
VITAMIN D & CALCIUM SUPPLEMENTATION | AXIAL SPONDYLOARTHRITIS | PPIs & ACUTE KIDNEY INJURY
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Prescribing newly-subsidised medicines for COPD
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CONTENT DEVELOPMENT
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REPORTS AND ANALYSIS
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DESIGN
Michael Crawford

WEB
Ben King

MANAGEMENT AND ADMINISTRATION
Kaye Baldwin
Lee Cameron

CLINICAL REVIEW GROUP
Dr Bryan Betty
Leanne Te Karu
Dr Neil Whittaker

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Dr Ben Brockway, Dunedin
Professor Ian Reid, Auckland
Associate Professor Simon Stebbings, Dunedin

CONTACT US:
Mail: P.O. Box 6032, Dunedin
Email: contact@bpac.org.nz
Phone: 03 477 5418
Free-fax: 0800 27 22 69
www.bpac.org.nz

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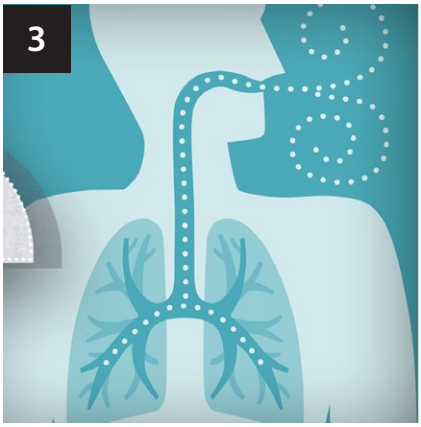

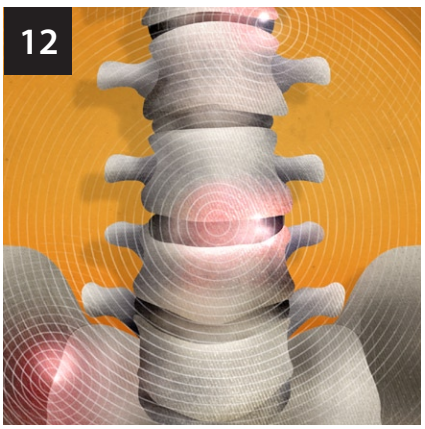

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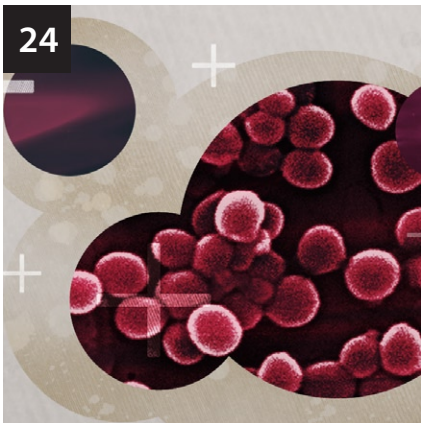

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Tips for prescribing newly-subsidised **medicines for patients with COPD**

In March, 2016, subsidy changes came into effect for medicines used to treat patients with COPD. The large number of changes created the possibility for confusion among patients and prescribers. To provide clarity for health professionals in primary care, bpac[nz] asked respiratory physician Dr Ben Brockway for his thoughts on how the recent changes are likely to affect the management of patients with COPD. In order to provide point-of-care assistance to prescribers Dr Brockway also helped bpac[nz] develop a novel prescribing tool.

Dr Ben Brockway is a consultant in respiratory medicine and senior lecturer at the Dunedin School of Medicine.

For further information see: "Newly-subsidised medicines for the treatment of patients with COPD", BPJ 74 (Mar, 2016)."

1. These new medicines for COPD are confusing. How do you decide what to prescribe for each patient?

They appear confusing at first, but it gets much easier if you consider two things:

a) The class of medicine you wish to use, and

b) The type of inhaler device you want.

