prescribed. Not recommended with amiodarone as symptomatic bradycardia has been reported. Absorption is reduced with proton pump inhibitors. Some statins may require dose reduction – rosuvastatin should not be co-prescribed.	
Sofosbuvir/ velpatasvir	NS5B RNA polymerase inhibitor + NS5A inhibitor	Genotypes 1–6	Co-administration of potent CYP2B6, CYP2C8 and CYP3A4 inducers is not recommended. Not recommended with amiodarone as symptomatic bradycardia has been reported.	
Daclatasvir	NS5A inhibitor	Approved only for genotypes 1 and 3 but pan-genotypic. Always used with sofosbuvir.	Phenytoin should not be co-prescribed. Some drug–drug interactions occur. Some statins may require dose reduction.	
Paritaprevir/ ritonavir/ ombitasvir + dasabuvir	Ritonavir-boosted NS3/4A protease inhibitor + NS5A inhibitor + non-nucleoside polymerase inhibitor	Genotype 1 only	Phenytoin should not be co-prescribed. Multiple drug–drug interactions occur – ritonavir is a potent inhibitor of CYP3A4. Some statins may require dose reduction – simvastatin or atorvastatin should not be co-prescribed.	Can be used in renal failure. Contraindicated in liver failure.
Elbasvir/ grazoprevir	NS5A inhibitor + NS3/4A protease inhibitor	Genotypes 1 and 4	Phenytoin should not be co-prescribed. Multiple drug–drug interactions occur. Some statins may require dose reduction.	Can be used in renal failure. Contraindicated in liver failure.
Ribavirin	Nucleoside-analogue	Pan-genotypic, must be used in combination with other drugs.		Contraindicated in pregnancy. Dose adjustment needed in renal impairment.

CYP cytochrome P450
eGFR estimated glomerular filtration rate
* Antiviral treatments should not be administered during pregnancy or lactation.

Tolerability and drug interactions

In general, antiviral regimens are well tolerated, however there are some nuances. All regimens can potentially interact with concomitant drugs, and it is strongly recommended that potential interactions be assessed and managed. A full review of all prescription, over-the-counter and complementary medicines is essential. The use of a web-based interaction checker is invaluable.[8] Because the hepatitis C treatment is relatively short, consider withholding interacting drugs, for example statins (see Table 2).

Sofosbuvir is currently not recommended for patients with an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2. Protease inhibitors are contraindicated in patients with decompensated cirrhosis. These patients should be managed by a specialist, rather than by community prescribers. Also those co-infected with hepatitis B should be managed by a specialist as there are concerns about hepatitis B reactivation during hepatitis C treatment. Because of reports of severe hepatitis B reactivation, the US Food and Drug Administration and the Australian Consensus Statement (January 2017 update)[2] recommend screening all patients for hepatitis B before starting antiviral treatment. The recommended tests are for HBsAg, anti-HBc and anti-HBs. Patients who are HBsAg positive require either concomitant antiviral treatment for hepatitis B, or close monitoring of alanine aminotransferase (ALT) and hepatitis B DNA during and after treatment.

Ribavirin is a teratogen and both men and women must ensure two forms of contraception and avoid pregnancy until at least six months after completion of a ribavirin-containing regimen.

Treatment adherence

It is obviously important that patients adhere to the prescribed treatment schedule and any barriers to adherence should be identified before treatment begins. Information regarding the number of tablets to be taken and at what time of day, advice on what to do if a dose is missed, and how to obtain medicines from the pharmacy, should all be provided to the patient. Patients should be informed that hepatitis C medicines are not readily available from most community pharmacies for same-day supply. If patients are admitted to hospital, ensure they take their medicines with them to avoid missing doses. Some patients may benefit from regular phone calls or check-ups to ensure adherence. Adherence guidelines[9] and a quick reference guide[10] have been developed by the Australian Hepatology Association and emphasise the need for a patient-centred approach.

Post-treatment follow-up

While little, if any, blood test monitoring is required while patients are on antiviral treatment (although haemoglobin should be regularly monitored when ribavirin is used), it is essential that patients undergo a blood test for viral RNA 12 weeks after completing a course of therapy. This is to ensure that treatment has been successful and there is no evidence of ongoing liver disease. Undetectable hepatitis C RNA at 12 weeks after treatment (sustained virologic response – SVR12) is highly likely to be durable. Patients who did not have cirrhosis before treatment, achieve SVR12 and have a complete normalisation of liver enzymes (regarded as an ALT of ≤30 U/L in men and ≤19 U/L in women) require no further follow-up.

Successful clearance of hepatitis C does not protect against reinfection, and patients with ongoing risk factors require regular testing. In this situation, they should be tested for hepatitis C RNA (PCR) every 6–12 months. Serology for hepatitis C antibodies has no role in ongoing monitoring as it remains positive in all individuals who have ever had exposure to hepatitis C.

Patients who fail to achieve a sustained virologic response or do not have normalisation of liver enzymes require further assessment. In those who take a complete course of therapy, this is generally due to the emergence of drug-resistant variants, most commonly to the NS5A component of the regimen. These variants may have been pre-existing. Non-adherence or an incomplete course of therapy could also result in post-treatment failure. Patients with detectable hepatitis C RNA in post-treatment follow-up should be referred for specialist consultation to determine the most appropriate re-treatment regimen.

When liver enzymes fail to normalise, additional causes of liver disease should be sought. These include non-alcoholic fatty liver disease (associated with type 2 diabetes and being overweight or obese), alcoholic liver disease due to ongoing excessive alcohol intake, genetic haemochromatosis and autoimmune liver disease. Patients with comorbidities that increase their risk for chronic liver disease should be monitored and managed long term despite viral clearance.

