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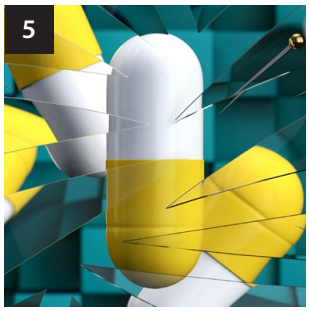

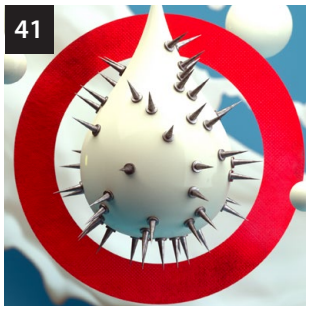

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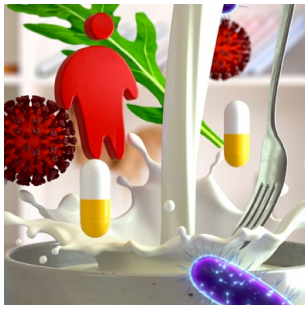

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Clinical Audit: The appropriate requesting of laboratory urinalysis in adults with a suspected UTI

This audit helps healthcare professionals identify whether laboratory requests for microscopy, culture and sensitivity analysis of urine samples (urinalysis) were clinically appropriate in adults with a suspected urinary tract infection (UTI). Laboratory urinalysis is not required in most adults with an uncomplicated lower UTI as it is unlikely to affect treatment decisions.

For more clinical audits, visit: **bpac.org.nz/audits**

Peer group discussion: Gabapentinoids: when and how should they be prescribed?

Limited pharmacological treatment options to manage chronic non-neuropathic pain can lead to the inappropriate prescribing of gabapentin and pregabalin. Gabapentin and pregabalin, known as gabapentinoids, are indicated in New Zealand for use in people with neuropathic pain and for seizure control in some people with epilepsy. The benefit of gabapentinoids, even for conditions they are indicated for, is variable; evidence of efficacy for other types of pain, e.g. cancer-related pain, episodic migraine, is very limited. This summary includes questions that can be used as discussion points for clinical peer groups, study groups or self-reflection of practice.

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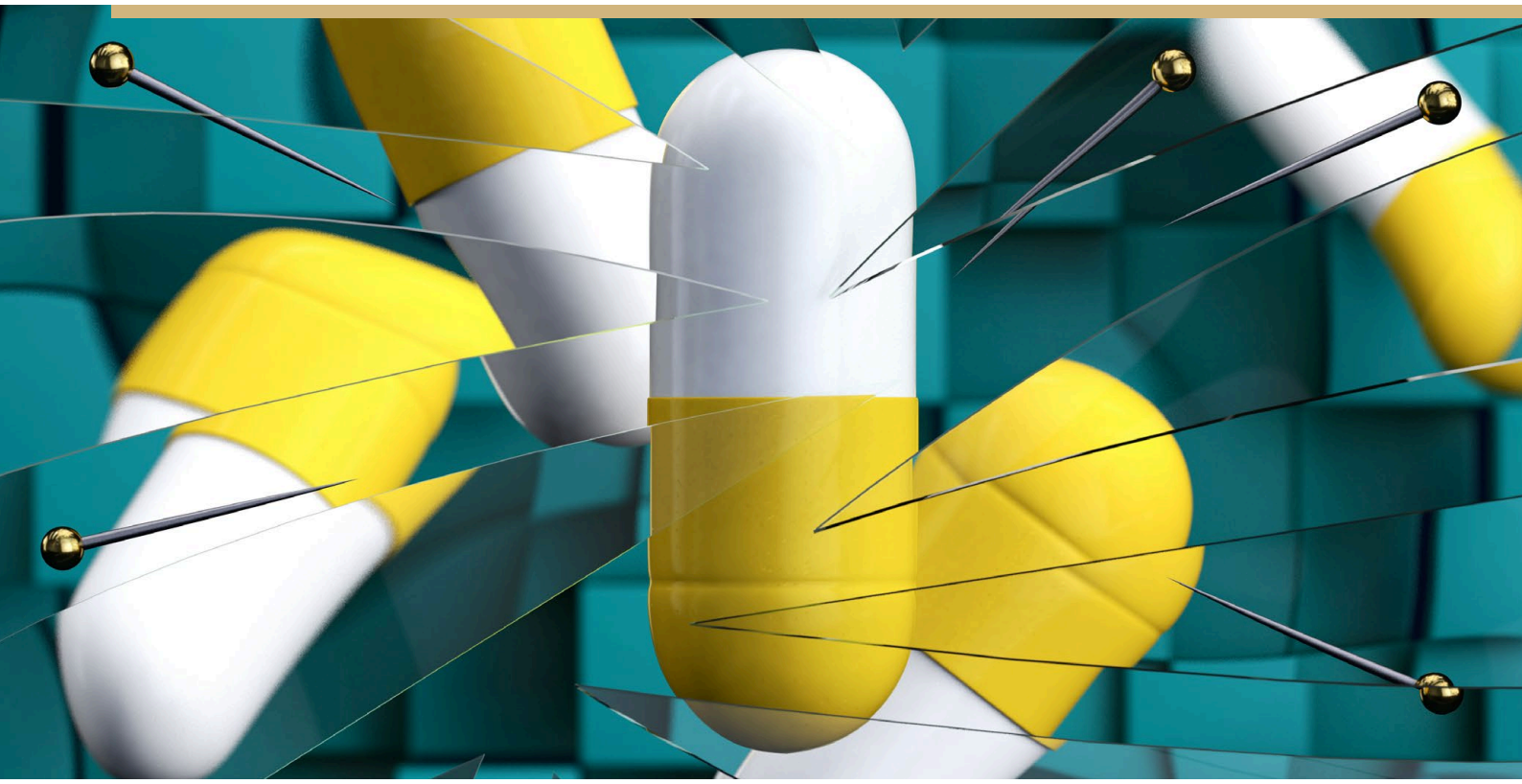


Gabapentinoids: when and how should they be prescribed?

Limited pharmacological treatment options to manage chronic non-neuropathic pain can lead to the inappropriate prescribing of gabapentin and pregabalin. Gabapentinoids are an effective treatment for post-herpetic neuralgia and painful diabetic neuropathy; there is increasing evidence that they are not effective for people with sciatica or non-specific low back pain. There is also growing concern of a rise in gabapentinoid misuse and dependence.

KEY PRACTICE POINTS:

- Gabapentin and pregabalin, known as gabapentinoids, are funded in New Zealand for use in people with neuropathic pain and for seizure control in some people with epilepsy
- Gabapentinoids should not be prescribed for people with chronic non-neuropathic pain, e.g. non-specific low back pain, and are no longer recommended for people with sciatica
- Response to gabapentinoids is variable
- A multidisciplinary approach to managing pain is usually required, combining pharmacological, physical and psychological treatments to achieve an effective regimen; in some cases, all pharmacological options will be unsuccessful
- Gabapentin and pregabalin have the potential for misuse or diversion; evaluate patients for a history of substance misuse prior to initiation and monitor for any signs of gabapentinoid misuse
- Regularly review patients to assess treatment response and the continued need for treatment; once pain is stable, attempt a gradual dose reduction
- A tapering period of at least one week is generally recommended when withdrawing or changing gabapentinoids to minimise adverse effects; cross tapering, start/stop and taper down and up-titration, are three approaches that can be used to switch between gabapentinoids

What are gabapentinoids?

Gabapentin and pregabalin – jointly referred to as gabapentinoids – were originally introduced to manage seizures in people with epilepsy, however, in practice they have been more widely prescribed for patients with chronic pain, despite mixed evidence of benefit.

Gabapentinoids are thought to function through stabilising neuronal cell membrane excitability.[1] It is possible that some of their analgesic and anticonvulsant activity derives from activating pre-synaptic calcium channels that are widely distributed in the body, reducing the release of several neurotransmitters associated with neuropathic pain and seizure propagation, such as glutamate, noradrenaline, serotonin and dopamine.[1, 2]

The role of gabapentinoids in neuropathic pain

Neuropathic pain is caused by damage to the somatosensory nervous system which results in painful sensations often described as burning, shooting or tingling.[3] In some people, neuropathic pain is ongoing due to an underlying degenerative or non-treatable condition, e.g. multiple sclerosis, but in others, improvement is possible or expected, e.g. post-herpetic neuralgia or post-surgery.

The tricyclic antidepressants (TCAs), amitriptyline and nortriptyline (unapproved indications), and the gabapentinoids gabapentin and pregabalin, are all first-line pharmacological treatment options for neuropathic pain*.[4, 5] Duloxetine is often a first line choice for neuropathic pain in other countries, however, it is neither an approved nor funded medicine in New Zealand.

* Carbamazepine is recommended as the first-line medicine for people with trigeminal neuralgia[5]

A meta-analysis (115 studies including 18,087 participants) of first-line medicines used for neuropathic pain found insufficient evidence that any one medicine was more effective than another (Table 1).[4–6] There is some evidence that efficacy may be improved with combined treatment, for example in people with diabetic peripheral neuropathy, nortriptyline and pregabalin taken together are more effective at reducing pain than when each medicine is taken alone.[3]

N.B. Topical capsaicin cream may be considered for people with localised neuropathic pain, e.g. post-herpetic neuralgia or painful diabetic neuropathy, if oral treatments are not appropriate.[5]

The risks associated with gabapentinoid use

In mid-2018, the funding for gabapentinoids in New Zealand widened (see: "Pregabalin dispensing is on the rise"), which has resulted in increased use and growing safety issues.[2] The Medicines Adverse Reactions Committee has expressed concern that gabapentinoids are not being prescribed or taken appropriately.[2] Following a safety review of gabapentin and pregabalin, the Committee suggested that greater awareness is needed of the potential for people to misuse gabapentinoids, the potential for gabapentinoids to interact with opioids and of the low-quality evidence for gabapentinoids in treating chronic non-neuropathic pain conditions, e.g. pruritis associated with end-stage renal disease.[2]

Adverse effects are common

Problems with balance and sedation are frequently reported: up to one in four patients taking gabapentinoids experiences sedation and up to 35% experience dizziness or balance difficulties (Table 2).[7]

Weight gain is likely: Both gabapentin and pregabalin are associated with a variable amount of weight gain (due to increased appetite and/or oedema), which is dose dependent and typically occurs between 2 – 12 months after initiation.[1] Most patients taking pregabalin maintain their weight within ± 7% of their baseline weight, but up to 16% can gain ≥ 7% from their baseline.[1]

Table 1: Comparison of the average number needed to treat and average number needed to harm for first-line neuropathic pain medicines.[6] N.B. Other first-line medicines were included in this analysis but are not available in New Zealand or not commonly used for neuropathic pain.

Medicine	Daily dose	Average number needed to treat	Average number needed to harm
Amitriptyline	25 – 150 mg	3.6	13.4
Pregabalin	150 – 600 mg	7.7	13.9
Gabapentin	900 – 3,600 mg	6.3	25.6

Changes in mood may occur: In clinical trials, up to 10% of patients taking pregabalin at therapeutic doses reported experiencing euphoria; similar effects occur with gabapentin.[2,8] Pregabalin and gabapentin are anti-epileptic medicines, and anti-epileptic medicines in general have been associated with a small increased risk of suicidal thoughts and behaviour, regardless of indication.[9]

Respiratory depression is possible: Evidence shows that in rare cases, gabapentinoids can cause respiratory depression.[2] Lower doses may be necessary in patients at increased risk, including those with respiratory or neurological disease, renal impairment, older people with frailty and those who take other CNS depressants, e.g. opioids.[2]

N.B. Pregabalin is currently on the Medicines Monitoring scheme to investigate a potential association with bullous dermatitis and exfoliating skin reactions.[10]

For further information on the adverse effects associated with gabapentin and pregabalin, see: **www.nzf.org.nz/nzf_2629** and **www.nzf.org.nz/nzf_2631**

Table 2: Common adverse effects reported by patients taking gabapentin or pregabalin.[1,4,7,8,11,12]

	Percentage of patients experiencing adverse effect
Dizziness/balance	13 – 35%
Sedation	11 – 25%
Gait disturbance	14%
Weight gain	Up to 25%
Peripheral oedema	7 – 17%
Constipation	6%
Dry mouth	15%
Euphoria*	1 – 10%
Abnormal thinking	6%

* In a review of 102 clinical trials of pregabalin, 1 – 10% of patients reported experiencing euphoria.[8] There are no similar clinical trial data for the incidence of euphoria when gabapentin is taken as prescribed, however, both medicines are misused for their euphoric effects.[2] See: "Misuse and dependence" for further information.

Pregabalin dispensing is on the rise

Since mid-2018, both gabapentin and pregabalin have been available fully funded without restriction.[15] Prior to 2018, gabapentin was funded with Special Authority approval and pregabalin was not funded. Since the funding changes in 2018, the dispensing of pregabalin has increased significantly, while the dispensing of gabapentin plateaued (Figure 1).[16] N.B. Concurrent use of gabapentin and pregabalin is not funded, i.e. only one medicine will be funded at a time.[15]

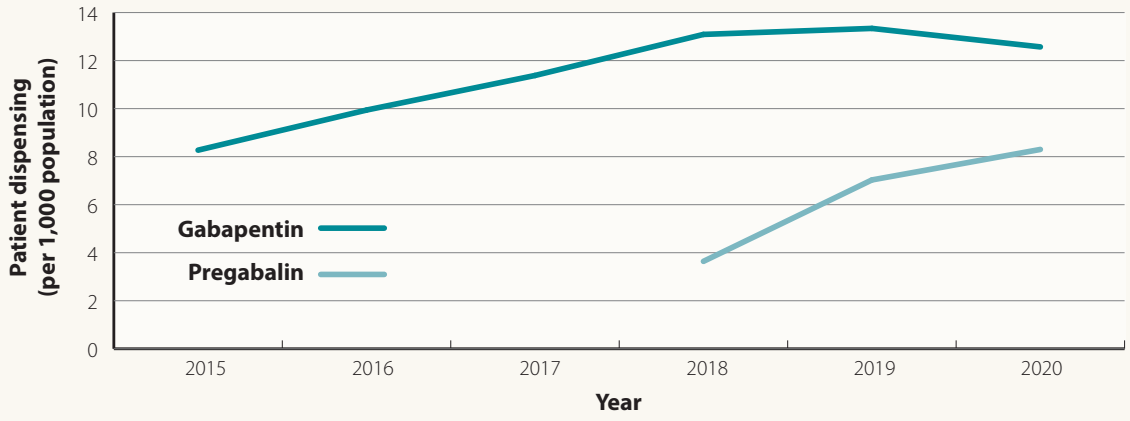


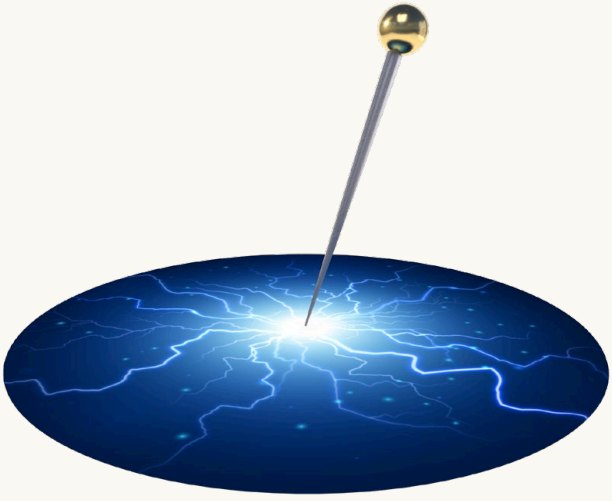
Figure 1: Number of patients per 1,000 dispensed gabapentin and pregabalin in New Zealand from 2015 to 2020.[16] N.B. In 2018, both gabapentin and pregabalin were funded without restriction; prior to 2018, gabapentin was funded with Special Authority approval.

TCAs, topical capsaicin and non-pharmacological treatments for neuropathic pain

Before initiating a trial of gabapentin or pregabalin, also consider other possible treatments for neuropathic pain:

- **TCAs**, e.g. amitriptyline or nortriptyline (both funded; unapproved indications), may be a good option for pain that is especially troublesome at night or for people with a history of misuse where gabapentinoids may be inappropriate
- **Topical capsaicin cream** (0.075% cream funded by endorsement; 0.025% used for osteoarthritis subject to Special Authority criteria) for people with localised neuropathic pain who wish to avoid or cannot tolerate oral treatment or when oral treatments are ineffective[5]
- **Non-pharmacological strategies**, with or without pharmacological treatment, such as:[3, 5, 17]
  - Address common psychological co-morbidities, e.g. anxiety and depression
  - Physical and psychological interventions, e.g. exercise, physiotherapy, massage, mindfulness, relaxation techniques and goal setting
  - Lifestyle changes to improve overall health, e.g. smoking cessation, healthy eating, reducing excessive alcohol and illicit drug use

Information for patients about neuropathic pain is available from: **www.healthnavigator.org.nz/health-a-z/n/nerve-pain/**



Misuse and dependence

Gabapentinoids may be misused due to their potential to cause euphoria, a state of relaxation and sociability or amplify the effects of recreational drugs.[2] People taking pregabalin are at higher risk of misuse and dependence as it has greater bioavailability at high doses, a faster onset of action and is more likely to induce euphoria, compared to gabapentin.[2] The risk of misuse is also higher in people who misuse other substances such as opioids or alcohol;[2] it is estimated that among people with an opioid use disorder, up to 68% misuse pregabalin and up to 22% misuse gabapentin.[4]

The likelihood of gabapentinoid dependence is increased with escalating dose and duration of use;[13] concurrent use of opioids also increases the likelihood of dependence.[14]

When might gabapentinoids be considered

Gabapentin is indicated for the treatment of:[9]

- Neuropathic pain in adults aged 18 years and older
- Partial seizures with or without secondary generalised tonic-clonic seizures in adults and children aged three years and older who have not achieved adequate control with standard anti-epileptic medicines

Pregabalin is indicated for:[9]

- The treatment of neuropathic pain in adults
- Adjunctive treatment in adults with partial seizures with or without secondary generalisation

There is evidence of benefit for people with neuropathic pain who take gabapentinoids, however, response is highly variable due to multiple factors, e.g. pathophysiology, pain tolerance, genetics, age and renal function.[18]

Systematic reviews have found **moderate quality evidence to support the use of gabapentin and pregabalin in people with peripheral diabetic neuropathy and post-herpetic neuralgia**.[4] Approximately 40% of people taking pregabalin (600 mg, daily) and 30% of people taking gabapentin (≥ 1,200 mg, daily) for at least eight weeks achieved ≥ 50% improvement in pain, compared with 10 – 20% of people taking placebo.[4]

Due to a lack of benefit and evidence of harm, **gabapentinoids are not recommended for people with sciatica or non-specific low back pain**;[19] evidence for benefit in other types of pain, e.g. cancer-related neuropathic pain, HIV and episodic migraine, is very limited.[4]

Gabapentinoids may be considered for unapproved uses but there is limited evidence of their efficacy, and in many cases, there will be other preferred treatments that are more effective or safer. Use of gabapentinoids for unapproved indications is "off label" and informed consent should be obtained from patients following a discussion of the risks and benefits.