The new medicines are still divided into the same classes – long-acting muscarinic receptor antagonists (LAMAs), long-acting beta$_2$ agonists (LABAs) and a new, once daily, inhaled corticosteroid (ICS).

The key to which of these classes to use can be found in the GOLD classifications in Table 1. At first glance these again look confusing, but they boil down to making assessments of how "bad" the patient is, i.e. symptoms and/or spirometry, and how often they exacerbate. The online tool helps make these assessments. Symptoms can be readily measured – for instance with the COPD Assessment Test (CAT) or a similar metric.

As a rule-of-thumb, long-acting bronchodilators are preferable for symptom relief in patients with anything other than mild disease. As the patient's symptoms worsen, one long-acting agent can be added to another – and indeed can be combined in the same inhaler. Thus, patients with moderate or severe breathlessness may be on both a LABA and a LAMA.

Table 1: GOLD patient classification.

Patient category	Characteristics	Exacerbations per year	Spirometric classification	mMRC	CAT
A	Less symptoms: low exacerbation risk	≤ 1 not leading to hospitalisation	GOLD 1–2 FEV_1 ≥ 50% predicted	0–1	< 10
B	More symptoms: Low exacerbation risk	≤ 1 not leading to hospitalisation	GOLD 1–2 FEV_1 ≥ 50% predicted	≥ 2	≥ 10
C	Less symptoms: high exacerbation risk	≥ 2, or 1 requiring hospitalisation	GOLD 3–4 FEV_1 < 50% predicted	0–1	< 10
D	More symptoms: high exacerbation risk	≥ 2, or 1 requiring hospitalisation	GOLD 3–4 FEV_1 < 50% predicted	≥ 2	≥10

Patients with multiple exacerbations per year and severe airflow obstruction may benefit from an ICS as well. The role of inhaled steroids is currently under intense debate, as across the class they are associated with a rise in incidence of pneumonia when used by patients with COPD. It is reasonable to suggest that ICS treatment in COPD is decreasing and their precise role may be better defined in the future – perhaps on the basis of a biomarker such as eosinophilia, in blood or sputum, or exhaled nitric oxide. Data for these approaches, however, are currently contradictory. This is not the case in asthma, however, where they remain the bedrock of treatment.

It is also worth reiterating that all patients should have a short-acting reliever, usually a SABA, i.e. salbutamol or possibly terbutaline. It is not wise to prescribe ipratropium (SAMA) containing medicines, e.g. Atrovent or Duolin, if the patient is also using a LAMA such as tiotropium, umeclidinium, or glycopyrronium as they may compete for the same muscarinic receptor binding sites and reduce efficacy.

There is no current convincing evidence to favour any of the new medicines in each class over their competitors.

For further information see: "Upfront: Are blood eosinophil counts helpful in predicting patient responses to inhaled corticosteroids in COPD?", BPJ (Mar, 2016).

2. Do you have any potential safety concerns with the introduction of the new medicines?

There is a dearth of high quality safety data for all the medicines used to treat patients with COPD, although some specific agents have been studied in select populations, e.g. tiotropium in the TIOSPIR (Tiotropium Safety and Performance in Respimat) study.[1] Nonetheless, direct safety studies often exclude just the type of multi-morbid patients whom we typically see with COPD. The short answer therefore is that we do not see much difference in safety profile between the new medicines and the existing ones as yet, but the whole area is in need of more study at a national/population level.

3. Are there any specific groups of patients who are likely to benefit from a change to one of the new medicines?

From a patient perspective, the biggest change they would see with the new inhalers are the inhaler types and the shift to once daily dosing. So patients who sometimes struggle to remember to take the 12-hourly medicines may be happy to have a once daily alternative.

The new inhalers include a combination not previously available: the LABA/LAMA combinations.