Patients with cirrhosis before treatment require long-term surveillance for complications regardless of whether their liver enzymes or liver stiffness (assessed by transient elastography) normalise or reduce. Six-monthly liver ultrasound examinations are indicated in these patients, and in patients with advanced fibrosis and ongoing risk factors for liver disease (e.g. metabolic syndrome or excessive alcohol intake). New liver nodules that might represent early hepatocellular carcinoma may be amenable to curative treatment, whereas late presentation with symptomatic

disease is usually associated with a poor prognosis. Many patients at risk for hepatocellular carcinoma will prefer to be monitored in the community rather than in specialist centres. Clinicians should be aware that hepatocellular carcinoma may develop many years after viral eradication and ensure ongoing monitoring.

Conclusion

Community-based management is essential to reduce hepatitis C in Australia. Broad access to short-duration, well-tolerated treatments provides this opportunity. Despite its relative simplicity, treatment may still be challenging for some individuals, however benefits such as reduced transmission rates and improved clinical outcomes mean that all clinicians should identify a means to deliver these treatments. Support from an experienced nurse, pharmacist and specialist should be sought where necessary. Future advances in antiviral treatments will make management in the community even simpler. ≺

Simone Strasser has received honoraria and travel support for advisory boards and speaking from Gilead, AbbVie, Bristol-Myers Squibb and MSD. She is honorary treasurer of the Gastroenterological Society of Australia.

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ARTICLE

Prescribing for people with acute rheumatic fever

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SUMMARY

Acute rheumatic fever and its consequence, rheumatic heart disease, remain important problems in remote indigenous Australian communities.

Aboriginal and Torres Strait Islander people living in urban settings, Maori and Pacific Islanders, and immigrants from developing countries are also likely to be at elevated risk.

Guidelines and resources are available for healthcare professionals working with at-risk populations, and for patients with acute rheumatic fever or rheumatic heart disease and their families.

There have been some recent changes in Australian recommendations for antibiotic use, dose of aspirin, first-line choice for management of severe Sydenham's chorea, and prevention of endocarditis.

For individuals diagnosed with acute rheumatic fever, the recommended treatment to prevent recurrences and development of rheumatic heart disease is benzathine penicillin G administered as an intramuscular injection every four weeks.

Introduction

Acute rheumatic fever is an autoimmune disease occurring in response to infection with group A streptococci. Repeated or severe acute rheumatic fever episodes lead to rheumatic heart disease, a form of valvular heart disease with high morbidity and mortality.[1]

Many healthcare providers have little experience with acute rheumatic fever and rheumatic heart disease and may be unaware of the many resources to guide diagnosis and management (see Box 1).

Much of the information available on acute rheumatic fever treatment derives from old data,[2] observational studies[3] and small open-label comparative studies.[4-6] It is important to be aware of the current evidence base, principles of prescribing for people with acute rheumatic fever and rheumatic heart disease, recent changes in guidelines, and available resources.

High-risk populations

Group A streptococcal infection is associated with socioeconomic factors such as household crowding.[7,8] Acute rheumatic fever and rheumatic heart disease are now rare in affluent societies. High rates persist among Aboriginal and Torres Strait Islander populations, especially those living in rural or remote settings. The most recent Australian Institute of Health and Welfare report highlighted rheumatic heart disease as one of the conditions accounting for the greatest rate of discrepancy between indigenous versus non-indigenous

Box 1 **RHDAustralia contacts and educational resources**

Control program contacts

Northern Territory (Top End)	08 8922 8454
Northern Territory (Central)	08 8951 6909
Queensland	1300 135 854 or 07 4226 5544
Western Australia	1300 622 745
South Australia	08 7425 7146
New South Wales	1300 066 055 or 02 9391 9195

Videos and other resources
https://www.rhdaustralia.org.au/resources

Online training modules for patients
www.rhdaustralia.org.au/health-worker-modules

Online training modules for staff
www.rhdaustralia.org.au/clinician-modules

Diagnosis calculator
www.rhdaustralia.org.au/apps

Australians.[9] Current estimates for definite and borderline rheumatic heart disease in Australian children range from less than 1 per 1000 population in low-risk children, to 33 per 1000 in parts of the Northern Territory.[10] Maori and Pacific Islanders and immigrants from developing countries are also likely to be at elevated risk.[1]

Diagnosis

The diagnosis of acute rheumatic fever is made using the modified Jones criteria (Table 1).[11] These were updated in 2015 by the American Heart Association and endorsed by the World Heart Federation to incorporate Australian recommendations for improved diagnostic sensitivity in high-risk populations. These criteria have been built into a freely available diagnosis calculator available as a smart device application (see Box 1).[12]

The most challenging aspect of diagnosis is recognition, since cases can present subtly, for example as a single painful joint. There is no diagnostic test, although work towards this is an active field of research.

Acute rheumatic fever is notifiable to public health units in Australian states and territories which

Table 1 **Australian guidelines for the diagnosis of acute rheumatic fever**

Diagnosis	Modified Jones criteria	
Definite initial episode of acute rheumatic fever	2 major **or** 1 major and 2 minor manifestations **plus** evidence of a preceding group A streptococcal infection*	
Definite recurrent episode of acute rheumatic fever in a patient with known past acute rheumatic fever or rheumatic heart disease	2 major **or** 1 major and 1 minor **or** 3 minor manifestations, **plus** evidence of a preceding group A streptococcal infection*	
Probable acute rheumatic fever (first episode or recurrence)	A clinical presentation that falls short by either 1 major or 1 minor manifestation, or the absence of streptococcal serology results, but one in which acute rheumatic fever is considered the most likely diagnosis. Such cases should be further categorised according to the level of confidence with which the diagnosis is made: • highly suspected acute rheumatic fever • uncertain acute rheumatic fever	
	High-risk groups †	**All other groups**
Major manifestations	• Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram) • Polyarthritis ‡ or aseptic monoarthritis or polyarthralgia • Chorea • Erythema marginatum • Subcutaneous nodules	• Carditis (excluding subclinical evidence of rheumatic valvulitis on echocardiogram) • Polyarthritis ‡ • Chorea • Erythema marginatum • Subcutaneous nodules
Minor manifestations	• Monoarthralgia • Fever § • ESR ≥30 mm/h or CRP ≥30 mg/L • Prolonged P-R interval on ECG #	• Polyarthralgia or aseptic monoarthritis • Fever § • ESR ≥30 mm/h or CRP ≥30 mg/L • Prolonged P-R interval on ECG #

* Evidence includes elevated or rising antistreptolysin O or other streptococcal antibody, or a positive throat culture or rapid antigen test for group A streptococci.