For further information on the unapproved uses of gabapentinoids, see: **nzf.org.nz/nzf_2631** and **nzf.org.nz/nzf_2629**

When use of gabapentinoids should be avoided

Gabapentin and pregabalin should not be used as general analgesics or on an "as needed" basis. They should generally be avoided or prescribed with caution in people with a history of substance misuse or dependence on prescription medicines.

Gabapentinoids have minimal medicine interactions due to negligible protein binding and no known interference with major metabolising enzymes, however, they can potentiate the effects of other psychoactive medicines.[4]

Gabapentinoids should be avoided in people taking CNS depressants, e.g. alcohol or benzodiazepines.[1] If concurrent use cannot be avoided, prescribe lower doses and closely monitor.[14]

Add opioids with caution. For some people with severe neuropathic pain, first-line medicines will be insufficient and they may also require an opioid, e.g. tramadol or morphine; there is no evidence that opioids are effective for long-term pain management.[3]

When combined with opioids or other sedating medicines, gabapentin increases the likelihood of respiratory depression.[2] Gastrointestinal transit is slowed, raising the bioavailability of gabapentin and higher plasma concentrations are reached; the risk of accidental overdose is increased and the ability to perform tasks such as driving or operating machinery may be impaired.[1, 2] Studies have shown a greater risk of opioid-related overdose and death (odds ratio 1.49) in people taking a gabapentinoid and an opioid, compared to an opioid alone.[4]

For further information on the role of opioids in pain, see: **bpac.org.nz/2018/opioids-chronic.aspx** and **bpac.org.nz/2018/opioids.aspx**

Prescribing gabapentinoids

If pain is still uncontrolled following a trial of non-pharmacological interventions and other suitable analgesics, perform a risk-benefit analysis to assess if a gabapentinoid is appropriate:

- Consider whether there is evidence that gabapentin or pregabalin is effective for managing the patients specific type of neuropathic pain [20]
- Check other medicines the patient is currently taking; assess for potential interactions, e.g. with CNS depressants [5, 17, 20]
- Assess the risk of misuse, dependence or diversion*[1, 20]
- Consider and discuss potential adverse effects[1,17]
- Ensure the patient understands the importance of adherence with their regimen, e.g. following instructions for dose titrations and not taking on an "as needed" basis[1, 5]

* If there is clinical need to prescribe a gabapentinoid to a patient with a history of misuse, consider prescribing in short courses, i.e. every seven days rather than the standard 28 days, to monitor and minimise the risk of misuse

An example of an opioid risk tool that may also be applicable for patients taking gabapentinoids is available at: **www.drugabuse.gov/sites/default/files/opioidrisktool.pdf**

Set measurable outcomes for assessing treatment response

As with the treatment of almost any condition, managing patient expectations is key to treatment success, such as in achieving pain management. Patients may expect complete resolution of their symptoms from pharmacological treatments when, in practice, only a small reduction in symptom severity (30 – 50% reduction in pain) is achieved and pain is unlikely to completely resolve; often gabapentinoids reduce pain in a way that only modestly improves quality of life.[1]

Set measurable and realistic outcomes to assess treatment response, e.g. a reduction in pain score and/or the ability to perform a task or participate in an activity they could not do before.

A pain diary can help patients assess the effectiveness of treatment, a template is available from: **www.guild.org.au/__data/assets/pdf_file/0023/5945/patient-resource-my-pain-diary-nps-medicinewise.pdf**

Select gabapentin or pregabalin – start low, increase dose to effect

Both medicines have similar efficacy, however, in practice, pregabalin may be preferrable for some people as lower doses can be used , dosing is typically less frequent and the titration period is often faster compared to gabapentin.[1] Pregabalin displays a linear dose-response relationship, where plasma concentrations increase in proportion to increasing dose, whereas with gabapentin, plasma concentrations do not increase proportionally with the dose.[1] N.B. There is limited evidence to support the preferential use of pregabalin as patient variation, e.g. pathophysiology, pain tolerance, genetics, age and renal function, greatly influences treatment success.[1]

Once the decision has been made to initiate a gabapentinoid, take a stepwise approach to pain management:[3, 17]

1. Start low and titrate the dose to achieve maximum benefit or to reach the maximum tolerated dose within dosing recommendations (Table 3)
2. Allow an adequate trial period of at least four weeks or after at least two weeks at the maximum tolerated dose
3. Assess response to treatment, e.g. a reduction in pain score and/or the ability to perform a task or participate in an activity they could not do before
4. If response is inadequate or adverse effects are intolerable, consider changing to the other gabapentinoid or a different class of medicine, e.g. TCAs, or trialling a combination of first-line neuropathic pain medicines (see below)
5. Regularly review and re-address lifestyle factors if the pain is inadequately managed or becomes progressively worse

Table 3: Gabapentin and pregabalin dosing protocol for neuropathic pain.[9]

	Gabapentin dose (available in funded 100, 300 and 400 mg capsules)		**Pregabalin dose** (available in funded 25, 75, 150 and 300 mg capsules)	
General population	Day 1: 300 mg, once daily Day 2: 300 mg, twice daily Day 3: 300 mg, three times daily Titrate, if required, up to a maximum of 3,600 mg, daily **OR** Day 1: 300 mg, three times daily Every two to three days thereafter: increase by 300 mg, daily, in three divided doses (i.e. 100 mg per dose) up to a maximum dose of 3,600 mg, daily		Day 1: 75 mg, twice daily Increase, if necessary, after 3 – 7 days to 150 mg, twice daily Increase further after 7 days, if necessary, to a maximum of 300 mg, twice daily For divided doses, consider uneven splitting of doses, with a larger dose taken at night	
Frail/older people	Consider initiating at a lower dose, e.g. 100 mg, once daily at night; **and/or** slower titration, e.g. 100 mg, twice daily, then one week later begin 100 mg, three times daily, based on tolerability and response		Consider initiating at a lower dose, e.g. 25 – 75 mg, once daily; **and/or** a slower titration based on tolerability and response	
Renal impairment	**Creatinine clearance**			
	50 – 80 mL/min	Reduce dose to 600 – 1,800 mg, daily in three divided doses	30 – 60 mL/min	Initially 75 mg, daily; maximum 300 mg, daily in one or two divided doses
	30 – 49 mL/min	Reduce dose to 300 – 900 mg, daily in three divided doses		
	15 – 29 mL/min	Reduce dose to 300 mg, on alternate days (up to a maximum dose of 600 mg, daily) in three divided doses	15 – 29 mL/min	Initially 25 – 50 mg, daily; maximum 150 mg, daily in one or two divided doses
	< 15 mL/min	Reduce dose to 300 mg on alternate days (up to a maximum dose of 300 mg, daily) in three divided doses	< 15 mL/min	Initially 25 mg, once daily; maximum 75 mg, once daily

N.B. To reach a dose that is maximally effective, whilst minimising adverse effects, clinicians may prefer to use a slower titration.[21]

For further information on the dosing regimen of gabapentin and pregabalin, see: **www.nzf.org.nz/nzf_2629** and **nzf.org.nz/nzf_2631**

Recommended duration of use

As pain reduction is a more realistic expectation than pain elimination, patients are encouraged to continue taking pregabalin or gabapentin if some benefit is gained, provided the adverse effects and other risks from treatment do not outweigh the benefit.[17]

If patients report a partial response to treatment and pain remains problematic, consider adding an additional first-line neuropathic pain medicine to their regimen, e.g. a TCA.[17] In practice, combination treatment may be more tolerable, as smaller individual doses are often used, however, some people may experience an increase in adverse effects.[3, 5, 6]

N.B. Concurrent use of gabapentin and pregabalin is not funded.[15]

 For information on alternative medicines for neuropathic pain, see: **nzf.org.nz/nzf_2556#nzf_70735**

If treatment has been ineffective or adverse effects are intolerable, gradually discontinue pregabalin or gabapentin and/or switch to an alternative medicine.[17]

The effectiveness of pregabalin in the treatment of neuropathic pain has not been assessed in clinical trials for longer than 12 weeks; the risks and benefits to each patient should be assessed before continuing treatment beyond this point.[2]

Monitor for adverse effects and manage as required

Adverse effects, e.g. weight gain and sedation, tend to be dose related and transient and often resolve within the first few weeks to months of initiating treatment.[1, 18]

Cognitive effects of gabapentinoids, e.g. sedation, dizziness and euphoria. Advise patients to avoid driving, or operating large machinery until the effect of these medicines is known.[1] Consider reducing doses or switching to a TCA if sedation is intolerable; TCAs also cause sedation, however, these are usually taken once daily at night.

Monitor patients and encourage them to report any unusual changes in mood, e.g. euphoria, depression or suicidal thoughts/behaviour.[18] If a patient is taking a gabapentinoid and a CNS depressant, e.g. opioids, closely monitor for signs of CNS depression, e.g. somnolence, sedation or respiratory depression; adjust dose as required.[14]

Potential for misuse. Primary care clinicians, including community pharmacists, should be alert for:[2, 22]

- Early requests for repeats, reports of lost prescriptions or contact with after-hours services for medicine supply
- Patients obtaining prescriptions from multiple doctors
- Escalating doses

Special precautions in older people. Older people who experience dizziness and/or gait disturbances from taking gabapentin or pregabalin may be at an increased risk of falls;[1, 2] adjust dose, as required or discontinue use.

Assess the goals of treatment regularly and the continued need for medicines

People regularly taking gabapentinoids for neuropathic pain require periodic review. Each review should include assessment of pain control, dose and the continued need for treatment, patient tolerability, adverse effects and assessment for misuse and/or dependence.[5] Reviews can be conducted:[3, 17, 23]

- At least four weeks after initiation or after at least two weeks at the maximum tolerated dose
- After four to six weeks of switching to an alternative neuropathic pain medicine
- Monthly in people with a history of misuse
- At least every three months for people concurrently taking opioids
- Approximately every three to six months for other patients taking gabapentinoids long term

After pain is stable, attempt a gradual dose reduction

For patients taking a gabapentinoid long-term, an attempt should be made after six months of responding to treatment, to gradually reduce the dose or stop treatment, as appropriate, i.e. if pain has resolved.[17, 18]

Opportunities for a dose reduction or discontinuation may include:[23]

- Every six months for people taking gabapentinoids long-term
- Inadequate response to treatment
- On request from the patient
- If the patient is experiencing intolerable adverse effects
- If there is evidence of misuse, diversion or non-adherence to the prescribed regimen
- If the patient is pregnant, breastfeeding or planning to conceive (unless the benefits outweigh the potential risk to the fetus or infant)

How to switch between gabapentinoids or stop

There are three approaches used to switch between gabapentinoids described in the literature, although efficacy and safety of these has not yet been established. Clinical judgement – considering individual characteristics, such as

age and tolerability to the original medicine – can help to guide which method is used to switch.[21]

1. **Stop/start:** Take the last dose of original medicine at night and start the target dose of the new medicine in the next scheduled dose period (Table 4). Two studies reported this method was effective and well-tolerated.[1, 21]
2. **Cross-taper:** This involves halving the dose of the original medicine and introducing the new medicine at half of the intended dose for four days, then stopping the original medicine while continuing with the new at the full dose.[21]
3. **Taper down and stop original medicine, then gradually titrate up the new medicine:** Recommended by manufacturers; a gradual reduction may be more likely to avoid withdrawal symptoms (Table 5).[21] N.B. there may be a loss of analgesia during the tapering down and up-titration phases.[21]

Switching from gabapentin to pregabalin

Evidence has demonstrated that people who switched from gabapentin to pregabalin (after responding to gabapentin) achieved greater pain relief and fewer adverse effects, however, people who did not respond to gabapentin and experienced adverse effects, also experienced adverse effects with pregabalin.[1] An example of a direct switch from gabapentin to pregabalin is shown in Table 4.

Switching from pregabalin to gabapentin

To reduce the risk of adverse effects, consider titrating down pregabalin, then gradually adding in and titrating up gabapentin (Table 5).[24]

A gradual dose taper is required when stopping a gabapentinoid completely

If treatment is inadequate, adverse effects are intolerable or pain has resolved, the gabapentinoid should be stopped by

Table 4: Conversion dose equivalence estimates for the start/stop approach when switching between gabapentinoids.[21]

Gabapentin dose	Equivalent dose of pregabalin
100 mg, three times daily	50 mg, twice daily
200 mg, three times daily	75 mg, twice daily
300 mg, three times daily	100 mg, twice daily
400 mg, three times daily	125 mg, twice daily
500 mg, three times daily	150 mg, twice daily
600 mg, three times daily	150 mg, morning and 175 mg, night
700 mg, three times daily	175 mg, twice daily; OR 175 mg, morning and 200 mg, night
800 mg, three times daily	200 mg, twice daily
900 mg, three times daily	200 mg, morning and 225 mg, night
1,000 mg, three times daily	225 mg, twice daily
1,100 mg, three times daily	225 mg, morning and 250 mg, night
1,200 mg, three times daily	250 mg, twice daily
1,600 mg, three times daily	300 mg, twice daily

N.B. The dose of pregabalin should be reduced in people with an eGFR ≤ 60 mL/min/1.73m^2.[21]

gradually reducing the dose. Gradual dose tapering allows for the monitoring and minimisation of withdrawal symptoms such as headache, anxiety, sweating and agitation.[1] Factors such as the length of time the gabapentinoid was taken for, the dose and physiological factors, e.g. age, gender and body weight, influence the duration of dose tapering.[18] For example, if a patient took pregabalin for a short duration at a low dose, withdrawal symptoms should be minimal and a one week taper period is likely appropriate;[18] if a patient has taken a gabapentinoid for longer, e.g. 6 – 12 months, the taper period should also be longer, i.e. several weeks to months.

To minimise withdrawal symptoms, a suggested regimen is to reduce the daily dose of:[23]

- Pregabalin at a maximum rate of 50 – 100 mg, per week*
- Gabapentin at a maximum rate of 300 mg, every four days*

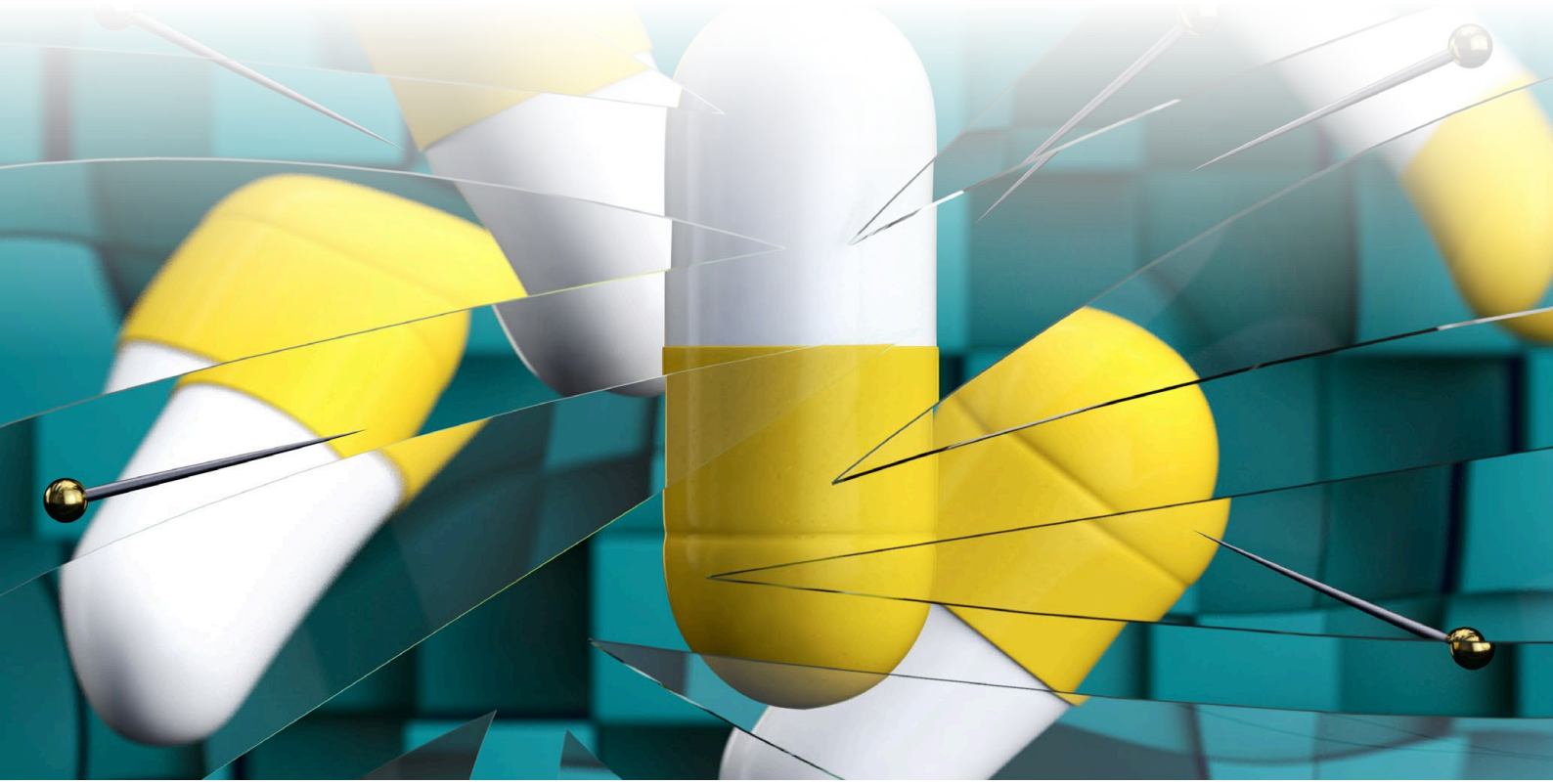
* As tolerated; tailored to the patient

Reconsider the diagnosis of neuropathic pain or consider whether an underlying condition is worsening if patients have trialled multiple first-line medicines without benefit.

A tool to assess the likelihood a patient is experiencing opioid withdrawal may also be useful for patients withdrawing from gabapentinoids, e.g.: **www.mdcalc.com/cows-score-opiate-withdrawal**

Table 5: Example of a dose reduction of pregabalin (150 mg, twice daily) for conversion to gabapentin.[24]

Day	Pregabalin dose	Gabapentin dose
1	150 mg, twice daily	–
2	100 mg, morning and 150 mg, night	300 mg, night
3	100 mg, twice daily	300 mg, twice daily
4	50 mg, morning and 100 mg, night	300 mg, three times daily
5	50 mg, twice daily	300 mg, three times daily
6	50 mg, morning	300 mg, three times daily
7	–	300 mg, three times daily
8	–	300 mg, morning and afternoon, and 600 mg, night



Clinician's Notepad: gabapentinoids

Before prescribing

- Consider other treatments for neuropathic pain, including non-pharmacological strategies (e.g. exercise, physiotherapy, behavioural and cognitive interventions), and other pharmacological treatments (e.g. TCAs [unapproved indication])
- Perform a risk benefit analysis
  - Is there evidence gabapentinoids are effective for managing the patient's specific type of neuropathic pain?
  - Check for concomitant medicines that may interact, e.g. CNS depressants
  - Assess the risk of misuse, dependence or diversion
  - Discuss potential adverse effects
- Set measurable and realistic outcomes to assess treatment response, e.g. a reduction in pain score, or the ability to perform a task or participate in an activity they could not do before

Prescribing gabapentinoids

- Select gabapentin or pregabalin. Both medicines are equally effective but individual response is variable.
  - Lower doses of pregabalin are taken to achieve efficacy equivalent to gabapentin
  - Titration of pregabalin may be faster than gabapentin
  - Pregabalin is associated with a higher risk of misuse
- Start low and titrate dose to achieve maximum benefit or to reach the maximum tolerated dose. Use lower doses of gabapentin and pregabalin in people with frailty or renal impairment.
- Allow an adequate trial period of at least four weeks or after at least two weeks at the maximum tolerated dose
- Assess treatment response
- Monitor for adverse effects and manage as required
- Assess the goals of treatment regularly and review the continued need for medicines; after pain is stable, attempt a gradual dose reduction

Switching or stopping medicines

- Consider switching to or adding another neuropathic pain medicine if initial response is inadequate
- Based on patient tolerability to the original medicine and clinical judgement, a stop/start, cross taper or taper down and up-titration method can be used to switch between gabapentinoids
- A gradual dose taper is required when stopping a gabapentinoid completely
- Reconsider the diagnosis of neuropathic pain or consider whether an underlying condition is worsening if patients have trialled multiple first-line medicines without benefit

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www.bpac.org.nz/2021/gabapentinoids.aspx

Urinary tract infections (UTIs) – an overview of lower UTI management in adults

Lower urinary tract infection (UTI) is one of the most common community-acquired infections, with more than half of all females experiencing at least one episode during their lifetime. In the absence of complicating factors, initial empiric antibiotic treatment is usually sufficient in otherwise healthy, non-pregnant, pre-menopausal females with an acute or intermittent UTI, without the need for laboratory sensitivity testing.