- Indacaterol/glycopyrronium (Ultibro Breezhaler)
- Umeclidinium/vilanterol furoate (Anoro Ellipta)
- Olodaterol/tiotropium (Spiolto Respimat)

These were initially positioned for patients with a lot of symptoms but not too many exacerbations i.e. GOLD group B, but recent information from a trial investigating the effect of indacaterol/glycopyrronium versus fluticasone/salmeterol on exacerbation rates in patients with moderate to very severe COPD (the FLAME trial) suggests they are also effective at reducing exacerbation frequency.[2] A LABA/LAMA combination is therefore a reasonable starting point for patients in GOLD groups B and C, and may be an acceptable choice in D as well. However, note that the Special Authority criteria for the LABA/LAMA classes states that the "patient has been stabilised on a LAMA", so they must have been given tiotropium, glycopyrronium, or umeclidinium previously before commencing a combination LABA/LAMA.

4. There are some new types of inhaler devices now available. How do you work out which inhaler is best for your patient? Are some devices easier to use than others?

First up, none of the new devices can be used with a spacer. As always, you will need to carefully instruct the patient and check their inhaler technique regularly. Just giving out a script

is a recipe for failure and runs the risk of patients losing faith in the new device.

- The Ellipta device is preloaded and chunky, so a reasonable choice for those with limited manual dexterity.
- The Breezhaler devices are similar in design to tiotropium handihalers: the active medicine capsule must be taken from the foil pouch and placed in the device, pierced and inhaled (and definitely not swallowed!). Because the capsules are transparent they can be visually checked to see that all the medicine has been inhaled.
- The Respimat device is initially tricky to prime – the cartridge that contains the active ingredients is loaded into the base and requires some strength – but once loaded the device is good for four weeks and requires very little inspiratory flow. I look upon this device as being a good choice for patients in supported environments such as residential homes.

All of the new devices are renewed with each prescription and as none are recyclable they are disposed of in the household rubbish.

5. Do you have any suggestions for reducing patient confusion when prescribing medicines for COPD?

Firstly, I suggest minimising the different types of inhaler devices for each patient. Bear in mind that many will still be using a salbutamol metered dose inhaler (MDI), so try and stick to one new device only. More device types means more confusion! If you are sure a once daily ICS is needed, then the only once daily medicine on the market is the vilanterol/fluticasone furoate combination in the Breo Ellipta formulation; so if a LAMA is needed as well then stick to the Ellipta range by adding umeclidinium (Incruse Ellipta). I struggle to see much point in a patient using, say, a once daily LABA/LAMA and a twice daily ICS.

6. Sometimes it's hard to know when to refer patients with COPD. At what stage would you like to see COPD patients in your respiratory clinic?

An excellent question. Almost all patients with anything but the mildest disease should be considered for pulmonary rehabilitation. Depending on local protocols I would recommend this be a priority. Most of the studies suggest that pulmonary rehabilitation gives three or four times the improvement in quality of life that one of these "fancy pants" new inhalers does. In terms of respiratory clinic assessment, this is recommended for patients in whom there is diagnostic uncertainty (especially if there are concerns about malignancy, coexistent fibrotic disease or bronchiectasis), those in whom long-term oxygen is considered, and those in whom assistance or guidance is needed for advanced care planning.

7. What do you think is the most important point to remember when caring for patients with COPD?

Inhalers are just a small but helpful component of COPD management, and it is easy to "take your eye off the ball" by stressing about inhaler options when the interventions that make a big difference, i.e. smoking cessation and pulmonary rehabilitation, are the keystones of treatment. These patients are often complex, multi-morbid and generally and generally have a high burden of disease, and deserve the best of care.

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New medicines, new combinations, new inhaler devices and changes to Special Authority approval, have transformed the range of subsidised medicines for patients with COPD in New Zealand. But with change can come confusion.

bpac^{nz} has created an online prescribing tool to help you and your patients make sense of these changes and make the right treatment decisions.