† High-risk groups are those living in communities with high rates of acute rheumatic fever (incidence >30/100 000 per year in 5–14 year olds) or rheumatic heart disease (all-age prevalence >2/1000). Aboriginal and Torres Strait Islander people living in rural or remote settings are known to be at high risk. Data are not available for other populations, but Aboriginal and Torres Strait Islander people living in urban settings, Maoris and Pacific Islanders, and potentially immigrants from developing countries, may also be at high risk.

‡ A definite history of arthritis is sufficient to satisfy this manifestation. Note that if polyarthritis is present as a major manifestation, polyarthralgia or aseptic monoarthritis cannot be considered an additional minor manifestation in the same person. Chorea does not require other manifestations or evidence of preceding infection with group A streptococci, provided other causes of chorea are excluded. Care should be taken not to label other rashes, particularly non-specific viral exanthemas, as erythema marginatum.

§ Fever is defined as oral, tympanic or rectal temperature ≥38 °C on admission, or a reliably reported fever documented during the current illness.

If carditis is present as a major manifestation, a prolonged P-R interval cannot be considered an additional minor manifestation.

ESR erythrocyte sedimentation rate

CRP C-reactive protein

Source: Adapted from Table 3.2 of the Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edition) with permission from RHDAustralia[1]

have rheumatic heart disease control programs – Western Australia, Northern Territory, Queensland, South Australia and New South Wales.[13]

Management

The management of acute rheumatic fever involves treatment of the infection, management of the inflammatory process and complications, and secondary prevention.

Eradication of streptococcal infection

The clinical onset of acute rheumatic fever is typically 1–4 weeks after group A streptococcal infection (longer for Sydenham's chorea).[1] Given this time frame, it is often not possible to isolate streptococci from cultures, but antibiotic eradication therapy is recommended nonetheless (Table 2).[1,14-16] Acute rheumatic fever is well documented to occur following group A streptococcal pharyngitis (throat infection).[17] In Australian indigenous communities, there is much circumstantial evidence that high rates of acute rheumatic fever can also occur after skin infection with group A streptococci.[18,19] A recent case report from New Zealand implicates antecedent skin streptococcal infection or non-group A streptococci in acute rheumatic fever.[20]

In most instances, penicillin can be used to clear group A streptococcal infection. It should be given as a single intramuscular dose of benzathine penicillin G (also known as benzylpenicillin). The injection forms the first of the 21- or 28-day dosing schedule required for continuing secondary prophylaxis.

It is estimated that only 10–20% of patients reporting penicillin allergy are truly allergic when assessed by skin testing.[21] However, in rare instances of true allergy, azithromycin is now recommended by Therapeutic Guidelines: Antibiotic,[14] Therapeutic Guidelines: Rheumatology[15] and US guidelines[22] for clearance of the antecedent streptococcal infection due to drawbacks with other macrolides. For example, roxithromycin appears poorly effective in achieving group A streptococci microbiological cure,[23] and erythromycin is poorly tolerated.

Group A streptococci are consistently penicillin-susceptible, probably due to a lack of capacity to express beta-lactamase or to develop low-affinity penicillin-binding proteins under antibiotic pressure.[24] However, macrolide resistance was present in 3.4% of invasive group A streptococcus isolates in Darwin in 2005–2009,[25] and in at least 30% of isolates in international studies.[26,27] This is a further reason to ensure that penicillin is the treatment used whenever possible. It is important to note that penicillin or other antibiotic therapy does not influence the course or outcome of the acute rheumatic fever episode itself.

Symptomatic management of joint symptoms

Once a diagnosis of acute rheumatic fever is made, aspirin is commenced for symptomatic management. Non-steroidal anti-inflammatory drugs (NSAIDs) also appear effective. However, a major Jones criterion is migratory arthritis. If this is masked, the opportunity to make a definite diagnosis can be missed. Since joint symptoms of acute rheumatic fever often respond promptly to salicylates or NSAIDs, these should be withheld pending diagnostic certainty, with other analgesics used in the interim (Table 2).

Aspirin

Previously the recommended dose of aspirin was 80–100 mg/kg/day in divided doses. However, due to toxicity (gastrointestinal, tinnitus), the revised starting dose is 50–60 mg/kg/day although up-titration may be needed (Table 2).[1,15] This is then tapered as symptoms improve and continued for 1–2 weeks after they resolve. Rebound of symptoms can occur with a rapid taper or early cessation, hence acute rheumatic fever symptoms within approximately three months of an initial episode are counted as the same episode rather than a recurrence.[28]

NSAIDs

The effectiveness of naproxen has been reported in a retrospective chart review of 19 patients,[4] and in an open-label comparative study of naproxen and aspirin in 33 children.[3] In the open-label trial, efficacy was similar to aspirin, but gastrointestinal adverse effects were fewer with naproxen. Hence although published data are scanty, NSAIDs are endorsed as an alternative to aspirin.[1]

Symptomatic management of chorea

Sydenham's chorea is usually self-limiting and treatment is only considered in severe cases. Carbamazepine and sodium valproate appear to have similar efficacy,[5,6] with carbamazepine being recommended as first line due to a better safety profile.[1] This replaces older recommendations to use haloperidol.[5] A recent case report from South America describes successful use of leviteracitam for Sydenham's chorea.[29] This may warrant further investigation.