KEY PRACTICE POINTS:

- In most cases, the diagnosis of an uncomplicated lower UTI is guided by clinical symptoms and signs, along with urine dipstick analysis if required
- Empiric antibiotics should be prescribed for females with an uncomplicated UTI
- Obtaining a midstream urine sample for microscopy, culture and sensitivity analysis is generally only recommended in people with UTIs who are at higher risk of complications, e.g. males, pregnant females and people with diabetes, recurrent infections, renal failure or a urinary catheter
- Self-care strategies should be discussed with all patients who have a UTI to help reduce the risk of future infections, e.g. sufficient fluid intake, improving hygiene and toileting practices and voiding after sexual intercourse
- Non-antibiotic prophylactic strategies can be considered in patients who experience recurrent UTIs but are not routinely recommended in current guidelines due to low-quality evidence of benefit
- Antibiotic prophylaxis is highly effective at preventing recurrent UTIs, however, this should usually only be considered as a "last resort" if other strategies are unsuccessful – primarily due to the risk of antibiotic resistance
- Patients with asymptomatic UTIs should generally not be treated with antibiotics; the exception is pregnant females, who should be screened at the first antenatal appointment (via urine culture) and subsequently treated if an infection is identified, regardless of whether symptoms are present

Distinguishing "uncomplicated" and "complicated" UTIs

Urinary tract infections (UTIs) are one of the most common reasons for antibiotic prescribing in New Zealand.[1] The lower urinary tract is most often affected due to bacteria, usually from the gastrointestinal tract, entering the urethra and proliferating in the bladder.[1] When this occurs as a one-off or intermittent infection and remains confined to the urethra and bladder in an otherwise healthy, non-pregnant, pre-menopausal female or male with normal anatomy, it is broadly referred to as an uncomplicated lower UTI (or cystitis).[2–4] In contrast, "complicated UTIs" include infections in people with risk factors that increase the probability of bacterial colonisation, or that decrease the potential efficacy of antibiotic treatment, e.g. indwelling catheters, pregnancy, renal calculi, immunosuppressive conditions or anatomical abnormalities.[2, 3] Despite this terminology, the criteria for distinguishing UTIs as being "uncomplicated" or "complicated" varies across the medical literature, and the significance of risk factors – and the potential need for a referral – differs according to the specific person and their clinical history. Ultimately, the focus of UTI management in any patient is to promptly resolve the infection before it ascends via the ureters to involve one or both of the kidneys (pyelonephritis), which is associated with an increased risk of sepsis and multiorgan involvement.[2, 3]

Females have an increased risk of UTI

Females have an increased UTI risk compared with males, predominantly due to the shorter length of their urethra and the shorter distance between their urethra and anus.[5] It is estimated that one-third of females have a UTI before age 24 years, and more than 50% have one during their lifetime.[6] In females, the risk of experiencing UTIs can be greater due to a number of factors, including:[5, 7]

- Personal hygiene practices, e.g. wiping back to front
- Sexual activity, e.g. high frequency, spermicide or diaphragm use
- Incomplete voiding, urinary retention or other urinary issues
- Vaginal wall prolapse, e.g. cystocoele
- Vulvovaginal atrophy
- Other anatomical abnormalities
- A personal or family history of UTIs (particularly in first-degree female family members, i.e. mothers, sisters, daughters)

The cause of uncomplicated lower UTIs is highly predictable

Escherichia coli is the cause in 70 – 95% of all uncomplicated UTIs;[3] other possible causative species include *Staphylococcus saprophyticus*, *Proteus spp*., *Klebsiella spp*. and *Enterococcus spp*.[4] Complicated UTIs are also more commonly caused by *E. coli*, however, the range of possible causative species is much broader than for uncomplicated infections.[3] Although rare in the community, complicated UTIs can occur as the result of fungal infection, which is generally associated with *Candida* species, e.g. in people with an indwelling catheter.[1, 4]

The symptoms and signs of an uncomplicated UTI

Uncomplicated lower UTIs can be diagnosed with a high level of confidence in people with a focused history of lower urinary tract symptoms in the absence of complicating factors or red flags (Figure 1). Although subtle or atypical presentations are possible, the combination of two or more "classic" features of a UTI – without vaginal irritation or discharge in females – generally indicates that a UTI is likely.[2] The classic features of UTI are:[2]

- New onset dysuria
- Increased urinary frequency
- Increased urinary urgency
- Suprapubic abdominal pain

For example, nine out of ten young females with a history of new onset dysuria and polyuria, without vaginal irritation or discharge, will have a UTI.[3] Less commonly, people with a UTI may present with other features such as odorous, discoloured or cloudy urine, however, this can also occur due to non-infectious causes, e.g. dehydration, diet or renal calculi.[2] In addition, a UTI cannot be ruled out completely if only a single symptom or sign is present, and further investigation may be required depending on individual clinical circumstances and history (see: "Urinalysis: indications and conclusions").

Physical examination is not required but can help exclude differential diagnoses

A physical examination is not required to clinically diagnose an uncomplicated lower UTI but can be helpful to ensure systemic features are not present, e.g. measuring temperature and other baseline observations, as well as an assessment of the abdomen and flank, primarily checking for renal tenderness on palpation that may indicate the infection has spread to the kidneys (Figure 1). Pelvic examination is generally unnecessary in females if an uncomplicated UTI is suspected; this should only be performed if the patient's suprapubic pain is significant, or if an alternative diagnosis is suspected, such as vaginitis, urethritis associated with sexually transmitted infections (STI) or pelvic inflammatory disease or anatomical abnormalities.[2, 8]

Other demographic-specific considerations

Males. UTIs are rare in males aged less than 50 years, but the risk increases with age.[9] Although the symptoms and signs are generally similar to those observed in females, UTIs in males are commonly associated with genitourinary tract

abnormalities such as prostatic enlargement.[9] As a result, it is important to ask about any prostate symptoms, features indicative of epididymo-orchitis or a STI, alongside an abdominal examination (and bedside ultrasound, if available) to check for urinary retention.[9] If there is a family history of prostate cancer or relevant symptoms, e.g. a weak or altered urine flow, a prostate examination should be performed.[9] A referral is not usually required for males experiencing their first uncomplicated UTI, but if they have a subsequent infection then a renal/bladder ultrasound and a non-acute urology assessment should be arranged.[9]

People at risk of a sexually transmitted infection. A STI check may be considered in people with an increased STI risk to exclude conditions such as chlamydia or gonorrhoea as a possible cause of symptoms, particularly if vaginal or urethral discharge is reported.[3] Risk factors include having a partner with a STI, having two or more concurrent sexual partners or a new sexual partner within three months.[5]

Older people. Diagnosing a UTI in older people can be challenging due to the presence of co-morbidities or the use of multiple medicines, which can obscure or resemble UTI symptoms and signs.[10] While classic UTI symptoms can often be present, atypical features such as acute confusion (delirium), fatigue and anorexia may also occur.[10] Urinary incontinence and other non-specific urinary symptoms are relatively common in older people, but alone this is not predictive of a UTI.[10]

For further information on the diagnosis and management treatment of UTIs in older people, see: **bpac.org.nz/BT/2015/July/guide.aspx**

Red flags for a complicated UTI

Most UTIs can be managed in primary care. However, the presence of red flags may indicate a more serious situation requiring secondary care advice or referral (Figure 1).[3, 8] In particular, pregnant females with suspected pyelonephritis (e.g. systemic symptoms, fever > 38°C, significant flank, back or suprapubic abdominal pain) should be immediately referred for an acute obstetric appointment, and their lead maternity carer contacted due to the increased risk of maternal and fetal complications.[11] In addition, people with suspected pyelonephritis and signs of sepsis (e.g. tachycardia, lower than normal blood pressure, increased respiratory rate) usually require referral to secondary care for intravenous antibiotics and fluids.

Urinalysis: indications and interpretation

Dipstick testing can strengthen diagnostic certainty in symptomatic patients

In most females aged less than 65 years without complicating factors, a lower UTI can be reliably diagnosed according to the clinical presentation alone, without additional urinalysis. However, if there are atypical features, complicating factors or diagnostic uncertainty, then urine dipstick testing can be useful to indicate if an infection is the likely cause of their symptoms.[2, 8] The key aspects to consider are:[2, 12]

- **Nitrite status** – sterile urine generally should not contain detectable traces of nitrite. Most UTIs are caused by bacteria belonging to the Enterobacteriaceae family, which can metabolise nitrates to nitrites.
- **Leukocyte esterase status** – leukocyte esterase is an enzyme produced by white blood cells. If the test is positive, it may indicate that white blood cells have been generated by the body in response to infection, and that they are present in the urine (pyuria).

A positive result for either nitrites or leukocyte esterase, in the presence of lower UTI symptoms, is sufficient to confirm a lower UTI diagnosis and proceed with treatment.[8] However, negative results from urine dipstick testing may not reliably exclude the possibility of a UTI, e.g. some UTIs caused by bacterial species that are unable to produce nitrites, and early pyelonephritis may not produce positive results.[8] Haematuria on dipstick can also be an informative finding as this is commonly associated with a UTI but not urethritis.[2, 3] However, if microscopic haematuria is persistently present in patients with recurrent or ongoing lower urinary tract symptoms, or if gross haematuria is observed (i.e. visible blood in the urine sample), then other diagnoses should be strongly considered, e.g. renal calculi or urinary tract malignancy.[2, 3]

Routine urine dipstick screening for infection in the absence of UTI symptoms (asymptomatic bacteriuria) is not recommended as this should not be treated in patient groups other than pregnant females. This is due to the risk of antibiotic-related adverse effects, selecting for antibiotic-resistant bacteria and disruption to the patient's normal urinary microflora.[2] Pregnant females should be screened via urine culture for asymptomatic bacteriuria, at their first antenatal appointment.

For further information on urine dipstick testing, see: **bpac.org.nz/bt/2013/june/urine-tests.aspx**

For further information on UTIs and asymptomatic bacteriuria in pregnancy, see: **bpac.org.nz/2019/pregnancy-care.aspx**

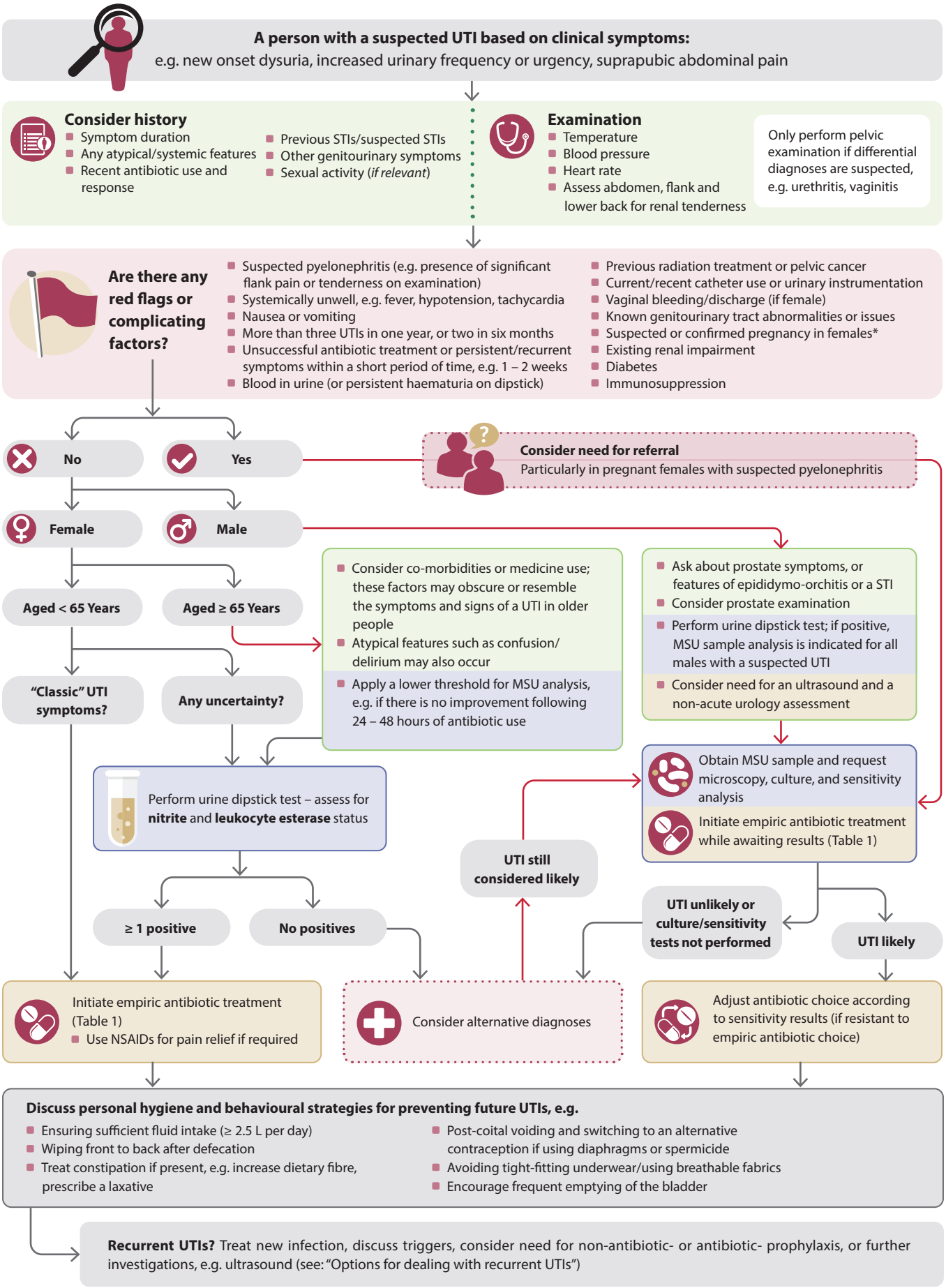


Figure 1. The diagnosis and management of symptomatic lower UTIs in adults.[2, 8]

* A midstream urine (MSU) sample should be obtained, and sent for laboratory analysis in all pregnant females, ideally as part of the first antenatal check; asymptomatic bacteriuria should be treated in this group due to the risk of complications

MSU, midstream urine; STI, sexually transmitted infection; UTI, urinary tract infection

Requesting analysis of a MSU sample is not routinely recommended

For females with uncomplicated cystitis, the causative bacteria and antibiotic sensitivity profile are often predictable. As such, requesting microscopy, culture and sensitivity testing is not necessary as it is unlikely to influence treatment decisions (see: "Empiric antibiotic selection").[2] Obtaining a urine sample – ideally mid-stream urine (MSU) – and requesting laboratory analysis is only indicated in certain circumstances if there is clinical suspicion of a UTI based on symptoms (Figure 1), including:[2, 8, 13]

- When dipstick testing is negative, but a UTI is still strongly suspected after considering differential diagnoses
- People with recurrent UTIs, atypical symptoms or persistent symptoms despite antibiotic treatment
- People with suspected pyelonephritis
- Females with complicating factors, e.g. pregnancy, catheterisation, urinary tract abnormalities, immunosuppression, renal impairment, diabetes
- Other high-risk groups, including males, children aged 14 years and under and people living in residential care facilities

The treatment of uncomplicated UTI

Antibiotic resistance is a global issue, primarily driven by inappropriate and excessive use.[14] In response, some international guidelines now recommend that NSAIDs are considered as an alternative first-line treatment for UTIs associated with mild symptoms rather than immediate antibiotic use in females aged less than 65 years.[2, 15]

However, while uncomplicated UTIs can be self-limiting in some cases, the natural course can vary between people, and symptoms may progress instead.[16] Therefore, it currently remains standard practice to prescribe antibiotics to most patients with uncomplicated UTIs in New Zealand primary care. A systemic review including 1,309 females with uncomplicated UTI found that the number needed to treat (NNT) with antibiotics rather than NSAIDs to achieve symptom resolution in one additional female by day 3 or 4 of treatment ranged from three to six, i.e. more females have a shorter UTI duration with antibiotic treatment versus NSAID use.[17] In addition, antibiotic use was associated with a lower risk of pyelonephritis and other complications.[17]

Empiric antibiotic selection

The initial antibiotic choice for patients with uncomplicated UTI should be empiric (Table 1).[2, 18] If symptoms do not resolve, or a patient experiences a recurrent infection within a short period of time, e.g. one to two weeks, consider sending a MSU sample for microscopy, culture and sensitivity analysis to guide the selection of an alternative choice.[2] If laboratory testing is performed at any time, and resistance to the empiric choice is demonstrated, an alternative antibiotic can be selected. However, MSU samples will not be cultured in some laboratories if the initial microscopy indicates that infection is unlikely, e.g. if white blood cells are absent.

Citrate sodium anhydrous + citric acid anhydrous + sodium bicarbonate + tartaric acid (Ural) is no longer routinely recommended during the acute treatment of UTIs as it raises the urinary pH, which in turn reduces the effectiveness of some antibiotics, e.g. nitrofurantoin.[8] Instead, NSAIDs can be considered as an add-on to antibiotic treatment for pain relief if required.[8]

Table 1. Empiric antibiotic regimens for uncomplicated UTI in adults.[18]

N.B. Treat for **seven days** in pregnant females and in all males, regardless of antibiotic choice.