Management of cardiac failure

Acute rheumatic fever with severe carditis may require pharmacological management of cardiac failure, in addition to bed rest and fluid restriction. Drugs typically include furosemide (frusemide), spironolactone, enalapril and digoxin.

Table 2 **Drugs used in acute rheumatic fever**

DURING ACUTE RHEUMATIC FEVER EPISODE

Indication	Drug (choice)	Comment
Eradication of inciting streptococcal infection	1. Benzathine penicillin G 900 mg (child 3–6 kg: 225 mg, 6–10 kg: 337.5 mg, 10–15 kg: 450 mg, 15–20 kg: 675 mg) given intramuscularly as a single dose* OR 2. Penicillin hypersensitivity: cephalexin 1 g (child: 25 mg/kg up to 1 g) orally, 12-hourly for 10 days 3. Immediate penicillin hypersensitivity: azithromycin 500 mg (child: 12 mg/kg up to 500 mg) orally daily for 5 days	Streptococcal infection may not be evident by the time acute rheumatic fever manifests (e.g. cultures often negative), but eradication therapy for possible persisting streptococci is still recommended. Intramuscular penicillin is preferred due to better adherence.
Initial analgesia while awaiting diagnostic confirmation	1. Paracetamol 15 mg/kg orally, 4-hourly up to a maximum of 60 mg/kg/day (not more than 4 g daily)	Preferred initial analgesia during diagnostic uncertainty, to avoid the masking effect anti-inflammatory use can have on migratory joint symptoms.
Symptomatic management of arthritis or arthralgia	1. Aspirin 50–60 mg/kg/day up to a maximum of 80–100 mg/kg/day in four or five divided doses 2. Naproxen (10–20 mg/kg/day) orally, twice-daily[3,4]	Due to the rare possibility of Reye's syndrome in children, aspirin may need to be ceased during an intercurrent acute viral illness, and an influenza vaccination provided if aspirin is used during influenza season. Naproxen may be safer than aspirin, and convenient due to twice-daily dosing and the availability of an oral suspension. However, there is less experience with naproxen in acute rheumatic fever.

SECONDARY PROPHYLAXIS

Indication	Drug	Comment
Prevention of subsequent streptococcal infections[16]	1. Benzathine penicillin G 900 mg (child <20 kg: 450 mg)* intramuscularly as a single dose once every 21 or 28 days 2. Immediate penicillin hypersensitivity: erythromycin 250 mg (child: 10 mg/kg up to 250 mg) orally 12-hourly	Rare breakthrough acute rheumatic fever cases occur despite regular dosing, due to waning penicillin concentrations towards the end of the 28-day period. Therefore an injection every 3 weeks is prescribed for some individuals (generally <2% of people with acute rheumatic fever). Oral penicillin is less effective and is not recommended except in exceptional circumstances (e.g. temporary inability to access injection while travelling).

ENDOCARDITIS PROPHYLAXIS IN ESTABLISHED RHEUMATIC HEART DISEASE

Indication	Drug	Comment
Individuals having high-risk dental or respiratory procedures †	1. Ampicillin 2 g (child: 50 mg/kg up to 2 g) intravenously within 60 min (ideally 15–30 min) before the procedure 2. Penicillin hypersensitivity: cefazolin 2 g (child: 50 mg/kg up to 2 g) intravenously within 60 min before the procedure 3. Immediate penicillin hypersensitivity: clindamycin 600 mg (child: 20 mg/kg) intravenously within 60 min before the procedure	Note intravenous ampicillin and clindamycin can be substituted with appropriately timed oral dosing of amoxycillin or clindamycin respectively.
Individuals having high-risk genitourinary, gastrointestinal or infected skin or soft tissue procedures	1. Ampicillin 2 g (child: 50 mg/kg up to 2 g) intravenously within 60 min (ideally 15–30 min) before the procedure 2. Penicillin hypersensitivity or immediate hypersensitivity: teicoplanin 400 mg (child: 10 mg/kg up to 400 mg) intravenously within 60 min (ideally 15–30 min) before the procedure	Note the drugs listed here which provide Gram positive cover are given in addition to any standard prophylactic recommendation required for that procedure (e.g. in combination with metronidazole plus cephazolin or gentamicin for colorectal surgery). Note vancomycin can be used instead of teicoplanin if the timing of administration can be appropriately arranged.

* Note that the child dose of benzathine penicillin G is higher for secondary prophylaxis than for primary treatment.
† High-risk procedures are defined in Therapeutic Guidelines: Antibiotic[14]
Source: References 1, 14 and 15

Disease-modifying treatments

There are currently no drugs for acute rheumatic fever that effectively target the immune perturbation, or reduce the progression to, or severity of, rheumatic heart disease. Trials of corticosteroids or related compounds (adrenocorticotrophic hormone) have been unconvincing, including a comparative study of methylprednisolone and oral prednisolone in 18 patients.[30] Meta-analyses have also failed to show benefit.[31] Despite this, the national guideline observes that 'corticosteroids are sometimes used for severe carditis, although there is no evidence that they alter the longer-term outcome'.[1] Internationally, steroids are used as a treatment of last resort. A randomised trial of intravenous immunoglobulin, with outcomes being time to resolution of inflammation and severity of cardiac disease, also identified no benefit in the intervention arm.[32]

Secondary prevention

To avoid recurrences of acute rheumatic fever and the development of rheumatic heart disease, future group A streptococcal infections need to be avoided using antibiotic prophylaxis with benzathine penicillin G (Table 2). Oral penicillin is strongly discouraged and is known to be associated with higher rates of acute rheumatic fever recurrence.[16] This should be accompanied by advice to families about the need for prompt treatment when a suspected group A streptococcal infection occurs. They should also be advised of ways to reduce exposure at home, for example by avoiding sharing of beds when possible and culturally appropriate.

The required duration of secondary prevention for those with mild or no rheumatic heart disease is for a minimum of 10 years or until age 21 (whichever comes later), until age 35 for those with moderate heart disease, and until age 40 or longer for those with severe heart disease.

Children embarking on the daunting prospect of at least 10 years of benzathine penicillin G injections require sensitive, culturally appropriate engagement with healthcare systems, use of strategies to minimise the pain of injections (Box 2), and provision of tools to support adherence. Adherence resources including smartphone applications, calendars, reminder cards and incentive programs are offered at some clinics.[33] Rheumatic heart disease control programs[13] are a vital resource in managing people with acute rheumatic fever or rheumatic heart disease (see Box 1) by providing education and support to clinicians and patients as well as coordinating the jurisdictional registers.

Shortages or unavailability of benzathine penicillin G occur regularly in Australia and neighbouring countries with heavy burdens of acute rheumatic fever and rheumatic heart disease (e.g. Timor Leste).[34] This adds a further challenge to the prevention of this serious and potentially fatal condition.

Changes in penicillin formulation over the years have required changes to the dose volumes stated in the manual provided for Aboriginal health workers and nurses working in remote areas. There have also been changes in recommendations regarding the safety of adding lignocaine to the syringe. Although adding lignocaine reduces the pain of injections,[35] the manufacturer of the pre-filled syringe recommends against its use for infection control reasons.

In the setting of true penicillin allergy, the recommended alternative drug is oral erythromycin (Table 2). This is in contrast to the recommendation for azithromycin treatment of acute group A streptococcal infection.

Conclusion

Healthcare providers working with people who have an elevated risk of acute rheumatic fever and rheumatic heart disease, such as in Australian indigenous communities, refugee health clinics or an area with high migrant populations, must be familiar with this important, preventable condition. Resources to aid diagnosis and management can assist clinicians working in these settings. Research is underway to generate improved knowledge and inform evidence-based guidelines. This will be incorporated in the third edition of the Australian guideline, anticipated for release in 2018. <

Conflict of interest: none declared

Box 2 Measures that may reduce the pain of benzathine penicillin G injections

Use a 21-gauge needle.

Warm syringe to room temperature immediately before use.

Allow alcohol from swab to dry before inserting needle.

Apply pressure with thumb for 10 seconds before inserting needle, or vibration before and/or during injection (e.g. see http://buzzy4shots.com.au).

Deliver injection very slowly (preferably over at least 2–3 minutes).

Distract patient during injection (e.g. with conversation).

The addition of 0.5–1 mL of 1% lignocaine is used elsewhere, but is not recommended with preloaded syringes currently available in Australia.

Source: Reference 1

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ARTICLE

Economic evaluation of medicines

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SUMMARY

In Australia the government must balance access to new drugs against the cost to the Pharmaceutical Benefits Scheme. Economic evaluations can be used to ensure health resources are allocated efficiently, maximising patient outcomes for every dollar spent.

There are several methods available to assess the efficiency of funding decisions in health care. Examples are cost-effectiveness, cost-utility, cost-minimisation and cost–benefit.

The Incremental Cost Effectiveness Ratio is a statistic used to summarise the cost-effectiveness of a new medicine relative to a comparator. It allows the decision maker to compare one treatment to another, thereby quantifying the opportunity cost of decisions.

Introduction

Funding medicines in a sustainable manner is an enduring challenge for health policy in many countries. In Australia, where the Federal Government operates as a healthcare monopsony or single payer, a balance must be achieved between access to new and innovative drugs and containing the cost of the Pharmaceutical Benefits Scheme. Recently the government decided to fund an innovative class of new drugs to treat hepatitis C, costing more than $1 billion over the forward budget estimates, but providing substantial benefits for patients by effectively curing the disease. This decision was made in part by balancing the benefits of the therapies against their cost through health economic evaluations.

Health economics lies at the interface between economics and medicine, applying economic concepts, such as opportunity cost, to healthcare funding decisions. In a world with scarce resources where choices must be made between competing alternatives, opportunity cost is the value of the best alternative forgone. For instance, if the government chooses to fund hepatitis C drugs instead of new cancer therapies, then the opportunity cost can be defined as the unrealised potential benefit from funding the cancer therapies. Although multiple factors are taken into account when deciding to fund new medicines, invoking this principle of opportunity cost helps us to understand how health resources can be allocated efficiently, and thereby maximise patient outcomes for every dollar spent.

Health economic evaluation methods

There are several methods available to inform funding decisions in health care. These include cost-effectiveness, cost-utility, cost-minimisation and cost–benefit analysis (Table). They allow decision makers to assess the benefits of funding decisions relative to the cost. In Australia these methods are used by the Pharmaceutical Benefits Advisory Committee (PBAC) to meet the legislative requirements in making funding recommendations for drugs to government.

The different types of economic evaluation vary according to the types of costs and outcomes being compared. When evaluating drugs, a key

Table **Summary of types of economic evaluation**

Method	Context	Cost measurement	Benefit measurement	Outcome
Cost-minimisation	When the drug is considered non-inferior to the comparator for health outcomes	monetary	none	cost comparison
Cost-effectiveness	When the drug is considered superior to the comparator for health outcomes	monetary	natural units (e.g. hospitalisations avoided or life-years gained)	incremental cost-effectiveness ratio
Cost-utility	When the drug is considered superior to the comparator for health outcomes	monetary	quality-adjusted life-years	incremental cost-effectiveness ratio
Cost–benefit	When costs and health outcomes are considered in monetary units.	monetary	monetary	cost–benefit ratio

consideration for an economic evaluation is the choice of the comparator or alternative drug. The PBAC currently defines a comparator as the 'therapy that prescribers would most replace in practice' with the proposed medicine.[1] The choice of comparator is critical because when completing an economic evaluation we are essentially interested in the incremental costs and outcomes of the proposed new treatment *over* the comparator. For instance, if placebo is chosen as a comparator instead of an active treatment then the bar is set lower for determining the therapeutic advantage and, by extension, the economic argument for the new treatment. The choice of comparator thus influences the question being posed, such as whether the medicine is considered superior or non-inferior, and the type of economic evaluation to be used.