	Antibiotic	Dose
First-line	Nitrofurantoin*†	Modified release (Macrobid): 100 mg, twice daily, for five days Immediate release (Nifuran): 50 mg, four times daily, for five days
Alternatives	Cefalexin	500 mg, twice daily, for three days
	Trimethoprim‡	300 mg, once daily, for three days

* Contraindicated in patients with a creatine clearance < 60 mL/min due to the risk of peripheral neuropathy. Prescribe nitrofurantoin by brand name to reduce errors as there are two different formulations.[19] Nitrofurantoin is not an appropriate first-line choice in patients with suspected pyelonephritis as it is associated with poor tissue penetration.[18]

† Avoid after 36 weeks gestation in pregnant females

‡ Avoid in the first trimester of pregnancy

Discuss self-care strategies with all patients

Before the patient leaves the appointment, it is important to discuss self-care in relation to behavioural and hygiene practices. In some cases, these changes may reduce the risk of future infections, and will likely have wider health benefits.[2, 3] Strategies include:

- Ensuring fluid intake is sufficient (at least 2.5 L per day)
- Avoid wearing tight-fitting underwear and using breathable fabrics such as cotton rather than synthetics, e.g. nylon or polyester

- Urinating when required (i.e. not "holding on" unnecessarily)
- Post-coital voiding; this behaviour has not been proven to reduce the risk of recurrence in controlled studies, but is anecdotally supported
- Switching to an alternative contraceptive method if diaphragms or spermicide are used (these are associated with an increased risk of UTI)
- Wiping front to back after defaecation or urination to avoid perineal or urethral contamination with faecal bacteria
- Treating constipation if present, by increasing dietary fibre intake or using a pharmacological intervention, e.g. docusate sodium + sennoside B (Laxsol) or lactulose; constipation may exert pressure on the bladder, or even obstruct it, leading to incomplete voiding which increases the risk of a UTI

Options for dealing with recurrent UTIs

UTIs are considered recurrent when there are at least three symptomatic episodes within 12 months, or two or more within six months.[3] In most cases, recurrent UTIs are thought to be caused by reinfection of the urinary tract rather than relapse linked to the previously treated isolate – assuming a complete antibiotic course was taken.[2] If the recurrence occurs within a short period of time, e.g. less than two weeks after finishing the antibiotic course, it is more likely to be caused by the same original strain. In these cases, consider obtaining a MSU sample for microscopy, culture and sensitivity testing to refine treatment selection.[3]

Non-antibiotic prophylactic treatments can be discussed

In all patients with recurrent UTIs, first reiterate the importance of self-care strategies, and investigate known triggers specific to the patient's history, e.g. use of spermicide-containing contraceptives. Some other non-antibiotic prophylactic strategies that have a low risk of harm can be discussed, but their use is not routinely recommended due to a lack of high-quality evidence for efficacy.[2]

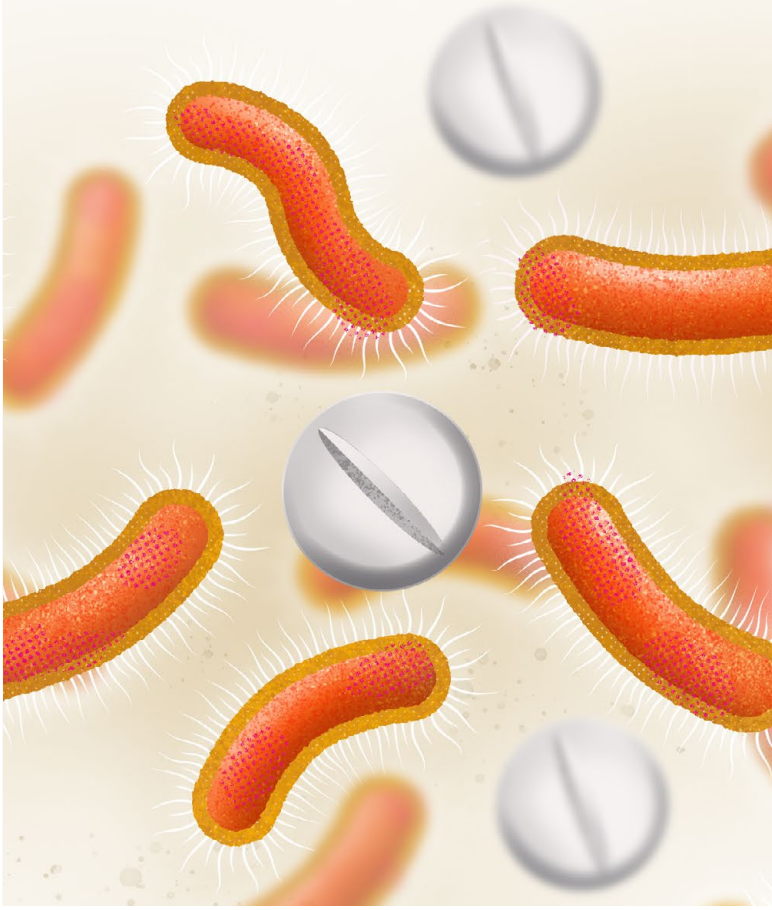
Prophylactic strategies for UTIs include:[2, 3]

Topical vaginal oestrogen (estriol; fully funded). The use of topical vaginal oestrogen has been found to consistently reduce the risk of UTI recurrence in postmenopausal females participating in small randomised controlled trials. However, given the heterogeneity in the application method used between trials, a pooled estimate of the effect size cannot be determined. Oral oestrogen supplementation has not been found to confer a similar benefit in clinical trials.

Why is trimethoprim no longer a first-line empiric antibiotic option?

Previously, trimethoprim was considered a first-line empiric option for managing uncomplicated UTIs, and it has been commonly prescribed by clinicians in primary care.[1] Since 2012, pharmacists who have completed a UTI training course have been able to supply trimethoprim without a prescription to females with a suspected UTI aged 16 – 65 years who are not pregnant and do not have any other complicating factors.[20]

However, there is now evidence that trimethoprim should not be a first-choice antibiotic for managing uncomplicated lower UTIs due to a growing pattern of resistance across New Zealand.[21] A multi-region audit of urine samples obtained between June 2016 and August 2018 demonstrated that approximately one-quarter of all *E. coli* isolates from females aged 15 – 55 years lacked trimethoprim sensitivity.[21] In comparison, < 1% of *E. coli* tested were resistant to nitrofurantoin, and < 5% were resistant to cefalexin.[21] Although trimethoprim is often preferred by people due to its once daily dosing, these findings suggest that nitrofurantoin and cefalexin are generally better empiric antibiotic treatment choices – unless there is recent community resistance data available to pragmatically guide such decisions.



Consumption of cranberry products, e.g. juices or concentrated capsules (not funded). Meta-analyses have demonstrated that patients with a history of recurrent UTIs taking cranberry products have a 47% relative risk reduction for future UTIs compared with control groups.[22] However, there is high variability in the "active ingredient" dose between products, inconsistent methodology and drop-out rates in clinical trials, and no standardised regimen exists. Overconsumption of cranberry products may cause gastrointestinal irritation, as well as exceed the recommended daily sugar intake.

Expert practice tip: when recommending a cranberry product, higher percentage formulations (e.g. ≥ 18%) are more likely to be effective than lower percentage formulations (e.g. 2 – 4%). Using a higher concentration product also means that a smaller volume or dose can be consumed (e.g. 200 mL of juice or two capsules, daily). Some people may find that taking cranberry products at night is more effective.

Products/supplements containing D-mannose (not funded). D-mannose has been proposed to limit the adherence of bacteria to cells in the urinary tract. There is weak evidence from unblinded randomised controlled trials that it reduces the risk of UTI recurrence. While these results are encouraging, further investigation is required to determine the optimal dose, frequency and duration of use.

***Lactobacillus* containing probiotics** (not funded). There is a plausible scientific basis for the use of probiotics in preventing UTIs, e.g. the competitive exclusion of UTI-causing bacteria. However, efficacy has not been demonstrated in clinical trials that use oral formulations. The application of *Lactobacillus* using an intravaginal suppository decreased the rate of recurrent UTIs by 12% compared with placebo in a small clinical trial (N = 50).[23] However, intravaginal probiotic suppositories for the treatment of UTIs are not readily available in New Zealand. If an oral formulation is to be trialled, ensure that one containing *Lactobacillus* bacteria is used; although there is insufficient clinical trial evidence to guide the selection of a particular *Lactobacillus* strain or dose, *L. rhamnosus* is among the most widely used in clinical trials at doses of ≥ 10^8 colony forming units (CFU)/capsule.[24]

Low-dose antibiotic prophylaxis should generally be a last resort

Females with recurrent UTIs are over six times less likely to experience another UTI if they take prophylactic antibiotics.[3] However, in keeping with the principles of antibiotic stewardship, this approach is not appropriate for all patients; it should generally only be considered in non-pregnant females* if behavioural and/or personal hygiene measures are ineffective in preventing recurrent UTIs.[19] The main options include a once daily night time dose of nitrofurantoin (immediate release formulation, 50 – 100 mg†), trimethoprim (150 mg) or cefalexin (125 – 250 mg).[3, 19] Single-dose antibiotic prophylaxis (unapproved indication) may also be considered for use after exposure to a known UTI trigger, e.g. taking a low-dose antibiotic (as above) two hours post-sexual intercourse.[3]

There is no convincing evidence on the optimal duration of long-term antibiotic prophylaxis; if it is prescribed, a review should be conducted within three to six months to consider the benefits and risks of continued use.[2, 3] If a decision is made to stop antibiotic prophylaxis, a "back pocket" antibiotic prescription can be provided to manage any acute UTIs that subsequently develop.[2]

Methenamine hippurate (Hiprex) 1 g every 12 hours can be considered as an alternative form of antimicrobial prophylaxis in patients with a history of recurrent UTIs to avoid long-term antibiotic use.[19] While methenamine hippurate has bacteriostatic properties, it is not considered a traditional antibiotic as its effect is non-specific; methenamine is progressively converted into formaldehyde within an acidic environment (below a pH 6), which then functions to indiscriminately denature bacterial proteins and nucleic acids.[25] In most cases, urine is already slightly acidic and hippurate acts to lower the pH further, thereby promoting formaldehyde production.[25] The use of methenamine hippurate has been shown to reduce the risk of recurrent UTIs in several small trials and it is generally well-tolerated in both females and males.[2, 25] however, there is not yet sufficient high-quality data to support routine prophylaxis.

* Antibiotic prophylaxis may also be trialled under the supervision of a renal specialist (e.g. nephrologist, urologist) in males and pregnant females who experience recurrent UTIs[19]

† Caution is required when considering nitrofurantoin for long-term antibiotic prophylaxis due to the risk of pulmonary toxicity; discontinue if any deterioration in pulmonary function is identified[19]

Further investigation for patients with recurrent UTIs

There is no compelling evidence for early investigation with imaging or cystoscopy in females aged less than 65 years with lower UTI symptoms unless other risk factors are present, e.g. suspected nephrolithiasis, or if differential diagnoses are strongly suspected.[2] Referral for non-acute urology assessment may be considered in:[2, 3, 10]

- Females if they continue to present with recurrent UTIs despite sensitivity testing and prophylactic antibiotics, particularly if they have had previous radiation treatment or pelvic cancer
- Females with recurrent UTI symptoms, in addition to microscopic haematuria and/or pyuria, despite negative urine cultures; multiple courses of antibiotics should

generally not be used if there is no other evidence of infection, e.g. nitrite/leukocyte positivity on dipstick testing

- Males who do not respond to initial treatment or who experience a second UTI; consider checking for urinary retention by examination or bedside ultrasound in older males
- Older people who do not improve with antibiotic treatment, even after requesting urine culture to confirm infection and sensitivity analysis to guide antibiotic selection

For further information on the diagnosis and management of UTIs in other groups:

- **Pregnant females: bpac.org.nz/2019/pregnancy-care.aspx**
- **Older people: bpac.org.nz/BT/2015/July/guide.aspx**
- **Children: starship.org.nz/guidelines/urinary-tract-infection/**

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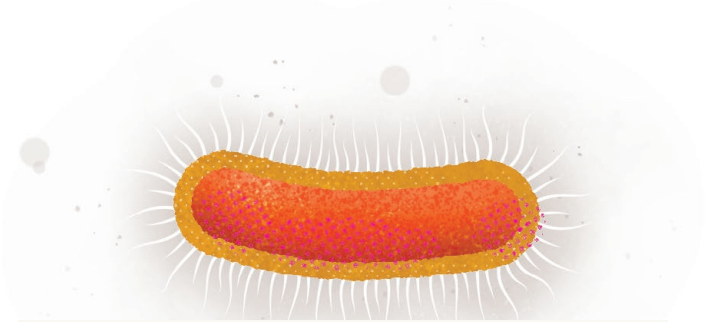

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MMR vaccination remains a priority

Measles, mumps and rubella are vaccine-preventable causes of significant morbidity and mortality (particularly for measles), that can affect people of any age. Historical gaps in vaccination coverage in New Zealand have left many people under-immunised. Furthermore, with the challenges of the COVID-19 pandemic, many countries have had disrupted immunisation programmes so New Zealand needs to be prepared for the potential for increasing international rates of measles over the next few years. There has also been a recent drop-off in the uptake of childhood immunisations in New Zealand, creating further potential immunity gaps in our younger population, particularly tamariki Māori.

KEY PRACTICE POINTS:

- Immunisation against measles, mumps and rubella requires two doses of the combined MMR vaccine, and is the best protection against all three diseases
- Historical gaps in vaccination coverage have left many New Zealand adolescents and young adults, aged between 15 and 30 years, under-immunised and at increased risk of infection, making this population group a priority for catch-up vaccination
- Catch-up doses of MMR are fully funded for people born from 1 January, 1969, without documented history of two doses of MMR
- The timing of MMR vaccination was amended in the National Immunisation Schedule in October, 2020, to include a first dose of MMR at age 12 months and a second dose at age 15 months
- Maintaining the infant immunisation programme and ensuring all infants receive two MMR vaccinations by 15 months remains vital to reduce the risk of developing further immunity gaps
- Practices should actively check for and recall all patients with uncertain or undocumented MMR vaccination history, particularly focusing on infants who have missed their dose at age 12 and/or 15 months and people aged between 15 and 30 years; there is no evidence to suggest receiving an extra dose causes any harm

Measles, mumps and rubella in New Zealand

Following the introduction of the combined measles, mumps and rubella (MMR) vaccine in 1990, the number of cases of all three diseases has significantly and progressively declined.[1] Since then, there have been very few large outbreaks and in 2017, the World Health Organization (WHO) verified New Zealand as free of both endemic measles and rubella (see: "Epidemiology definitions").[1] Historical issues in vaccination coverage, however, have left many adolescents and young adults in New Zealand more likely to have missed full MMR vaccination and at greatest risk of infection (see: "Adolescents and young adults in New Zealand are under-immunised").[1, 2] For this reason, the Ministry of Health now recommends that this population group is prioritised for recall for catch-up MMR vaccination to help to close the immunity gap, reducing the risk of future outbreaks.[1]

N.B. While adolescents and young adults are currently the priority for catch-up MMR vaccination, anyone born on, or after 1 January, 1969, without documented evidence of immunity to all three diseases may also receive funded catch-up MMR vaccination (see: "Encourage immunisation of susceptible individuals").[1]

Criteria for determining immunity

Evidence of immunity against measles, mumps and rubella requires documented history of two doses of MMR, or serologic evidence of immunity against all three diseases.[1] Clinical history of disease alone does not reliably indicate immunity.[1] Serologic evidence of protection against one disease (if tested), or documented history of measles-only vaccination, cannot be used as a proxy for immunity against the other two diseases; complete MMR vaccination is still required.[1]

N.B. In New Zealand, serological testing for immunity against rubella is typically only performed as part of the "antenatal screen" and serological testing is not funded or recommended for routine use;[1] if there is doubt about vaccination status, it is safe and effective to offer further vaccination rather than a serological test.

Adolescents and young adults in New Zealand are under-immunised

Since the early 1990s, several gaps in MMR coverage have resulted in certain cohorts in New Zealand being under-immunised, particularly adolescents and young adults aged between 15 and 30 years.[1] This gap in immunity is due to a combination of historical issues in vaccination coverage directly affecting this population group, including:[1]

Historically low national immunisation rates, with less than 60% of children being fully vaccinated by age two years in the 1991/92 National Childhood Immunisation Survey.[5, 6] Coverage increased to 63.1% in 1996 (with lower rates for those of Māori [44.6%] and Pacific [53.1%] ethnicity) and further increased to 77.4% in 2005.[5, 6] N.B. National immunisation coverage dropped again in the 2010s but increased to 88% (for children aged five years) between 2020 – 2021.[7]

Unfounded, but widespread vaccine safety concerns regarding a since discredited association between MMR vaccine and the development of autism in children in the late 1990s and early 2000s* (see: "Vaccination hesitancy" for further information on immunisation concerns)[8, 9]

Changes to the timing of the second dose in the MMR vaccination schedule in 2001; from age 11 years to age four years

Potentially compromised vaccine quality, resulting from inadequate cold chain processes, which have now been rectified

Vaccine supply shortages, particularly during the 2019 measles outbreak[10, 11]

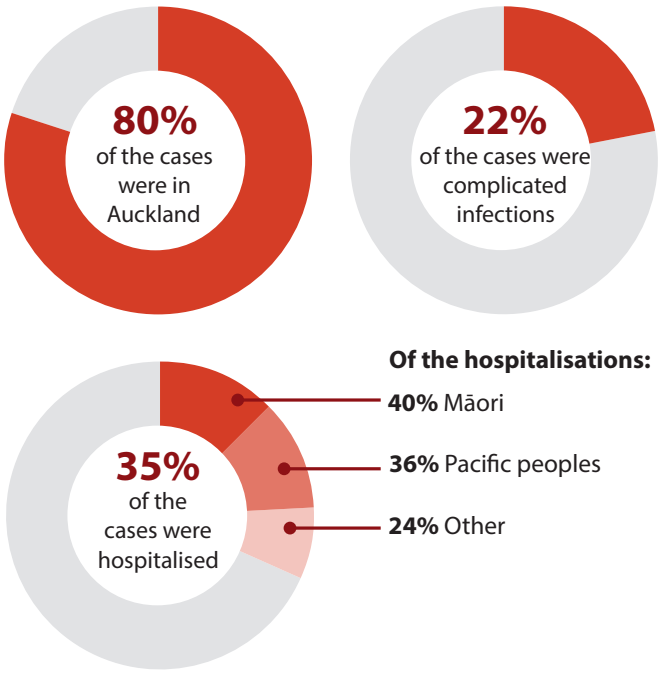
* These claims have been discredited, with over 30 years of epidemiological research confirming there is no evidence of a link between MMR and autism.[8, 9] The original study (1998) was retracted in 2004 due to dishonest and irresponsible methods, where it was later disclosed to have used incorrect laboratory reports and falsified patient data. For further information, see: **www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60175-4/fulltext**.[1]

Recent mumps and measles outbreaks highlight immunity gap

The most recent mumps and measles epidemics in New Zealand occurred in 2016/2017 and 2018/2019, with most cases located in the wider Auckland region (see: "Measles, mumps and rubella: an overview").[1, 12] Adolescents and young adults aged between 12 – 29 years* were the population group most affected by the outbreaks (Figure 1).[1, 12]

During the 2018/2019 measles epidemic, **nine outbreaks** occurred throughout New Zealand, resulting in **2,213 notified cases**, of which:[1, 13]

Six outbreak clusters were linked to imported cases; deriving from Australia, Thailand, Japan, Singapore and the Philippines



The highest burden of disease was among under-immunised young children, adolescents and young adults; particularly infants aged under two years and adolescents/young adults aged between ten and 30 years* (see: "Adolescents and young adults in New Zealand are under-immunised")

* The age range has been inconsistently reported, i.e. 10 – 15 and 20 – 30 years, and varies depending on data age groupings[1, 13, 14]