In general, a cost-minimisation analysis is used when two drugs are considered non-inferior in terms of health outcomes, such as drugs in the same therapeutic class and biosimilar drugs. Net costs are compared to establish the cheapest alternative. Recent examples of drugs listed via a cost-minimisation analysis include a vaccine for the prevention of diphtheria, tetanus and pertussis and an infliximab biosimilar.[2]

In contrast, a cost-effectiveness or cost-utility analysis is presented in tandem with a superiority argument. Net costs are compared to net health outcomes such as life-years or clinical parameters. A cost-utility analysis (considered a subset of cost-effectiveness analysis) compares net costs against net health outcomes as measured by the quality-adjusted life-year (QALY). As a cost-utility analysis provides a consistent unit of measure (incremental cost per QALY gained), comparisons can be made between funding options, and therefore this analysis is preferred by the PBAC. Tamoxifen,[3] for the primary prevention of breast cancer, is a recent example of a drug listed via a cost-utility analysis. Conversely an example of a drug de-listed due to unacceptable cost-effectiveness (calculated via cost-utility analysis) was cinacalcet for the treatment of patients with end-stage renal disease receiving dialysis who have uncontrolled secondary hyperparathyroidism.[4]

A cost–benefit analysis considers costs and health outcomes in monetary units. Health outcomes can be converted to monetary units by calculating society's willingness to pay to avoid poor health, or by calculating the cost of illness through lost wages or the cost of treatment. Although the PBAC does not generally accept cost–benefit analyses (without an accompanying cost-utility analysis), previous submissions have used this type of analysis to assist with determining an appropriate price.[5]

Perspective

When conducting a health economic evaluation, the perspective that is adopted is a fundamental consideration. This determines the scope of the costs and benefits included. Different perspectives can be categorised as single payer (such as government, health insurance or individuals) or a broader societal perspective. Guidelines for submissions to the PBAC mandate applicants to adopt a healthcare system perspective.[1] This considers costs and benefits relevant to the Australian health system which typically includes the patient, and the public or private healthcare provider.

Health outcomes

In Australia, the PBAC predominantly makes funding recommendations based on cost-minimisation or cost-utility analyses. In order to present a cost-utility analysis, health outcomes must be transformed into QALYs. This allows a ratio of net cost to net QALYs to be calculated, which can be compared against other funding options.

A QALY is a measure of disease burden. It includes the length of life and the quality of life (measured as utility) in one summary metric. A QALY of 1 indicates one year in full health and is derived from the length of time (in this case 1 year), multiplied by the utility (for full health, utility = 1). A QALY of 0.5 can mean 0.5 years in full health or one year at 50% of full health (utility = 0.5). The score can be calculated for any condition or disease, so QALYs are useful for comparing one disease with another.

Utility values are based on community-derived preferences for different health states and they can be calculated by several methods. Today it is common for clinical trials to include questionnaires such as the EQ-5D or SF-36 which allow quality-of-life utilities to be calculated. Other methods include Time Trade-Off or Standard Gamble which allow participants to trade years of life for reduced quality of life.

Costs

Common costing approaches in health economic evaluations include patient-specific and non-patient specific. A patient-specific approach involves the task of measuring resource use (services, tests, drugs etc.) based on individual patient data. In contrast, a non-patient-specific approach uses generic cost assumptions for a group of patients such as using national cost weights to estimate the cost of a hospital stay.[6]

Patient-specific costing is generally built stepwise by defining relevant resources, quantifying the resources consumed and, finally, estimating the value of each

resource. Relevant resources will depend on the perspective adopted and often include resources consumed over several years extending to a patient's lifetime. For economic evaluations of new drugs, relevant costs include the drug itself as well as resources associated with its delivery and the 'downstream' consequences of the disease. These costs can include direct costs such as clinical consultations, co-dependent tests, investigative procedures, hospital visits and other drugs, as well as indirect costs such as lost productivity.

Quantifying resource use can be achieved by collecting individual data (prospectively or retrospectively) or by estimating resource use based on sources such as clinical guidelines or expert advice. While prospective individual data collection is more accurate, it must be weighed against the time burden and cost of data collection.

Estimating the value of resources is achieved by assigning a monetary cost to a given resource, which depends on the perspective being adopted. In submissions to the PBAC, where a healthcare system perspective is adopted, it is common to assume the cost of a resource reflects the amount paid by government. This includes pharmaceutical costs, medical and pharmacy service costs, and costs associated with hospital stays, all of which can be sourced from government websites.

Incremental cost effectiveness ratio

The incremental cost effectiveness ratio (ICER) is a statistic used to summarise the cost-effectiveness of a new drug (A) relative to the comparator (B). The ICER is calculated by the net cost divided by the net effect (commonly the net QALYs gained) and is reported in monetary units as cost per health outcome (such as cost per QALY gained).

$$\text{ICER} = \frac{\text{Cost A} - \text{Cost B}}{\text{Effect A} - \text{Effect B}}$$

When considering whether to fund a new medicine, the ICER can be used to guide decision making. It allows the decision maker to compare one treatment with another, thereby quantifying the opportunity cost of decisions.

In Australia, the PBAC does not have a specific threshold for funding new medicines, although a new drug with a cost less than $50 000 per QALY gained is more likely to be recommended for funding. The PBAC will consider the ICER in tandem with other factors such as clinical need and equity issues.[7] More importantly, the PBAC will consider the uncertainty of the ICER to varying underlying assumptions (such as the clinical benefit or the cost of therapy) and the time frame over which it is calculated (such as over the trial period or extrapolated to a patient's lifetime). The ICER is therefore a supportive tool to guide decision making and should be considered within the appropriate clinical and social context.