Rubella infection is still rare in New Zealand

The most recent rubella outbreak occurred between 1995 – 1996, mostly involving young adult males, and likely due to the earlier under-immunisation of young males (see: "Vaccination history of measles, mumps and rubella in New Zealand").[1] Since 1998, no incidences of congenital rubella syndrome (CRS), and very few cases of rubella, have been reported.[1] In 2017, New Zealand was verified by the WHO as rubella-free, and since then only three imported cases of rubella have been reported (Figure 1).[1]

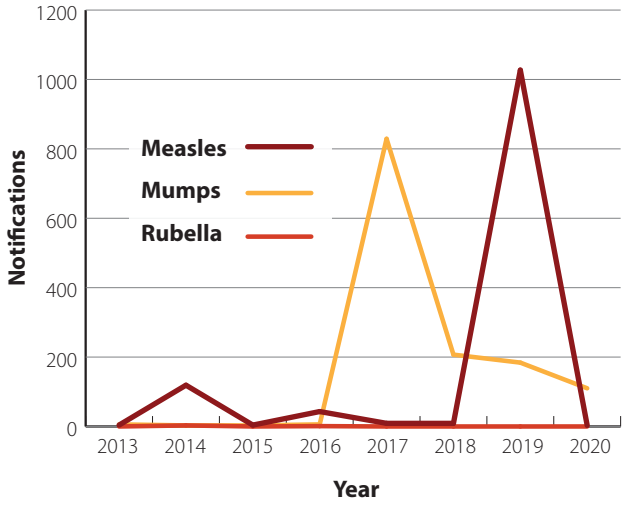


Figure 1. Measles, mumps and rubella notifications for adolescents and young adults aged 15 – 29 years in New Zealand from 2013 – 2020.[12]

Epidemiology definitions

Cluster: a greater than expected accumulation of cases of a health condition (e.g. disease or injury) which are grouped together in place and time.[3] N.B. The expected number of cases is not always known.[3]

Endemic: the constant presence of a disease, infectious organism or health condition within a given population and in a given geographic area.[3]

Epidemic: an increase in the number of cases of a disease, illness, health-related event or health-related behaviour that far exceeds the expected number within a community, region, or any other group of people at a particular period.[3, 4]

Outbreak: technically synonymous to epidemic, outbreak, however, is typically used to describe a more localised increase in the number of cases of a health condition (e.g. disease or injury), such as within a community, town or institution.[3, 4]

Pandemic: an epidemic on a much larger scale, spreading to many countries or continents and therefore usually affecting a larger number of people around the world.[3]

Table 1. History of measles, mumps and rubella vaccination in New Zealand.[1]

Date	Measles	Rubella
1969	**Single dose measles-only vaccine:** introduced for children aged between ten months and five years, and those at high risk aged under ten years N.B. People born prior to 1 January, 1969, are considered immune due to wild-type virus exposure.	
1970		**Single dose rubella-only vaccine:** introduced for all children aged four years (to reduce wild-type virus transmission in children aged five to nine years) N.B. The Department of Health* also initiated a school-based immunisation programme resulting in the vaccination of 95% of children aged five to nine years during 1970.
1974	**Recommended age change:** single dose measles-only vaccination changed to age 12 months	
1979		**Recommended age change for girls:** single dose rubella schedule changed to age 11 years for girls only, due to a low uptake of rubella vaccination at age four years (especially in boys)
1981	**Recommended age change:** single dose measles vaccination changed to age 12 – 15 months	
1990	**Single dose combined MMR vaccine:** introduced to the National Immunisation Schedule for all infants aged 12 – 15 months, replacing the separate measles and rubella vaccines N.B. Vaccination against mumps was not included in the National Immunisation Schedule before the combined MMR vaccine in 1990.	
1992	**Double dose combined MMR:** a second dose was added to the National Immunisation Schedule for boys and girls aged 11 years	
1996	**Measles, mumps and rubella became notifiable diseases**	
2001	**Recommended MMR age change:** the timing of the second dose of MMR was changed from age 11 years to age four years and a school-based, catch-up vaccination programme was offered to all children aged five to ten years	
2014	**Vaccination available following immunosuppression:** MMR became available for (re)vaccination following immunosuppression. Two-dose schedule remained at ages 15 months and four years.	
2020	**Recommended MMR age change:** following the 2019 measles outbreak, the recommended age for vaccination changed in October, 2020, to age 12 months (for dose one) and age 15 months (for dose two)	

* In 1993, the Department of Health became the Ministry of Health[20]

N.B. Measles, mumps and rubella are all notifiable diseases and all suspected and confirmed cases must be immediately reported to the local Medical Officer of Health.[1]

Vaccination history of measles, mumps and rubella in New Zealand

The history of measles, mumps and rubella vaccination in New Zealand can provide information to help identify people who are likely to be under-immunised (Table 1).[1]

N.B. People vaccinated in other countries may have received monovalent measles or measles-rubella only vaccines, and if applicable, still require immunisation with MMR for full protection.

Immunisation is the best protection

In cases of highly infectious vaccine-preventable diseases such as measles, mumps and rubella, a high percentage of the population needs to be fully immunised to prevent wide-spread community transmission (Table 2).[1] With a basic reproduction number (R0) of 12 – 18, measles is one of the most contagious and communicable of all infectious diseases.[1, 15] Influenza and coronavirus disease 2019 (COVID-19) have comparatively lower basic reproduction numbers (Table 1).[1, 21]

Table 2. Disease transmissibility ratings and herd immunity thresholds required to prevent wide-spread community transmission.[1]

Disease	Basic reproduction number (R0)*	Herd immunity threshold
Measles	12 – 18	92 – 94%
Mumps	4 – 7	75 – 86%
Rubella	6 – 7	83 – 85%
Coronavirus (COVID-19)	4.08†	Unknown
Influenza	1.4 – 4	30 – 75%

* R0 values are estimated values, often deriving from global averages, such is the case with COVID-19.[21] R0 values represent the estimated spreading potential of an infection by calculating the number of secondary cases that can be infected by one infectious case, within a given, and susceptible population.[1] Ranges can therefore vary greatly between populations depending on the means of calculation and the specific population.[21]

† The mean R0 number of the delta variant of COVID-19 is estimated to be 5.08 (range 3 – 8)[22]

First MMR dose now recommended at age 12 months

Following the 2019 measles outbreak, the National Immunisation Schedule was revised on 1 October, 2020, recommending that children now receive the first MMR dose at age 12 months, and a second dose at age 15 months (previously recommended at age 15 months and age four years).[1] MMR vaccination is fully funded for New Zealand citizens and residents, and contacts of confirmed cases, including catch-up vaccinations (see Table 3 for recommended MMR vaccination schedule).[1]

Encourage immunisation of susceptible individuals

Any person born on or after 1 January, 1969, who has not received two documented doses of the combined MMR vaccine, is considered susceptible to one or more of measles, mumps and rubella, and includes those who have:[1, 16]

- **Received partial vaccination** with one or two doses of a measles-only vaccine (or measles-rubella vaccine for people vaccinated overseas)
- **Clinical history of infection** of one or more of the diseases without further documentation of immunity (see: "Criteria for determining immunity")

All susceptible individuals should receive one or two doses of MMR vaccine (see Table 3 for dosing recommendations).[1] If vaccination history is not available or is uncertain (i.e. number of doses and/or type of vaccine), advise patients that there is no safety concern in re-vaccinating with MMR and this is recommended.[1] However, as a live attenuated vaccine, there are certain people for whom MMR is contraindicated (see: "Contraindications and cautions").[1]

New Zealand population groups at higher risk of infection

In New Zealand, people most at risk of measles exposure and infection include those:[1]

Who are not fully vaccinated with MMR, particularly children aged under two years, and adolescents and young adults, aged between 15 and 30 years (see: "Adolescents and young adults in New Zealand are under-immunised")[13]

Returning from recent travel overseas with uncertain immunisation history, due to higher risk of exposure in measles-endemic countries

Born in countries where complete vaccination with all three antigens is less likely or access is difficult

Working in certain occupations including health care, early childhood education services and other high-contact occupations*, who are at increased risk of both contracting and transmitting infections

* High-contact occupations include those working in emergency and essential services such as armed forces, immigration/refugee centres, long-term care facilities, correctional facilities and border workers[1]

Table 3. Recommended MMR immunisation schedule. Adapted from the "Immunisation Handbook" (2020).[1]

Patient group	Recommended vaccination (all doses of MMR must be given at least four weeks apart)
Childhood immunisation schedule for children born in New Zealand	**Two doses of MMR***; dose one at age 12 months and dose two at age 15 months
Early vaccination for infants during an outbreak	**A single dose of MMR0 [zero]** can be given to infants aged between six and 11 months for early protection N.B. Any infants receiving the MMR0 vaccine still require two further doses of MMR, as per the usual childhood schedule.
Catch-up schedule for those born from 1 January, 1969, without documented history having received two doses of MMR or evidence of serologic immunity against all three diseases	**Two doses of MMR;** recommended catch-up doses for patients with vaccination histories of: ■ **No prior MMR** – two doses ■ **One MMR** – one dose ■ **Any number of measles, mumps or rubella vaccines** (alone or combined, e.g. measles-rubella) **and no MMR** – two doses N.B. Pregnancy should be avoided for at least four weeks following final vaccination.
Women who are pregnant	**MMR is contraindicated during pregnancy** (due to the possibility of fetal harm) N.B. MMR can be given to women who are breastfeeding.
Immunocompromised individuals	**MMR is contraindicated;** close contacts should be vaccinated (see below)
People born in New Zealand before 1 January, 1969	**MMR is not required** as they are considered immune to measles (due to presumed exposure to wild-type measles before the introduction of MMR) N.B. Those born before 1980 are considered immune to mumps.

For further information on occupation-related vaccination, see: **www.health.govt.nz/our-work/immunisation-handbook-2020/4-immunisation-special-groups#4-8**

MMR immunity gap increases the risk of fetal rubella infection

Although rubella cases have remained low, a large number of women falling within this immunity gap are now of childbearing age and susceptible to rubella infection, increasing the risk of fetal infection and serious complications such as CRS (see: "Measles, mumps and rubella: an overview").[1] Women of childbearing age, especially those who are planning pregnancy, should be asked if they are fully immunised against rubella with MMR (see Table 2 for recommended vaccination schedule if catch-up is required).[1]

N.B. In New Zealand, serological testing for immunity against rubella is typically only performed as part of antenatal care and is not funded as a precautionary measure for women planning pregnancy.[1] If serology results indicate a lack of immunity during pregnancy, MMR vaccination should be given following delivery.[1]

Further information on MMR immunisation catch-ups is available from: **www.health.govt.nz/our-work/immunisation-handbook-2020/appendix-2-planning-immunisation-catch-ups**

Further information on MMR immunisation for special groups is available from: **www.health.govt.nz/our-work/immunisation-handbook-2020/4-immunisation-special-groups**

Scheduling MMR with COVID-19 vaccination

The requirements for spacing between administration of mRNA COVID-19 vaccine with other vaccines, with the exception of the vaccine for herpes zoster, have been removed. Previously, it was recommended that a gap of two weeks be observed between COVID-19 vaccination and any non-live vaccine, or four weeks with a live vaccine, such as MMR.[1] If a person therefore requires MMR vaccine and also COIVD-19 vaccine, the advice is that they can now be administered concurrently, and that MMR can be given either immediately before or after COVID-19 vaccine.[1]

Measles, mumps and rubella: an overview

Measles

Measles is a highly infectious viral disease caused by a paramyxovirus.[1] It can be transmitted through both airborne spread (coughing, sneezing, breathing) and direct person-to-person contact (via transfer of infectious droplets).[1, 15, 16] Measles is characterised by clinical features of fever and a distinctive maculopapular rash, and causes an acute immune suppression that leads to widespread infection.[1, 15] After exposure, the virus has an incubation period of approximately ten days before symptoms appear, typically in three characteristic stages.[1, 16]

Measles infection increases the risk of further complications such as pneumonia, encephalitis and myocarditis and in rare cases, sub-acute sclerosing panencephalitis*.[1]

* Sub-acute sclerosing panencephalitis is a rare but serious and fatal degenerative nervous system disease, that arises from persistent, wild-type measles infection and typically appears 7 – 11 years following initial infection[17]

Mumps

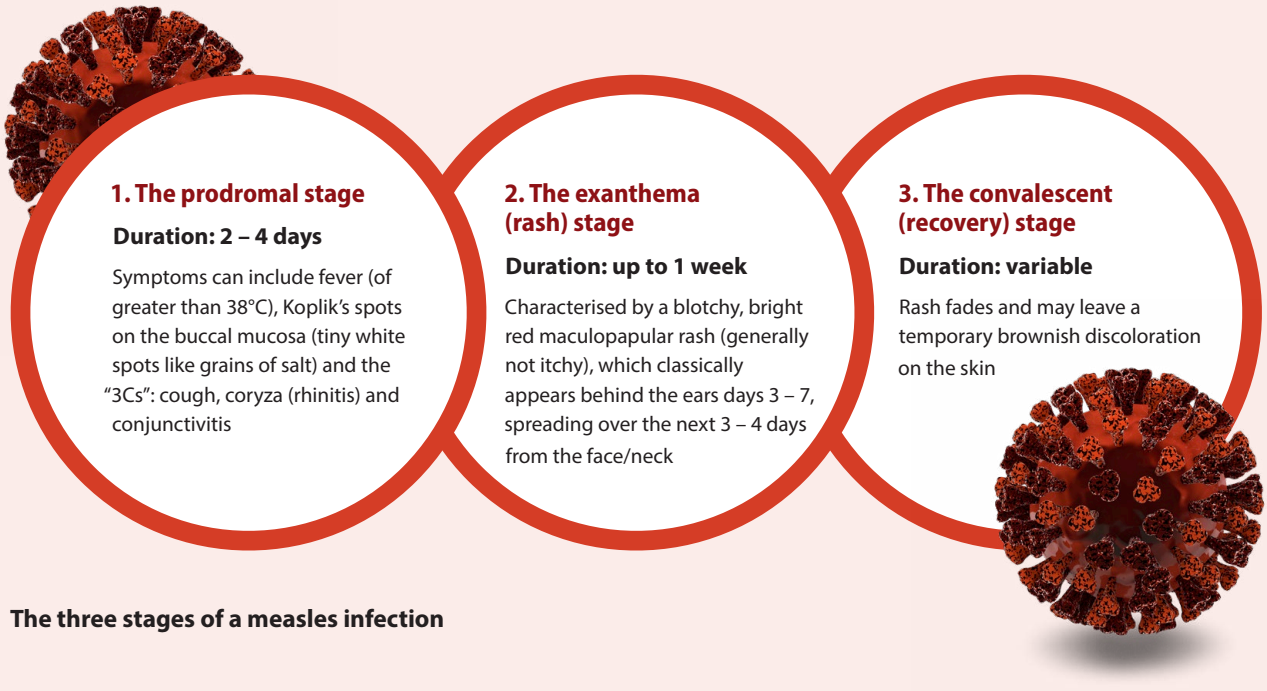
Mumps is an acute viral infection also caused by a paramyxovirus, and characterised by clinical features of headache, fever and parotitis (parotid salivary gland swelling and tenderness).[1] It is transmitted both indirectly (through airborne droplets) and directly (through contact with urine or saliva), and is most infectious for the period of two days before and five days after onset of parotitis.[1] Widespread mumps infection can lead to further complications such as meningitis, encephalitis, hearing loss, mastitis and oophoritis in females and orchitis in males that can decrease fertility or lead to temporary sterility; it is unknown whether mumps can result in permanent sterility.[1, 18]

N.B. Parotid gland swelling is most common, but swelling can also occur in other salivary glands and other structures, e.g. the brain and testes.[1]

Rubella

Rubella is an infectious disease caused by a togavirus that affects both adults and children.[1] The virus is comparatively less infectious than measles (Table 1), however, maternal infection can lead to serious consequences for the unborn child, particularly if contracted during the first trimester of pregnancy.[1]

Congenital rubella syndrome (CRS) is the most severe complication following rubella and results from maternal infection during pregnancy.[1, 19] CRS is characterised by a number of serious consequences including miscarriage, fetal death and severe congenital defects including hearing impairment, congenital heart disease, cataracts and developmental delay.[1, 19] Fetal damage can occur in up to 80% of infants if rubella is contracted within the first 12 weeks of pregnancy, decreasing to 50% after 16 weeks and 25% after the end of the second trimester; multiple defects are common.[1, 19]



The three stages of a measles infection

Further information about COVID-19 vaccination is available from the Immunisation Handbook (see Section 5.4.5 for information on co-administration with other vaccines): **www.health.govt.nz/our-work/immunisation-handbook-2020/5-coronavirus-disease-covid-19**

Contraindications and cautions

As MMR is a live vaccine, people with contraindications include those:[1]

Who are pregnant

Who are immunocompromised

With proven anaphylaxis to either the vaccine itself or a component within it, e.g. gelatin or neomycin. N.B. People with egg allergies (including anaphylaxis) can safely receive the vaccine.

Who have been immunised with another live vaccine* within the previous four weeks; All vaccines can be given concurrently with MMR vaccine (with separate syringes and different injection sites), however, a four week gap is required for administration of any other live vaccine if not administered concurrently. There is no longer a requirement for spacing with inactivated vaccines, e.g. the COVID-19 vaccine.

* Additional live attenuated vaccines include varicella, rotavirus, tuberculosis (BCG) and zoster[1]

Further information about co-administration of MMR with other vaccines is available from the Immunisation Handbook (see Section 12.4.4) **www.health.govt.nz/our-work/immunisation-handbook-2020/12-measles#11-6**

Vaccination hesitancy

Vaccine hesitancy is a complex barrier to immunisation and refers to a patient or caregiver's refusal, or delayed acceptance of vaccination, even when the services are fully funded and available.[1, 24] According to a recently published longitudinal study, over time approximately 30% of the New Zealand population is showing decreasing levels of confidence in the safety of childhood vaccination.[25] Between 1 April, 2020, and 31 March, 2021, the National Immunisation Register (NIR) reported:[7]

- **3,290 parents or caregivers (5.2%) had declined/opted out of any one vaccination for their child** (i.e. children turning the milestone age five years during that 12-month period)
- **366 had opted to move their child off the NIR (0.6%)**

Vaccine hesitancy is complex and can involve varying factors, including:[1, 24]

- **Vaccine and vaccination-specific concerns;** general concern about vaccine safety (i.e. risks/benefits), associated costs
- **Individual and/or social group influences;** knowledge, beliefs and attitudes about health and prevention, perceptions of risks/benefits, personal or anecdotal experience with vaccination, philosophical or conspiratorial beliefs, complacency
- **Contextual issues;** culture, religion, socio-economic status, gender, policies and politics, influential leaders, geographical barriers, historical influences, distrust in health professionals or pharmaceutical industry, media environment (i.e. ease of access to and abundance of anti-vaccine sentiment)
- **Access barriers;** physical or geographical access, costs and affordability, ability to understand vaccine information (i.e. language and/or health literacy)[26]

Understanding and addressing concerns through effective communication

Clinicians should respectfully correct any misconceptions patients and/or caregivers may have, addressing poor sources of information with clear, evidence-based research and at the appropriate level of health literacy for the individual.[1, 24, 25] Information should include the benefits, risks and possible adverse effects of vaccination, the risks of disease without vaccination and advice on what they should do if adverse effects occur.[1, 25]

For further guidance on addressing vaccination concerns, visit: **www.health.govt.nz/our-work/immunisation-handbook-2020/3-vaccination-questions-and-addressing-concerns#3-2**

Two doses are needed for full immunity

Following the second dose of MMR the serologic evidence of immunity increases to 99% against measles, 83 – 88% against mumps, and is likely higher than 90 – 97% against rubella.[1] Almost all people who do not develop protective immunity following the first MMR dose, do so after the second. Rarely, fully immune people can still contract measles following two doses, however, it is usually less severe and hospitalisation is less likely.[1]

Inform patients about potential adverse reactions

Following vaccination, some patients may experience common, mild adverse reactions such as rash, fever, submaxillary gland swelling or joint pain.[1, 23] Mild reactions typically resolve within a few days without treatment. Patients can manage symptoms by resting, drinking plenty of fluids and relieving fever or discomfort with mild analgesia if required (e.g. paracetamol or ibuprofen).[1, 23] Advise patients to contact a health professional if they are concerned about troublesome and/or unexpected symptoms.[1]

N.B. Adverse events following immunisation should be reported to the Centre for Adverse Reactions Monitoring (CARM).[1]

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N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac^{nz} retains editorial oversight of all content.

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This article is available online at:
www.bpac.org.nz/2021/mmr.aspx

Plant-based diets: are they healthy for a child?

With the increasing popularity of plant-based diets, there is much discussion about whether these are healthy and nutritious for young children. A well-planned and balanced vegetarian or vegan diet that includes adequate amounts of essential nutrients can be appropriate for people at all life stages. However, as infancy and childhood are periods of rapid growth and development, extra consideration is required to ensure children are getting sufficient energy and nutrients.

KEY PRACTICE POINTS:

- Vegetarian and vegan diets can be a healthy option in children; they are typically associated with leaner body weight and may be protective against diabetes, heart disease, hypertension and obesity in adulthood
- The greatest concern with a diet excluding animal products is nutrient deficiency; food sources of important nutrients should be recommended first before supplementation. However, supplementation will often be required for some nutrients that are difficult to obtain from diets excluding animal products, e.g. vitamin B12.
- A range of age appropriate and nutrient rich foods should be offered to young children eating a plant-based diet
- Strongly discourage use of home-made infant formulas or alternative "milks" as a replacement for breast milk or commercially prepared infant formulas
- All infants should be regularly exposed to common food allergens including peanuts, tree nuts, cows' milk, egg, wheat, soy, sesame, fish and shellfish before age 12 months, unless they are already allergic

Vegetarian and vegan diets: an overview

Vegetarianism and veganism are increasingly popular dietary choices. The most recent national data on plant-based eating in New Zealand is from 2018, but it is likely that numbers have since increased. A 2018 online survey of 1,000 participants aged ≥ 18 years in New Zealand found that 10% either completely avoided eating meat, or rarely consumed it; approximately twice the rate reported from the same survey in 2015.[1] In the 2018 New Zealand Attitudes and Values Study, that included responses from > 45,000 participants, it was found that 4.5% of adults exclusively followed a vegetarian diet and 1.1% followed a vegan diet.[2] The prevalence of plant-based diets in children in New Zealand is not known.

A plant-based diet is generally defined as being:[3]

- **Lacto-ovo** – the most common type of vegetarian diet, describing someone who excludes meat and seafood but consumes eggs and dairy products
- **Lacto** – a vegetarian diet where someone excludes meat, seafood and eggs but consumes dairy products
- **Vegan** – someone who abstains from eating all animal products, i.e. meat, seafood, dairy and eggs, sometimes honey. Achieving a nutritionally balanced vegan diet can be more challenging, so it is important to identify what foods are being excluded.

There are various other plant-focused diets that include certain kinds of meat or seafood, e.g. pescatarian (fish), pollotarian (chicken).

A well-planned diet that excludes animal products can be healthy and nutritious for an adult, but parents, other caregivers or healthcare professionals may be concerned about the growth and development of a child who is provided with a plant-based diet, particularly in infancy and pre-school years.

Benefits of plant-based diets for children

Data on the benefits of vegetarian and vegan diets in children, particularly young children, are limited.[4] The available data show that children who follow a properly designed plant-based diet grow and develop normally (Table 1), and typically have a lower intake of cholesterol and fat, a higher intake of fruit and vegetables and are leaner than omnivorous children.[5] Longer-term data suggest that a nutritionally balanced plant-based diet adopted at an early age may reduce the risk of developing obesity, type 2 diabetes, cardiovascular disease and hypertension in adulthood.[3, 5]

Risks of plant-based diets for children

Most concerns about vegetarian and vegan diets in children are around achieving an adequate intake of energy, protein and micronutrients from plant sources. Nutrients requiring particular attention include vitamin B12 (which is almost exclusively found in animal products), iron, calcium, zinc, iodine, omega-3 and vitamin D.[6] Plant-based diets that are restrictive (e.g. macrobiotic diets) or lacking in essential nutrients can result in poor growth, lower bone mineral density, anaemia, and in severe cases, developmental delay, irreversible cognitive damage and death.[6] Vegetarian and vegan diets may be suitable in children with pre-existing health conditions (e.g. ex-premature infants) or allergies (e.g. to soy or wheat) that make a plant-based diet more challenging to manage, but this should generally be under the guidance of a dietitian and/or clinician and involve regular monitoring.[3]

Risk of bone fractures likely relates to the quality of the plant-based diet

There is some evidence that people following plant-based diets have lower bone mineral density, however, there is inconsistent evidence about the effect of this on fracture risk. A meta-analysis of five studies found that vegans had an increased fracture risk compared to omnivores, while vegetarians did not.[7] However, when overall dietary quality was considered (one study only), there were no differences in bone mineral density between groups, suggesting that as long as the diet includes adequate sources of calcium, vitamin D, protein and vitamin B12 then potential adverse effects of a diet excluding animal products on bone health can be avoided.[7, 8]

Restricted diets in infancy may increase the risk of food allergies

To reduce the risk of food allergy in later life, infants should be introduced to, and regularly consume (e.g. twice weekly), common food allergens before age 12 months unless they are already allergic to the food.[9, 10] This includes peanuts and tree nuts (as nut pastes), cows' milk, egg, wheat, soy, sesame, fish and shellfish.[9, 10] In a randomised controlled trial including 640 infants with severe eczema or egg allergy enrolled before the age of 11 months, the rate of peanut allergy at age five years was 1.9% in those who regularly consumed peanuts as part of their diet, compared with 13.7% in infants who completely avoided peanuts.[11]

Ensure parents and caregivers are aware of the recommendations around the timing of food allergen exposure and the benefits of early exposure. Parents wishing to provide their infant with a vegan or a lacto-vegetarian (excludes eggs) diet should still be encouraged to expose them to animal-derived food allergens in the context of allergy risk reduction to reduce the likelihood of a life-threatening allergic reaction through inadvertent exposure or cross-contamination.

Further information, including a protocol for introducing peanuts, is available from the Australasian Society of Clinical Immunology and Allergy: **www.allergy.org.au/images/**

stories/pospapers/ASCIA_HP_guide_introduction_peanut_infants_2017.pdf

National and international position statements on the suitability of plant-based diets for children

New Zealand's Ministry of Health Healthy Eating Guidelines for Babies and Toddlers (2021)[10] and Food and Nutrition Guidelines for Healthy Children and Young People (2012, revised 2015)[3] defer to the position of the American Academy of Nutrition and Dietetics, which is that well-planned plant-based diets can meet nutritional needs and are suitable for all life stages, including infants and young children.[5] The Academy notes the increased protein requirements for young children provided with vegan diets and that vegans require vitamin B12 from fortified foods or supplements.[4, 5]

European organisations are more cautionary in their recommendations. In a 2017 statement on complementary feeding (introducing solid foods to infants) the European Society for Paediatric Gastroenterology, Hepatology and Nutrition emphasised that while vegan diets can theoretically meet infant nutrient requirements, receiving inadequate advice or failing to follow advice has severe consequences and parents choosing to provide a vegan diet for infants should receive regular medical and dietetic monitoring and follow appropriate nutritional advice.[12] Position statements released from individual European countries since largely reflect this stance,[4] however, in 2019 the French-Speaking Paediatric Hepatology, Gastroenterology and Nutrition Group stated a vegan diet is "*not recommended for infants, children, and adolescents due to the risk of multiple nutritional deficiencies that are inevitable in the absence of supplements*".[6]

Assessing the health of infants and children following plant-based diets

All infants and young children should have their growth and development assessed periodically. In many instances, this will occur routinely when attending general practice for childhood immunisations, opportunistically when presenting with an illness or during a Well Child/Tamariki Ora visit. Ensure parents/caregivers are asked about the child's diet and document any dietary preferences or exclusions in the clinical notes. Checking with parents or caregivers about their understanding of the nutritional requirements of a vegetarian or vegan diet is important, particularly for nutrients that are harder to obtain from plant-based diets, e.g. iron, zinc, vitamin B12 (Table 2).[3, 17]

Growth assessment of infants and young children (birth to age five years) is based on the New Zealand-World Health Organization (NZ-WHO) Growth Charts (see: **www.health.govt.nz/our-work/life-stages/child-health/well-child-tamariki-ora-services/growth-charts**); for older children, use the WHO Reference 2007 (**www.who.int/tools/growth-reference-data-for-5to19-years**) or the Centers for Disease Control Growth Charts (**www.cdc.gov/growthcharts/clinical_charts.htm**).[3] Growth velocity should be monitored; if there is deviation from growth running parallel to the centile lines, further investigation is required.[3] It is also important to document if the weight and height (or length in infants) percentiles differ; weight percentile is likely to be lower than the height (or length) percentile if there are nutritional issues.[18]

Reaching developmental milestones within the expected timeframe is a good indicator of a child's health and wellbeing. Nutrient deficiencies can result in developmental delay, therefore, diet should be considered in all infants and young children, particularly in those presenting with neurological abnormalities or faltering growth (previously referred to as failure to thrive).[19]

If there are concerns that the child is malnourished or not meeting developmental milestones, discuss with a dietitian and recommend dietary changes or supplementation as appropriate (see: "Infant feeding recommendations"). Arrange follow-up appointments to monitor effectiveness.

A description of developmental milestones by age is available here: **www.cdc.gov/ncbddd/actearly/milestones/index.html**

Infant feeding recommendations

Infants who are breastfed by a mother following a plant-based diet

Breast milk should be the only source of nutrition for breastfed infants until around age six months and continued until at least age one year.[10] Infants who have been transitioned to a plant-based diet should ideally continue to be breastfed for at least two years or longer to help bolster their nutritional intake.[10]

Mothers who follow a balanced vegetarian or vegan diet can produce breast milk that is nutritionally adequate and similar to that of non-vegetarian/vegan mothers.[23, 24] Discuss with mothers who follow plant-based diets who are breastfeeding how they are managing to include adequate nutrients in their diet. Food sources of nutrients should be encouraged before considering supplementation (Table 2), unless otherwise indicated, e.g. all breastfeeding women should routinely have iodine supplementation regardless of their diet.[10]

Supplementation advice for the mother

Vitamin B12. Vitamin B12 supplementation is recommended for breastfeeding mothers who follow a vegan diet, in addition to consuming vitamin B12-fortified alternatives (e.g. cereals,

Summary of recent studies on vegetarian and vegan diets in children

Table 1 describes three recent studies investigating the effect of plant-based diets on growth and nutrient levels in children. The evidence is limited and based on relatively small studies.

Table 1: Summary of recent international studies on vegetarian and vegan diets in children.[13, 14, 15]

Reference	Study design	Country	Number and age of participants	Key findings
Growth, body composition, and cardiovascular and nutritional risk of 5- to 10-year-old children consuming vegetarian, vegan or omnivore diets Desmond MA, Sobiecki JG, Jaworski M, *et al*.[13]	Cross-sectional	Poland	N = 187 (63 vegetarians, 52 vegans, 72 omnivores) Age 5 – 10 years	In comparison to omnivores: ■ **Vegetarian** children had similar total fat and lean mass, lower bone mineral density that was accounted for by smaller body size. Total cholesterol, HDL, and serum B12 and 25-hydroxyvitamin D [25(OH)D] were lower and glucose, VLDL and triglycerides were higher. ■ **Vegan** children had lower fat mass but similar lean mass, lower bone mineral content*, vegan children were shorter† and had lower total LDL and HDL, C-reactive protein, iron and serum B12 and 25(OH)D and higher homocysteine and mean corpuscular volume. Vitamin B12 deficiency, iron-deficiency anaemia, low ferritin, and low HDL were more prevalent while high LDL was less prevalent.
Vegan diet in young children remodels metabolism and challenges the statuses of essential nutrients Hovinen T, Korkalo L, Freese R, *et al*.[14]	Cross-sectional	Finland	N = 40 (10 vegetarians, 6 vegans**, 24 omnivores) Median age 3.5 years	■ No differences in height, BMI or mid-upper arm circumference between the different diet groups; intake of vitamins B12 and A was similar between the groups, and most participants, including all vegan children, took vitamin D supplements ■ **Vegetarian** children had lower saturated fatty acids and cholesterol and higher folate and iron than omnivorous children ■ **Vegan** children had lower intake of protein and saturated fatty acids, and higher intake of mono- and polyunsaturated fatty acids, fibre, folate, zinc and iron than omnivorous children; vegan children had very low cholesterol levels, borderline vitamin D level and insufficient vitamin A status (despite adequate estimated intake)
Nutrient intake and status of German children and adolescents consuming vegetarian, vegan or omnivore diets: results of the VeChi youth study Alexy U, Fischer M, Weder S, *et al*.[15]	Cross-sectional	Germany	N = 401 (149 vegetarians, 115 vegans, 137 omnivores) Age 6 – 18 years old, mean 13 years	■ Total energy intake did not vary between groups ■ Carbohydrate intake was higher in vegetarians and vegans than omnivores ■ Median protein intake was lowest in vegetarians, but all groups exceeded the daily reference value ■ Haemoglobin, vitamins B2 and D3, and HDL and triglycerides did not differ between groups ■ Ferritin concentrations were lower in vegetarians and vegans than omnivores

* May be explained by inadequate supplementation of vitamins D and B12[16]

† Height was still in the normal range and the height of the children's parents were not reported[16]

** Vegan children had been following a vegan diet since birth and had been breastfed by vegan mothers. Vegan children had been weaned at least one year prior to the study.

plant-based milk alternatives, yeast spreads).[5, 25] Vitamin B12 can be administered by intramuscular injection (funded) or orally (not funded – available over-the-counter [OTC]*). Injectable treatment provides more rapid improvement and should be considered for those with severe deficiency or neurologic symptoms.[26]

* Ensure patients check the product they are using – many OTC "B-complex vitamins" do not contain B12

Iron. Iron supplementation is not required for mothers who are breastfeeding unless they are deficient and unable to increase their intake through dietary sources.

Vitamin D. Vitamin D supplementation is not routinely recommended for breastfeeding mothers unless they are deficient or at risk of deficiency and cannot safely increase their sun exposure or achieve adequate intake by consuming vitamin D fortified foods. For further information, see: **www.health.govt.nz/your-health/pregnancy-and-kids/first-year/helpful-advice-during-first-year/vitamin-d-and-your-baby**

Infants who are formula fed

For infants who are not breastfed or who require a formula top-up after breastfeeding, the Ministry of Health recommends that a commercially prepared cows' milk-based infant formula should be the only other source of nutrition until around age six months and continue until at least age one year. Although cows' milk is not part of a vegan diet, it is strongly encouraged that vegan infants who are fully or partly formula fed should receive a cow's milk-based formula, and ideally continue use until age two years.[10] Commercially prepared cows' milk-based formulas are fortified with all essential nutrients required to support healthy growth; consumption of at least 500 mL of infant formula daily should provide infants with adequate vitamin D intake if it is not achieved via incidental sun exposure.[10] If use of cows' milk formula is not acceptable, a commercially prepared soy-based formula can be considered, but is generally only recommended in infants aged over 12 months and should not be given to infants aged under six months;[10] parents should discuss use of a soy-based formula with a medical practitioner or dietitian.

Guidance for introducing solids to infants

Iron stores deplete at around age six months

The natural depletion of iron (and zinc) stores in infants at around age six months alongside increased demands of growth means that another source of nutrition is required in addition to breast milk or formula.[10] The Ministry of Health recommends introducing solid foods (referred to as complementary feeding) at around age six months.[10] Given that iron is not absorbed as effectively from plant-based sources, children following these diets may need to consume larger quantities of iron-containing foods (Table 2).[3] Routine iron supplementation is not recommended for otherwise healthy children of normal birth weight and growth.[10]

Larger volumes of food are required in plant-based diets to meet energy requirements

Young children require a higher overall intake of nutrient dense foods than adults for growth and energy. Given that children have a smaller stomach capacity, small frequent meals are the best way to meet their energy requirements, rather than infrequent large meals.[3] If the diet excludes energy dense animal products, a larger volume of food may be required to meet energy requirements (Table 2); this volume can exceed the point where a child is satisfied, increasing the risk of inadequate energy intake.[10] Including some animal products in the diet, such as eggs and dairy products, and including more refined grains, e.g. white flour and white rice, may help children to meet their energy requirements, without the bulk of a high fibre diet.[3]

For further examples of nutrient dense foods that should be offered regularly to infants on a plant-based diet, see: **www.health.govt.nz/publication/healthy-eating-guidelines-new-zealand-babies-and-toddlers-0-2-years-old**

Alternative "milks"

Alternative "milk beverages", such as rice, oat or almond milk, or home-made formulas derived from these products are nutritionally inadequate and therefore not recommended as a substitute for breast milk or cows' milk or soy protein-based formulas in infants.[10] In children aged over one year, full fat cows' milk or soy milk fortified with vitamin B12 and calcium are appropriate milk options.[3, 10] At age two years, low-fat cows' milk or soy milk are acceptable provided a child's growth is tracking normally.[3] Rice, oat, almond or coconut milk should not be the main milk option for children aged under five years,[3] but can be considered as a complementary food from age 12 months onwards.