Conclusion

With the cost of health care continuing to rise, economic evaluations are a tool to help rationalise decision making and ensure that we maximise the health benefits from our expenditure on medicines. In Australia, the PBAC predominantly uses cost-minimisation and cost-utility analyses to quantify the comparative costs and benefits of funding decisions. For new medicines with superior efficacy, cost-utility analysis is used to estimate an incremental cost-effectiveness ratio, which quantifies the opportunity cost of decisions using a consistent unit of measure. ◀

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FEATURE

Medicinal mishap

Proton pump inhibitor-associated hypomagnesaemia and hypocalcaemia

Case

An 81-year-old man presented with light-headedness and paraesthesiae in his arms and legs. Past medical history included ischaemic heart disease, gastro-oesophageal reflux disease, chronic kidney disease, hypertension and loose stools, for many years. There was no previous history of peptic ulcer disease and a recent endoscopy was normal. He was taking aspirin 100 mg daily, perindopril 10 mg daily, amlodipine 10 mg daily, rosuvastatin 20 mg daily, omeprazole 20 mg daily and furosemide (frusemide) 40 mg daily. Examination was unremarkable, except for an unsteady gait.

Investigations revealed a normal full blood count, creatinine 142 micromol/L (normal range 64–108), estimated glomerular filtration rate 40 mL/minute (>60), potassium 3.5 mmol/L (3.5–5.2), sodium 142 mmol/L (135–145) and corrected calcium 1.10 (2.10–2.60). The presence of profound hypocalcaemia prompted the measurement of magnesium and parathyroid hormone. The results were magnesium 0.19 mmol/L (0.70–1.10), phosphate 1.87 mmol/L (0.75–1.50) and parathyroid hormone 3.7 pmol/L (1.0–7.0).

The proton pump inhibitor was considered to be the primary cause of the hypomagnesaemia, but the long history of loose stools, concomitant furosemide and chronic kidney disease could have contributed.

Omeprazole was therefore ceased and electrolytes successfully replaced, but due to ongoing reflux symptoms he was prescribed ranitidine. All other drugs were continued. One week later serum magnesium and calcium were normal.

The patient was readmitted nine days after discharge with a large bleeding duodenal ulcer requiring urgent endoscopy and subsequent embolisation. A proton pump inhibitor (pantoprazole) was restarted but the patient's magnesium dropped again. Magnesium concentrations were maintained initially with intravenous supplementation, but dropped to 0.51 mmol/L when this supplementation was ceased, despite oral magnesium sulfate 1 g three times a day. They subsequently stayed around this level with oral supplementation.

Comment

Hypomagnesaemia is a rare, potentially serious, adverse class effect of proton pump inhibitors, which is likely to be under recognised. The hypomagnesaemia is typically accompanied by hypocalcaemia, hypokalaemia and functional hypoparathyroidism. Recovery on stopping the proton pump inhibitor and recurrence on rechallenge, strengthen a causal association in this case.

There are increasing numbers of case reports, case series and retrospective reviews of hypomagnesaemia associated with long-term use of proton pump inhibitors. In a 2015 review, there were reports of the association in 64 individuals.[1] Life-threatening ventricular arrhythmias (torsades de pointes) have occurred in some cases. A search of the Australian Therapeutic Goods Administration Database of Adverse Event Notifications in August 2016 revealed 22 Australian reports of hypomagnesaemia. All proton pump inhibitors were implicated. Most reports described concomitant hypocalcaemia. In a cohort study of 366 patients hospitalised with hypomagnesaemia, current use of a proton pump inhibitor was associated with a 43% increased risk of hypomagnesaemia (adjusted odds ratio, 1.43; 95% confidence interval 1.06–1.93). The risk was increased in those on concomitant diuretics. There was no association with H_2 antagonists.[2]

Hypomagnesaemia is typically seen in patients over 50 years old on prolonged treatment (more than one year). It is more frequent when there are other factors that may lower magnesium, such as concomitant thiazides or loop diuretics, alcohol abuse and poor renal function. Symptoms can include lethargy, muscle weakness, cramping, carpopedal spasm, convulsions and arrhythmias. Hypomagnesaemia appears to be a class effect.

Low magnesium causes hypocalcaemia. This is likely to be due to interference with calcium-sensing receptor transduction, inhibition of parathyroid hormone release and end-organ resistance to parathyroid hormone. Parathyroid hormone concentrations are low or low-normal, in

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keeping with functional hypoparathyroidism. Both hypomagnesaemia and hypocalcaemia are associated with very low urinary magnesium and calcium excretion. Hypomagnesaemia-induced kaliuresis is the cause of the hypokalaemia.[3]

The suggested mechanism for proton pump inhibitor-induced hypomagnesaemia is impaired active and passive absorption of magnesium.[4]

Conclusion

Patients with suggestive symptoms, hypocalcaemia or 'idiopathic' hypoparathyroidism should be asked about their drug history. Consider measuring magnesium in those on proton pump inhibitors particularly if there are other predisposing factors for reduced magnesium concentrations.

Conflict of interest: none declared

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FURTHER READING

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App review

Drug names

Bevyn Jarrott and Matthew Hammond
Available for iPhone ($4.49) and Android ($4.99)

Drug Names is a smartphone app primarily targeted at junior doctors. The pharmacological knowledge of new medical graduates is generally weak and the simple task of interpreting a list of a patient's home medications can be daunting and challenging with so many generic and brand names on the market. This app provides this information at your fingertips and seeks to educate at the same time.