Table 2. Key nutrition points to guide discussions with the parents or caregivers of children following a plant-based diet.[3, 5, 10, 20]

Nutrient	Source	Notes and recommendations
Iron	Predominantly sourced from meat, poultry or seafood. Potential sources in plant-based diets include iron-fortified cereals and cooked and pureed/mashed broccoli, peas, lentils and chickpeas. Phytic acid, found in nuts, seeds, grains, rice, soybeans and legumes, interferes with iron absorption.	■ Plant sources are not as readily absorbed so the volume of iron-containing foods needed is approximately double that of non-vegetarians ■ Iron deficiency anaemia (or macrocytic anaemia, e.g. due to vitamin B12 deficiency) should be considered in infants or children with signs of anaemia, e.g. pale skin, conjunctiva and fingernails, and tachycardia (indicative of more severe anaemia) ■ Vitamin C rich foods should be offered alongside iron to enhance absorption ■ Children should not be given tea or coffee as the tannins inhibit non-haem iron absorption
Vitamin B12	Found naturally only in animal products, including dairy and eggs. Plant-based milks such as soy, yeast-extracts and cereals can be fortified with vitamin B12.	■ Vitamin B12 deficiency is of particular concern in infants and children with vegan diets because animal products are the most reliable dietary sources. Early symptoms and signs of severe B12 deficiency include faltering growth in young children, fatigue, tingling sensation in the extremities and poor cognition. Some of these symptoms and signs may be difficult to identify in young children. ■ Supplementation should be considered routine for vegan children who are no longer breastfed (see: "Infant feeding recommendations")
Vitamin D	Predominantly sourced from exposure to sunlight. Vitamin D2 (ergocalciferol) and D3 (colecalciferol) can be fortified in foods including alternative milks and margarine.	■ It is difficult to achieve adequate vitamin D levels from diet alone; supplementation is usually not required unless adequate levels cannot be achieved via sun exposure or consumption of vitamin D fortified foods ■ Vitamin D deficiency is often asymptomatic, but can manifest as rickets with clinical features such as swelling of the wrists and ankles, leg deformities, delayed tooth eruption, delayed fontanelle closure or motor development, poor growth and symptoms of hypocalcaemia (tetany, stridor or seizures)[21]
Calcium	Found in dairy products, legumes, some vegetables. Absorption is enhanced by adequate vitamin D and protein intake. Phytic acid and oxalic acid interferes with calcium absorption. Oxalic acid is found in spinach and other leafy greens, beans and brassicas, e.g. cabbage and Brussels sprouts.	■ Calcium-fortified alternatives, e.g. soy milk, may be required for children who do not consume cow's milk
Zinc	Predominantly sourced from meats and seafood. Phytic acid interferes with zinc absorption.	■ Plant sources are not as readily absorbed so the volume of zinc containing foods needed is 1.5 times more than non-vegetarians
Alpha linolenic acid (omega-3)	Long-chain omega-3 fatty acids docosahexaenoic [DHA] and eicosapentaenoic acid [EPA] are naturally found in seafood, eggs and red meat, but can be synthesised from plant-based α-linolenic acid in flaxseed oil, canola oil, chia seeds, walnuts and soybeans	■ Plant-based diets can be higher in linoleic acid (omega-6 fatty acid, found in plant oils, e.g. sunflower oil), which may then compete for the enzyme that converts α-linolenic acid to DHA and EPA; a ratio of no more than 4:1 of linoleic acid to α-linoleic acid is recommended ■ DHA supplementation may be required (see: "Guidance for introducing solids to infants")

Continued on next page

Iodine	Good sources include fish, meat, eggs and milk. Dried seaweeds are the main plant-based source (excluding kelp as the iodine content is too high for children); iodised salt is another source assuming it is consumed within recommended daily limits.	■ Vegan children are at increased risk of iodine deficiency as the best sources are from animals and their products ■ Children eating a plant-based diet should not receive large amounts of iodised salt to compensate; instead, supplementation may be required in cases of deficiency (see: "Guidance for introducing solids to infants")
Protein	Can be obtained from a wide range of foods. Plant-based protein sources include whole foods, such as beans, grains, nuts and seeds and green leafy vegetables.	■ Protein requirements increase as children get older; pre-school children require at least one to two servings of protein per day, school aged children require at least two servings and adolescents require three to four ■ Most children (and adults) in New Zealand have a dietary protein intake that exceeds the recommended minimum;[22] assuming a plant-based diet includes a variety of whole foods consumed across the day, protein intake is unlikely to be an issue[23]

N.B. Nuts are a choking hazard and should not be given whole until age five years; ground nut pastes can be given (and are encouraged) from age six months.

Patient information on the nutrient content of different foods is available from the New Zealand Nutrition Foundation: **nutritionfoundation.org.nz/**

The recommended daily intake of various nutrients and the nutrient content of foods is available from:

- Nutrient reference values: **www.nhmrc.gov.au/sites/default/files/images/nutrient-refererence-dietary-intakes.pdf**
- New Zealand food composition database: **www.foodcomposition.co.nz/downloads/concise-13-edition.pdf**

Supplementation advice for children following a plant-based diet

Vitamin B12. Ensuring adequate intake of vitamin B12 is particularly important for people following vegan diets as the main sources, i.e. animal products, are excluded. While incorporating vitamin B12-fortified foods into the child's diet should be encouraged, routine supplementation is recommended if they are no longer breastfed as it is the most reliable way of ensuring adequate intake – investigating serum B12 levels is not necessary.[23] There is limited evidence to guide selection of vitamin B12 for oral supplementation in children (not funded):

- Most studies use cyanocobalamin,[27] but this form is less likely to be found in individual vitamin B12 supplements
- Methylcobalamin and adenosylcobalamin are active forms of vitamin B12 that are commonly found in supplements; these do not appear to be more effective than cyanocobalamin.[5] A chewable tablet or sublingual form is recommended to increase absorption – the B12 binding protein in saliva helps transport vitamin B12 through the digestive tract.[27, 28]

Intramuscular vitamin B12 hydroxocobalamin (fully funded and available on a Practitioner's Supply Order) is indicated for the prevention and treatment of macrocytic anaemia associated with vitamin B12 deficiency, which is uncommon in children and usually due to an underlying cause, e.g. malabsorption, rather than dietary deficiency alone.[29]

Iodine, alpha linolenic acid (omega-3) and vitamin D. Iodine and DHA supplementation may be required if adequate intake cannot be achieved through dietary sources (Table 2).[30] Vitamin D supplementation is generally not required unless adequate levels cannot be achieved via sun exposure or consumption of vitamin D fortified foods.[13]

Further information on vegetarian and vegan diets for parents/caregivers is available from:

- HealthEd – Eating for Healthy Vegetarians/Ngā kai tōtika mā te hunga puku-huawhenua: **www.healthed.govt.nz/resource/eating-healthy-vegetariansng%C4%81-kai-t%C5%8Dtika-m%C4%81-te-hunga-puku-huawhenua**
- New Zealand Vegetarian Society: **www.vegetarian.org.nz**
- KidsHealth: **www.kidshealth.org.nz/healthy-eating-habits-vegetarian-diet-babies-children**
- Health Navigator: **www.healthnavigator.org.nz/healthy-living/v/vegetarianism-veganism/**

For general information to support health practitioners "teach" patients about plant-based diets, see: **www.doctorsfornutrition.org/professionals**

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Diagnosing and managing **lactose intolerance**

Primary lactase deficiency, the main cause of lactose intolerance, is estimated to affect 8% of people in New Zealand, with substantially higher rates among Māori, Pacific and southeast Asian peoples. Initial treatment is to avoid or minimise foods containing lactose in the diet, followed by a gradual reintroduction after symptoms settle. Lactose intolerance should not be mistaken for an allergy to milk.

KEY PRACTICE POINTS:

- Most lactose intolerance is due to primary lactase deficiency which is genetically determined; secondary lactase deficiency is transient and occurs mainly as a result of gastrointestinal illness
- Lactose intolerance can usually be diagnosed through dietary challenge, i.e. the return of symptoms following reintroduction of milk and milk products after an elimination period
- Lactose intolerance is initially treated by minimising or avoiding lactose-containing foods, however, most people can eventually tolerate one to two glasses of milk daily, if consumed in small portions with food
- People with primary lactase deficiency should be encouraged to gradually and regularly increase their intake of lactose-containing foods until a level of tolerance is achieved
- Infants with lactose intolerance can continue to be breastfed without altering the mother's diet
- Lactose intolerance is not a cows' milk protein allergy, which is an immune-mediated reaction, often distinguished by more severe gastrointestinal symptoms (including rectal bleeding), eczema and urticaria; it is managed by removal of all dairy products from the diet

What is lactose intolerance?

Lactose is a disaccharide naturally found in dairy products including milk, yoghurt, cream, chocolate, ice cream and cheese.[1] It can also be used as a flavour enhancer in processed foods such as potato chips, crackers, margarine and bread.[2]

Lactose malabsorption. Approximately 70% of the world's population aged ten years or older is affected by lactose malabsorption, i.e. the failure to absorb lactose in the small intestine due to lactase deficiency or other intestinal pathology, with most causes being genetically determined (see: "There are four types of lactase deficiency").[2, 3] People from Middle Eastern countries (70%), Asia (64%) and Africa (63 – 65%) have higher rates of lactose malabsorption, while lower rates are reported in Eastern Europe, Russia and former Soviet Republics (47%), Northern America (42%) and Northern, Western and Southern European countries (28%).[3] Within Asia, the prevalence of lactose malabsorption is estimated to range considerably; from 58% in Pakistan to 100% in South Korea.[3] Both males and females are affected equally worldwide.[4]

Lactose intolerance. When lactose malabsorption, i.e. the inability to digest lactose, causes gastrointestinal symptoms it is referred to as lactose intolerance (see: "Gastrointestinal symptoms characterise lactose intolerance").[2] Many people with lactose malabsorption will not develop lactose intolerance.[2] The likelihood of developing symptoms depends on the amount of lactose ingested, whether lactose is eaten with other foods that affect transit through the intestine to the colon, the amount of lactase expression in the small intestine, composition of the microbiome and history of gastrointestinal disorders or surgery.[2]

The estimated prevalence of lactose intolerance in New Zealand.

The prevalence of lactose intolerance is more difficult to estimate than lactose malabsorption as studies mainly rely on self-reported symptoms during a lactose challenge, which are rarely blinded; self-reported lactose intolerance has a sensitivity of 30 – 71% and specificity of 25 – 87%.[2, 5] Of the limited New Zealand data available, an increased prevalence of lactose malabsorption in Māori and Pacific peoples has been observed compared to New Zealand Europeans, based on breath hydrogen testing (see: "Laboratory tests have a limited role in diagnosing lactose intolerance in New Zealand").[6, 7] A study conducted in Christchurch in 2010 found that the overall prevalence of primary lactose intolerance determined by genetic testing was 8% (among 1,064 participants); of the 30 Māori and Pacific participants, the prevalence was 30%.[8]

There are four types of lactase deficiency that can result in lactose intolerance

Primary lactase deficiency is the most common cause of lactose intolerance (sometimes referred to as lactase non-persistence or adult or late-onset lactose intolerance).[2] Lactase concentrations reach their peak around the time of birth in most people, and decline after the usual age of weaning.[2, 9] The timing and rate of this decline is genetically determined.[10] Onset of primary lactase deficiency is typically subtle and progressive over several years, with most people diagnosed in late adolescence or adulthood.[2, 9, 10] However, acute development is also possible.[10]

Secondary lactase deficiency (also referred to as acquired lactase deficiency) is transitory and can occur after a gastrointestinal illness that alters the intestinal mucosa resulting in reduced lactase expression.[2, 11] Secondary lactase deficiency is common in children after rotaviral (and other infectious) diarrhoea. Giardiasis, cryptosporidiosis and other parasitic infections of the proximal small intestine often lead to lactose malabsorption.[9] Secondary lactase deficiency may also occur with coeliac disease, inflammatory bowel disease, small intestinal bacteria overgrowth, cows' milk protein allergy (CMPA)-induced enteropathy and immune-related illnesses such as HIV.[9] In addition, some medicines can cause villous atrophy resulting in secondary lactase deficiency, e.g. aminoglycosides, tetracyclines, colchicine, chemotherapy treatments.[12] Secondary lactase deficiency usually resolves after one to two months but may be permanent if caused by a long-term condition.

Developmental lactase deficiency (neonatal) occurs in premature infants.[9] This condition is usually temporary and rapidly improves as the intestinal mucosa matures.[9] Lactase and other disaccharidases are deficient until after 34 weeks gestation.[9]

Congenital lactase deficiency (alactasia) is a life-long genetic condition involving the complete deficiency of lactase expression from birth, despite the person having an otherwise normal intestinal mucosa.[2] Alactasia is extremely rare; it has been diagnosed in fewer than 50 people worldwide.[2, 9]

Gastrointestinal symptoms characterise lactose intolerance

In general, the symptoms of lactose intolerance are often non-specific, mild and vary between individuals.[2, 11] Symptoms usually occur between 30 minutes and a few hours after the ingestion of lactose.[13] The severity of symptoms is influenced by the degree of lactase deficiency and the amount of lactose consumed; typically the more lactose consumed, the more

frequent or severe the symptoms.[13] In children, diarrhoea is often more pronounced, particularly those with secondary lactose deficiency.[9]

Symptoms result from two main causes (see: "Pathophysiology of lactase deficiency"):[2]

1. **Undigested lactose acting as an osmotic laxative** (diarrhoea, abdominal pain)
2. **Intestinal bacteria using lactose as a growth substrate**, resulting in production of hydrogen, carbon dioxide and methane gases (flatulence, dyspepsia, abdominal distension or borborygmi [stomach gurgling])

Diagnosis of lactose intolerance

Lactose intolerance is usually diagnosed by dietary challenge

Step 1: Rule out other causes
Step 2: Dietary challenge
Step 3: Further investigation, if dietary challenge inconclusive

Lactose intolerance can be suspected in people who report gastrointestinal symptoms following the ingestion of milk or milk products. An accurate diagnosis is important as it can significantly relieve a person's anxiety and help them to avoid inappropriate investigation and treatment. For people who present in primary care with severe or persistent gastrointestinal symptoms, other potential causes should also be excluded (see: "Differential diagnoses to consider"). In particular, an underlying secondary cause of lactose intolerance should be ruled-out in children, e.g. rotavirus infection, giardiasis or coeliac disease. Self-diagnosis of lactose intolerance is not recommended as it could lead to unnecessary dietary restrictions and expense, lack of essential nutrients and most importantly, failure to detect a more serious gastrointestinal problem; other physiological and psychological factors can contribute to gastrointestinal symptoms that mimic lactose intolerance.[14]

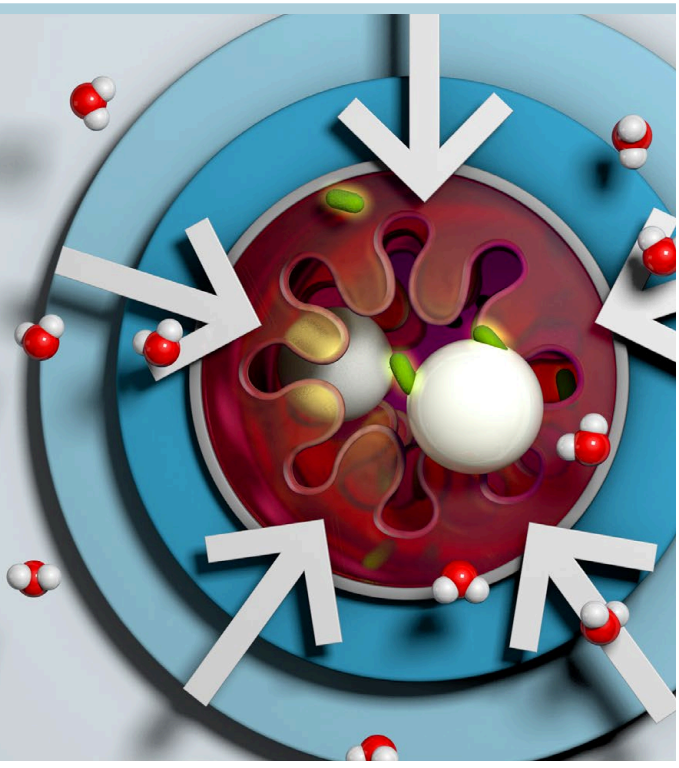
A lactose-free diet should be trialled for two to four weeks when lactose intolerance is suspected.[14] It is important that all sources of lactose are eliminated, so patients should be advised to read food labels carefully to identify "hidden" sources of lactose, which are particularly common in processed foods, e.g. whey, cheese, milk by-products, milk solids, milk powder.[14] Lactose can then be re-introduced to the diet. If symptoms improve during the two to four week period and return when lactose is reintroduced, the diagnosis can be made.[14]

N.B. Some prescription and over-the-counter medicines e.g. oral contraceptive pills and nitrofurantoin (100 mg, modified release), contain a small amount of lactose, but not enough to cause gastrointestinal symptoms in someone with lactose intolerance.[11]

If dietary challenge is inconclusive or self-reported symptoms are unreliable, further investigations may be required. However, laboratory testing for lactose intolerance (see below) will often not provide a definitive diagnosis and the availability of tests throughout New Zealand is variable.

Pathophysiology of lactase deficiency

Lactase is an enzyme produced by cells located in the microvilli of the small intestine which hydrolyses dietary lactose (a disaccharide sugar) into glucose and galactose (monosaccharide sugars) for transport across the cell membrane. In the absence or deficiency of lactase, unabsorbed lactose causes an influx of fluid into the bowel lumen, due to osmotic pressure. Unabsorbed lactose then enters the colon and is used as a substrate by intestinal bacteria, producing gas and short-chain fatty acids via fermentation. The fatty acids cannot be absorbed by the colonic mucosa, therefore more fluid is drawn into the bowel. A proportion of the lactose can be absorbed but the overall result of ingestion is a substantial rise of fluid and gas in the bowel, causing the symptoms of lactose intolerance.[2]



Laboratory tests have a limited role in diagnosing lactose intolerance in New Zealand

Although laboratory testing is often cited in literature to aid in the diagnosis of lactose intolerance, most of these tests are not widely accessible in New Zealand or not publicly funded, and some lack sensitivity and/or specificity. If there is significant uncertainty concerning a diagnosis, consider asking your local laboratory if any additional tests are available, such as:[2, 9, 14]

- **Breath hydrogen test** – measures the level of hydrogen in exhaled air after ingestion of lactose, following overnight fasting. Currently considered the most reliable laboratory method for diagnosing lactose malabsorption (sensitivity is 80 – 90%) but false negatives can occur due to breath hydrogen production associated with other conditions unrelated to lactose digestion, e.g. gut motility disorders. Breath hydrogen testing is usually not possible in young children due to the need for wearing a tight-fitting mask.
- **Lactose tolerance test** – measures blood glucose levels after ingestion of lactose. Less reliable than the breath hydrogen test (sensitivity is 75%). Requires significant adherence and is not suitable for children.
- **Faecal pH test** – non-specific marker for lactose (or other carbohydrate) malabsorption. A pH of < 6.0 suggests lactose intolerance. Because of the high rate of false-negative results, this test is only recommended in infants aged under two years.
- **Faecal reducing substances** – another indirect test for lactose (or other carbohydrate) malabsorption. A positive test suggests an absence of the corresponding enzyme. However, false negatives can occur if the person has not recently ingested lactose.
- **Small bowel disaccharidases** – requires duodenal biopsy in secondary care. This test may occasionally be considered in the context of secondary lactose intolerance where a gastroscopy is being performed to determine an underlying cause (e.g. coeliac disease, Crohn's disease, protracted diarrhoea).
- **Genetic testing for hereditary lactase persistence** – tests for a cytosine (C)/thymine (T) single nucleotide polymorphism upstream of the lactase gene; T/T or C/T genotypes are lactose tolerant, while C/C genotype is lactose intolerant[15, 16]

Do not routinely request skin prick or serum allergen-specific IgE tests as lactose intolerance is not immune mediated. However, these tests may be considered to rule out CMPA if this is suspected.

N.B. There are various online allergy testing services marketed to the public. These are recommended against by the Australasian Society of Clinical Immunology and Allergy (ASCIA) due to the potential for harms from misdiagnosis. The full ASCIA position statement is available here: **www.allergy.org.au/images/stories/pospapers/ASCIA_HP_Evidence-Based_Vs_Non_Evidence-Based_Allergy_Tests_Treatments_2021.pdf**

Differential diagnoses to consider

If a dietary challenge proves inconclusive, alternative diagnoses should be considered, including:[17]

- Irritable bowel syndrome
- Coeliac disease
- Diverticular disease
- Inflammatory bowel disease
- Bacterial infection, e.g. *Clostridium difficile*
- Parasitic disease, e.g. giardiasis
- Cystic fibrosis
- Inadvertent or excessive laxative ingestion, e.g. in products that act as natural laxatives
- Mechanical bowel compromise
- Bowel neoplasm or polyp

Dietary management of lactose intolerance

Lactose does not need to be completely restricted

Step 1: Confirm diagnosis of lactose intolerance
Step 2: Determine how much lactose can be tolerated without symptoms
Step 3: Encourage gradual reintroduction of milk and milk products – this usually improves symptoms and tolerance

The complete avoidance of all lactose-containing foods is not recommended to manage primary lactose intolerance.[1] Instead, people should start with a more restricted diet and gradually increase the consumption of lactose-containing foods according to their individual tolerance level.[18] Consistency is the key to building tolerance; continual exposure often enhances the number and efficiency of colonic bacteria capable of metabolising lactose, thereby producing fewer symptoms.[19] The majority of people, including children, can tolerate up to 5 g of lactose (approximately ½ cup milk) on its own, and up to one to two cups of milk in total per day, when eaten with other foods (e.g. cereal) or spread out across the day.[1, 2] Consuming lactose with meals rather than on an empty stomach slows the release of lactose in the small intestine, and people can experiment to see which foods are more tolerable.[18]

Some lactose-containing foods are better tolerated than others

Better tolerated dairy products include yoghurt with live

culture and hard cheese (especially aged) because the lactose is partially hydrolysed by bacteria during preparation and gastric emptying is slower due to their thicker consistency.[1, 9] Dairy products with a higher fat content or higher osmolality are also better tolerated due to delayed gastric emptying, e.g. ice cream or chocolate milk.[20] Symptoms may be more severe with skim milk (green top) than whole milk due to the higher lactose and lower fat content.[1, 20]

Probiotics may be beneficial for some people

Probiotic supplementation may be beneficial for symptom relief in some people with lactose intolerance by promoting lactose digestion.[21] A 2020 systematic review of randomised controlled trials found an overall positive association between probiotic supplementation and reduced gastrointestinal symptoms of lactose intolerance, although the effect size varied and the quality of evidence was low.[21] Probiotic strains that were shown to be beneficial included *Lactobacillus acidophilus*, *L. reuteri*, *L. rhamnosus* and *L. bulgaricus*, *Streptococcus thermophilus* and *Bifidobacterium longum* (dose range 10^8 – 10^{11} colony-forming units [CFU] per day).[21]

Lactose-free milks and milk alternatives are usually not required

Lactose-free milk or milk alternatives are generally not necessary unless large quantities of milk are consumed, or in the rare case of intolerance to even small amounts of milk (in which case lactose-free foods may also need to be considered). If these alternatives are required, the milk substitutes selected should be fortified with calcium and vitamin D to prevent deficiencies.[22] For children aged under five years, almond, coconut, rice and oat milk alternatives should not be used as the main milk source as they are not nutritionally adequate.[22] Fortified soy milk is recommended if an alternative to cows' milk is required in children. N.B. Soy milk or infant formula is generally not advised in children aged under 12 months (see: "Feeding options for infants").[23]

Maintaining calcium and vitamin D intake when minimising lactose in the diet

Adequate calcium and vitamin D intake are particularly important during childhood and adolescence for optimal peak bone mass.[24] People with lactose intolerance should continue to have at least two servings of milk or milk products daily if tolerated in multiple small doses or with food.[22] If this is not possible, calcium-fortified milk or fortified milk substitutes should be considered as tolerated, and the diet should be supplemented through intake of non-dairy calcium-rich food, e.g. bony fish, tofu, dark green leafy vegetables and nuts and seeds.[1, 22] As sunlight is the primary source of vitamin D, all people should be advised to take a daily walk or other form of outdoor activity.[25]

Lactose intolerance is NOT an allergy to milk

In cows' milk allergy, children are allergic to the protein in milk.

CMPA is one of the most common food allergies in young children (prevalence of 2 – 3% of children before age three years).[29] The prevalence in adults is much lower (approximately 0.5%).[30] CMPA is reported to resolve in approximately half of children before age 12 months, and in up to 90% by age five years.[31]

There are two types of clinical manifestation of CMPA:[29]

- **IgE-mediated** (Immediate): Symptoms usually develop within minutes to one hour after ingestion of cows' milk. Symptoms include eczema, urticaria, rhinitis, cough, wheezing, abdominal pain, vomiting, diarrhoea. Life threatening anaphylaxis is possible but rare.
- **Non-IgE mediated** (Delayed): Symptoms typically occur more than two hours or even days following ingestion of cows' milk. Symptoms include vomiting, diarrhoea, blood in stools, with or without eczema.

Differentiating between lactose intolerance and CMPA:

- CMPA can manifest during breastfeeding (due to cows' milk ingested by the mother), in an infant on a cows' milk-based formula or shortly after weaning. Lactose intolerance is usually seen after age two years.
- Infants with lactose intolerance may safely breastfeed without the need for any maternal dietary modification, but mothers may need to remove dairy products from their diet if their infant is diagnosed with CMPA
- Children with lactose intolerance can usually tolerate small amounts of dairy products, whereas in milk allergy, small traces usually cause symptoms. N.B. IgE mediated CMPA reactions typically have a more rapid onset than non-IgE-mediated reactions or symptoms of lactose intolerance.[29]
- Differentiation is usually possible based on clinical symptoms

For further detail on the diagnosis and management of CMPA, see "Managing cows' milk protein allergy in infants", available from: **bpac.org.nz/2019/cmpa.aspx**

Lactase enzymes may be helpful alongside dietary management

Lactase enzyme supplements (available over-the-counter, not funded) should be considered as an adjunct, not a substitute for dietary management; if dairy products can be tolerated in small amounts, enzyme supplements are unnecessary.[2] Enzyme supplements may not completely relieve symptoms and it is difficult to determine the effective dose.[2]

Feeding options for infants with lactose intolerance

In general, infants with lactose intolerance should continue breastfeeding.[9] Breastfeeding mothers do not have to eliminate lactose containing foods from their diets; the amount of lactose present in breastmilk is largely independent of maternal consumption.[9] Formula-fed infants may initially require a lactose-free formula, but reintroduction of lactose containing formula or foods should be trialled after two to four weeks, as tolerated.[9] In New Zealand, lactose-free and soy milk infant formulas are available from supermarkets and pharmacies (not funded). Ongoing use of soy formula in infants aged under 12 months is generally not recommended, but could be considered in infants aged over six months if they are unable to tolerate adequate quantities of cows' milk formula.[23] Lactose-free infant formula can be used in infants from birth.[26]

N.B. For guidance on feeding for infants with CMPA, see: **bpac.org.nz/2019/cmpa.aspx**

Clinician's Notepad: lactose intolerance

If a person reports gastrointestinal symptoms that consistently occur following the ingestion of milk or milk products

- First rule out other possible causes of symptoms – particularly if symptoms are severe or persistent, e.g. irritable bowel syndrome, inflammatory bowel disease
  - Secondary causes should be strongly considered in children, e.g. rotavirus infection, giardiasis or coeliac disease
- If there is no other obvious cause, a lactose-free diet should be trialled for two to four weeks; ensure the patient is aware of "hidden" sources of lactose which are common in processed foods
- At the end of the trial, the patient should re-introduce lactose; if symptoms have improved during the trial and return when lactose is reintroduced, then this is sufficient to diagnose lactose intolerance
  - Do not routinely request skin prick or serum allergen-specific IgE tests unless cows' milk protein allergy is suspected as lactose intolerance is not immune-mediated
- If the dietary challenge is inconclusive or there is uncertainty, discuss with your local laboratory whether additional testing is available, e.g. breath hydrogen testing, or consult with a secondary care clinician

Management of lactose intolerance

- Lactose usually does not need to be excluded from the diet; people should start with a more restricted diet and gradually increase the consumption of lactose-containing foods according to individual tolerance level
  - Most people can tolerate up to 5 g of lactose (approximately ½ cup milk) on its own, and up to one to two cups of milk in total per day, when eaten with other foods or spread out across the day
- Some lactose-containing foods are better tolerated than others, e.g. yoghurt with live culture or dairy products with higher fat content
- Lactose-free milks and alternative milks are usually not required but if used (or if sufficient quantities of cow's milk cannot be consumed) must be fortified with calcium and vitamin D to meet the recommended intake
- Probiotics or lactase enzyme supplements (not funded) may be beneficial for some people alongside dietary management, however, these are not routinely required and efficacy varies
- Infants with lactose intolerance should continue breastfeeding and the mother does not need to eliminate lactose from her diet; lactose-free infant formulas are available, if required
- A temporary lactose-free diet may be beneficial for people with secondary lactose intolerance, e.g. following a bout of infectious diarrhoea, to promote recovery from the primary illness

Managing secondary lactose intolerance

Short periods of lactose intolerance are common in children following infectious diarrhoea.[27] In infants aged under three months or malnourished children, this may negatively influence recovery from the primary illness.[28] A meta-analysis of clinical trials found that a lactose-free diet in non-breastfed infants may reduce the duration of diarrhoea by up to 18 hours.[27] Diluting lactose-containing milk has not been shown to resolve diarrhoea earlier compared to undiluted milk (low quality evidence).[27] Breastfed infants with temporary lactose intolerance can continue to safely breastfeed.[9]

In general, treatment of the cause of the secondary lactase deficiency will lead to restoration of lactase activity.[9] Therefore, a lactose-free diet is usually only required temporarily until secondary lactase deficiency resolves.

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N.B. Expert reviewers do not write the articles and are not responsible for the final content. bpac^{nz} retains editorial oversight of all content.

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This article is available online at:
www.bpac.org.nz/2021/lactose-intolerance.aspx

eBPJ 3 quiz

This CME quiz is designed to be completed after reading the following articles in eBPJ3*:

- Gabapentinoids: when and how should they be prescribed?
- Urinary tract infections (UTIs) – an overview of lower UTI management in adults
- MMR vaccination remains a priority
- Plant-based diets: are they healthy for a child?
- Diagnosing and managing lactose intolerance

* CME points can also be obtained for reading articles if a RNZCGP Learning Reflection form is completed for each one. For more information about claiming CME points, see: **bpac.org.nz/cme.aspx**

Complete this quiz here: **https://bpac.org.nz/Mybpac/quiz**

Question 1: Gabapentinoids

Which of the following statements about considering gabapentinoids as a treatment for pain are true?

- ☐ Gabapentin and pregabalin are the only first-line medicines recommended for neuropathic pain
- ☐ Before trialling a gabapentinoid, consider other possible treatments for neuropathic pain, e.g. non-pharmacological strategies
- ☐ Gabapentinoids are a recommended treatment option for people with non-specific low back pain or sciatica
- ☐ Gabapentinoids are effective for peripheral diabetic neuropathy
- ☐ Gabapentin and pregabalin are more effective than amitriptyline for neuropathic pain

Question 2: Gabapentinoids

Which of the following statements about the prescribing and monitoring of gabapentinoids are true?

- ☐ Lower doses of gabapentin and pregabalin may be required for older people with frailty
- ☐ The risk of misuse is reportedly higher in people taking gabapentin compared to those taking pregabalin
- ☐ If patients report a partial response to treatment and pain remains problematic, consider adding an additional first-line neuropathic pain medicine to their regimen
- ☐ Consider monthly treatment reviews for patients taking a gabapentinoid with a history of misuse
- ☐ The rate of gastrointestinal transit is increased with concurrent use of gabapentin and an opioid

Question 3: UTI

A 60-year-old female has symptoms indicative of an uncomplicated UTI, nitrite positivity on dipstick, and has not had a UTI previously. Which **one** of the following management strategies is the most appropriate?

- ☐ Prescribe a NSAID instead of an antibiotic
- ☐ Request sensitivity analysis of the urine sample to refine antibiotic selection before prescribing
- ☐ Prescribe nitrofurantoin as an empiric treatment
- ☐ Prescribe amoxicillin clavulanate as an empiric treatment
- ☐ Prescribe an antibiotic in combination with citrate sodium anhydrous + citric acid anhydrous + sodium bicarbonate + tartaric acid (Ural)

Question 4: UTI

Which of the following statements regarding recurrent UTIs are true?

- ☐ If recurrence occurs rapidly, it is usually caused by a different bacterial strain
- ☐ There is no evidence that cranberry products are effective for UTI prophylaxis
- ☐ *Lactobacillus* containing probiotics can be effective at reducing the risk of UTI recurrence for some people
- ☐ Low-dose antibiotic prophylaxis is recommended for most women who experience a second UTI within six months of their first
- ☐ Methenamine hippurate (Hiprex) is an appropriate alternative form of antimicrobial prophylaxis to avoid long-term antibiotic use

Question 5: MMR

Which of the following statements regarding MMR vaccine scheduling are true?

- ☐ Changes to MMR dose scheduling has contributed to the known immunity gap, particularly amongst adolescents and young adults aged between 15 and 30 years
- ☐ Infants aged between six and 11 months who receive a single dose of MMR0 [zero] for early protection only require one further MMR dose for full immunity
- ☐ Catch-up doses of MMR are fully funded
- ☐ People born in New Zealand before 1 January, 1969, are considered susceptible to measles and require two doses of the MMR vaccine
- ☐ Following the 2019 measles outbreaks, the National Immunisation Schedule now recommends that the first MMR dose be given at age 12 months

Question 6: MMR

Which of the following statements about MMR vaccination are true?

- [ ] A clinical history of measles, mumps, or rubella alone reliably indicates an immunity against the disease
- [ ] People working in residential care facilities are at higher risk of infection
- [ ] People with uncertain or undocumented vaccination history should not receive MMR vaccination due to safety concerns
- [ ] MMR can be given to women who are breastfeeding but is contraindicated during pregnancy
- [ ] Rubella cases in New Zealand have remained low and the risk of fetal infection and congenital rubella syndrome remain equally low

Question 7: Plant-based diets

Which of the following statements regarding the nutritional content of plant-based diets are true?

- [ ] Iron is absorbed better from animal sources than plant-based sources
- [ ] Phytic acid can enhance the absorption of many important nutrients
- [ ] Iodine can readily be obtained through the consumption of leafy green vegetables
- [ ] Children eating a plant-based diet need to consume approximately 1.5 times more zinc-containing foods than children who eat a diet containing meat
- [ ] Vitamin B12 is only found naturally in animal products

Question 8: Plant-based diets

Which of the following advice is appropriate to give parents of children following a plant-based diet?

- [ ] Home-made infant formulas can be a suitable replacement for commercial cows' milk-based formula if the infant is not breastfed
- [ ] Plant food allergens should generally be avoided before age 12 months
- [ ] Dietary sources of nutrients should be encouraged over supplementation
- [ ] Iron supplementation is not generally required for children following plant-based diets
- [ ] Increasing refined grain consumption can help the child meet energy demands

Question 9: Lactose intolerance

Which of the following statements regarding lactose intolerance and its diagnosis are true?

- [ ] Many people with lactose malabsorption do not develop lactose intolerance
- [ ] Secondary causes of lactose intolerance are uncommon in children
- [ ] If lactose intolerance is suspected, a lactose-free diet should be trialled for two to four weeks
- [ ] Laboratory investigation is necessary to diagnose lactose intolerance
- [ ] Referral for skin prick or serum allergen-specific IgE tests should be requested to support a diagnosis of lactose intolerance

Question 10: Lactose intolerance

Which of the following statements regarding the management of lactose intolerance are true?

- [ ] Infants with primary lactose intolerance can safely be breastfed without any alteration to the mother's diet
- [ ] A fortified soy-based formula can be used as the main milk option in infants of any age with primary lactose intolerance if they are not breastfed
- [ ] Diluting milk may help symptoms resolve more rapidly in children with secondary lactose intolerance
- [ ] Most adults with primary lactose intolerance need to eliminate dairy from their diet
- [ ] Some lactose-containing foods are better tolerated than others

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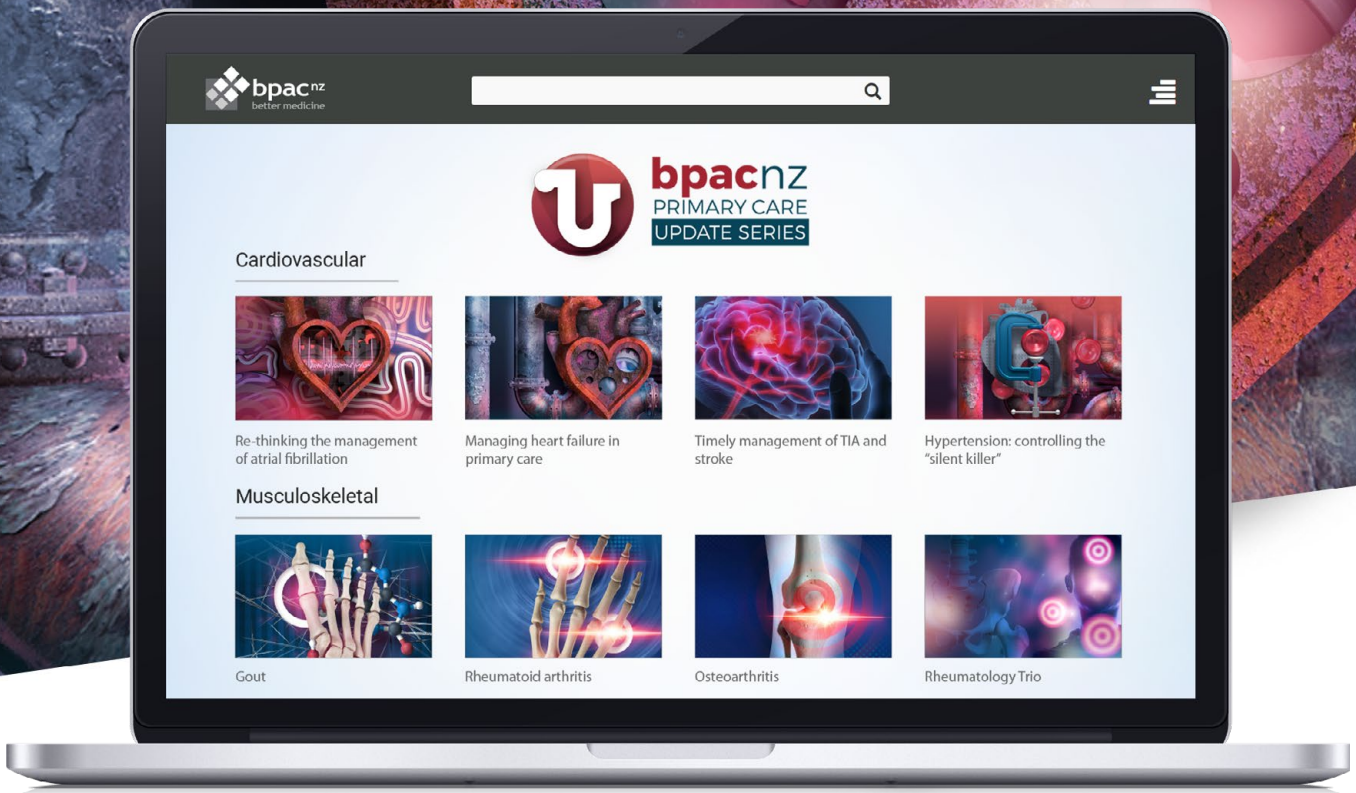

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