When you first load the app you notice it is very simple. Once downloaded, it does not require an internet connection and uses minimal storage. The search box lists results as you type. The ability to search by any part of a drug name is a useful feature. For example, 'sartan' will find you all the angiotensin receptor antagonists as well as the combination products. It contains simple information for each drug including class, common uses, dosage and mechanism of action.

However, as with any resource, the app does have limitations. Less common or new drugs may not be included and the information is intentionally concise for ease of use. There may occasionally be slight anomalies, but overall the information contained is accurate and relevant.

Its simplicity and Australian focus make it far more user-friendly than other resources. For the purposes of a busy junior doctor or a medical student trying to expand their medication knowledge on the go, this app fits the bill. I have found it useful in my own day-to-day activities and would recommend it to all prescribers, nurses and pharmacists of any level.

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NEW DRUGS

New drugs

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Ceritinib

Approved indication: non-small cell lung cancer
Zykadia (Novartis)
150 mg capsules
Australian Medicines Handbook section 14.2.4

Ceritinib is indicated for people with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer that has become resistant to crizotinib[1] or who cannot tolerate crizotinib. Rearrangements of the ALK gene lead to expression of oncogenic proteins which promote cell proliferation. As a tyrosine kinase inhibitor, ceritinib inhibits signalling of ALK. Up to 5% of people with non-small cell lung cancer have ALK-positive disease. These cancers are usually adenocarcinomas and are more common in non-smokers.

The approval of ceritinib is based on the results of a phase I (ASCEND-1)[2] and a phase II (ASCEND-2)[3] trial. Enrolled patients had advanced ALK-positive disease which had progressed despite other therapy. Many of them (60–71%) had brain metastases at baseline. Both trials were open-label without a control arm. Following treatment with ceritinib 750 mg once daily, 39–56% of patients had a partial or complete response, measured by regular CT and MRI scans of their tumours. Median progression-free survival was 5.7–6.9 months and median overall survival was 14.9–16.7 months (see Table).[2,3]

Diarrhoea, nausea and vomiting were very common in a safety cohort (n=525), occurring in 84%, 80% and 63% of patients respectively. Approximately 5% of these effects were serious. Grade 3 and 4 increases in liver enzymes were also very common and monitoring before and during treatment is important as dose reductions or interruptions may be required.

QT interval prolongation occurred in 6.5% of patients taking ceritinib. This was serious in some cases and the dose had to be reduced or discontinued. Ceritinib is not recommended in patients with congenital long QT syndrome or those taking drugs that prolong the QTc interval such as domperidone. Monitoring for electrolyte disorders is also important. Bradycardia was reported in 1.9% of patients and ceritinib should not be given with other drugs that have the same effect, such as beta blockers. Heart rate and blood pressure should be monitored regularly.

Severe and sometimes fatal pneumonitis has been reported with ceritinib and it was one of the most common reasons for permanent discontinuation in the trials, along with pneumonia. Other serious adverse effects included hyperglycaemia (5% of patients) and pancreatic toxicity (3%).

The recommended dose of ceritinib is 750 mg (5 capsules) taken at the same time each day. Capsules should be taken on an empty stomach (≥2 hours before or after a meal) as food increases exposure to the drug. Capsules should not be crushed or chewed.

Peak plasma concentrations are reached 4–6 hours after administration. The terminal half-life in plasma is 31–41 hours and steady state is reached after 15 days. Ceritinib is primarily metabolised by cytochrome P450 (CYP) 3A and most of the dose is excreted in the faeces. Moderate–severe hepatic impairment may increase plasma concentrations of ceritinib so the drug is not recommended in these patients.

Table **Efficacy of ceritinib in ALK-positive non-small cell lung cancer in the ASCEND trials**

Outcome	ASCEND-1[2] *	ASCEND-2[3]
Overall response rate †	56% (92 of 163 patients)	39% (54 of 140 patients)
Median duration of response	8.3 months	9.7 months
Median progression-free survival	6.9 months	5.7 months
Median overall survival	16.7 months	14.9 months

ALK anaplastic lymphoma kinase
* Results refer only to the cohort of patients who had been previously treated with an ALK-inhibitor.
† Partial and complete responses were measured by regular CT and MRI scans.

Some of the views expressed in the following notes 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.

Ceritinib is a substrate of CYP3A and P-glycoprotein. Strong CYP3A inhibitors (e.g. ketoconazole and ritonavir) can increase ceritinib concentrations, and inducers (e.g. carbamazepine, phenytoin, St John's wort) can decrease them. Concomitant use of these drugs should be avoided if possible and patients should be advised not to drink grapefruit juice. If a strong CYP3A inhibitor is needed, the ceritinib dose should be reduced by one-third. Caution is urged with inhibitors and inducers of P-glycoprotein.

Ceritinib may inhibit CYP3A and CYP2C9 directly so it can affect drugs that are metabolised by these enzymes. Doses of interacting drugs may need to be reduced and drugs with a narrow therapeutic index such as fentanyl, phenytoin and warfarin should be avoided.

The solubility of ceritinib decreases as gastric pH increases therefore antacids, proton pump inhibitors and H_2 receptor antagonists can potentially reduce ceritinib's bioavailability and effect.

Up to half of the patients in the trials responded to ceritinib and on average their response lasted around 8–9 months. However, there were no comparators in the studies so it is not known how ceritinib compares to other options. Given the drug's toxicity, the benefits of treatment need to be balanced against the risk of serious and sometimes fatal adverse effects.

[X] manufacturer did not respond to request for data

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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 and the European Medicines Agency.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True

Correction

Long-term prescribing of new oral anticoagulants

http://dx.doi.org/10.18773/austprescr.2017.025
First published 20 February 2017

The article by Paul KL Chin and Matthew P Doogue on long-term prescribing of new oral anticoagulants (Aust Prescr 2016;39:200-4) has been corrected.

In the Table "Characteristics of oral anticoagulants", the value of excretion unchanged in urine for apixaban should read 34%, not 50%.

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