To access this tool see the bpac^{nz} website:
www.bpac.org.nz/copd

Vitamin D and calcium supplementation in primary care: an update

KEY PRACTICE POINTS

- Most people can achieve adequate levels of vitamin D through exposure to sunlight
- Vitamin D supplementation should be reserved for frail older people or those at risk of deficiency; routine supplementation for the general population is not recommended
- There is no evidence of vitamin D toxicity at doses recommended to treat mild deficiency, although this practice may increase the risk of renal tract stones
- Testing vitamin D levels is rarely beneficial for patients, is expensive and often unreliable; in most cases deficiency is likely to be a consequence of poor health rather than a cause
- Encourage an increase in dietary calcium before considering calcium supplementation, i.e. two to three serves of dairy products a day

In 2011, bpac^{nz} produced guidance on vitamin D supplementation for primary care. In the past five years vitamin D use has risen substantially and it is now the 12th most frequently prescribed medicine in New Zealand. Previously, prescribing vitamin D on the basis of deficiency risk was recommended, without testing. This is still broadly considered best practice, however, it is now more evident which groups of patients are likely to benefit from supplementation. Dietary calcium should be optimised in people taking vitamin D supplements, but routine supplementation with calcium is not recommended. Despite the growing number of studies reporting associations between vitamin D deficiency and non-skeletal diseases, there remains no convincing evidence of a causal link from meta-analyses or randomised controlled trials.

For further information on vitamin D, see: **www.bpac.org.nz/BPJ/2011/june/vitamin-d.aspx**

Sunlight is the preferred source of vitamin D

People derive approximately 80% of their circulating vitamin D from the ultraviolet B (UV-B) rays in sunlight.[1] Most healthy people can achieve adequate vitamin D levels by spending time outdoors during the day. Skin needs to be exposed to direct sunlight to allow the synthesis of vitamin D to occur as glass blocks UV-B rays.

How much sunlight is enough?

To prevent vitamin D deficiency, a daily walk in the early morning or late afternoon from September to April in the Southern hemisphere with face, arms and hands exposed is recommended.[1] At the height of summer as little as six to eight minutes of sun exposure may be sufficient to produce 1000 IU of vitamin D.[2] From May to August outdoor activity is best scheduled around noon as approximately 30 – 50 minutes of sun exposure is required to produce the same amount of vitamin D.[1, 2] Dark skin pigmentation is correlated with decreased rates of vitamin D production and people with darker skin may require three to six times more sun exposure to achieve equivalent levels of vitamin D production.[2] It is not possible to develop vitamin D toxicity due to exposure to sunlight.[1]

The use of sun beds to boost vitamin D levels is not recommended as this practice is associated with an increased risk of melanoma which rises with greater use and earlier age of first use.[1]

Diet is a secondary source of vitamin D

Diet contributes approximately 5 – 10% of a person's vitamin D requirement.[2] Diet can be an important source of vitamin D during winter months or when sun exposure is reduced. Cod liver oil is the best dietary source of vitamin D while oily fish, e.g. salmon, tuna, eel and warehou, are rich whole food sources.[1] Milk, yoghurt and margarine fortified with vitamin D are now available in New Zealand.

Prescribing of vitamin D is increasing

As in 2011, guidance continues to recommend prescribing vitamin D supplements based on risk of deficiency (see below).[1] However, the number of people prescribed vitamin D each year is increasing (Figure 1) and it is questionable whether all of those prescribed supplements are at risk of long-term deficiency. Colecalciferol (vitamin D_3) is the predominant formulation prescribed; in 2015 it was the 12th most frequently prescribed medicine in New Zealand.[4]

Benefits versus risks of vitamin D supplementation

Severe vitamin D deficiency reduces bone mineralisation which causes osteomalacia and increases fracture risk. This can be prevented by empiric supplementation of people who are at risk. Since 2011, evidence has accumulated that only a limited number of patients benefit from supplementation with vitamin D.

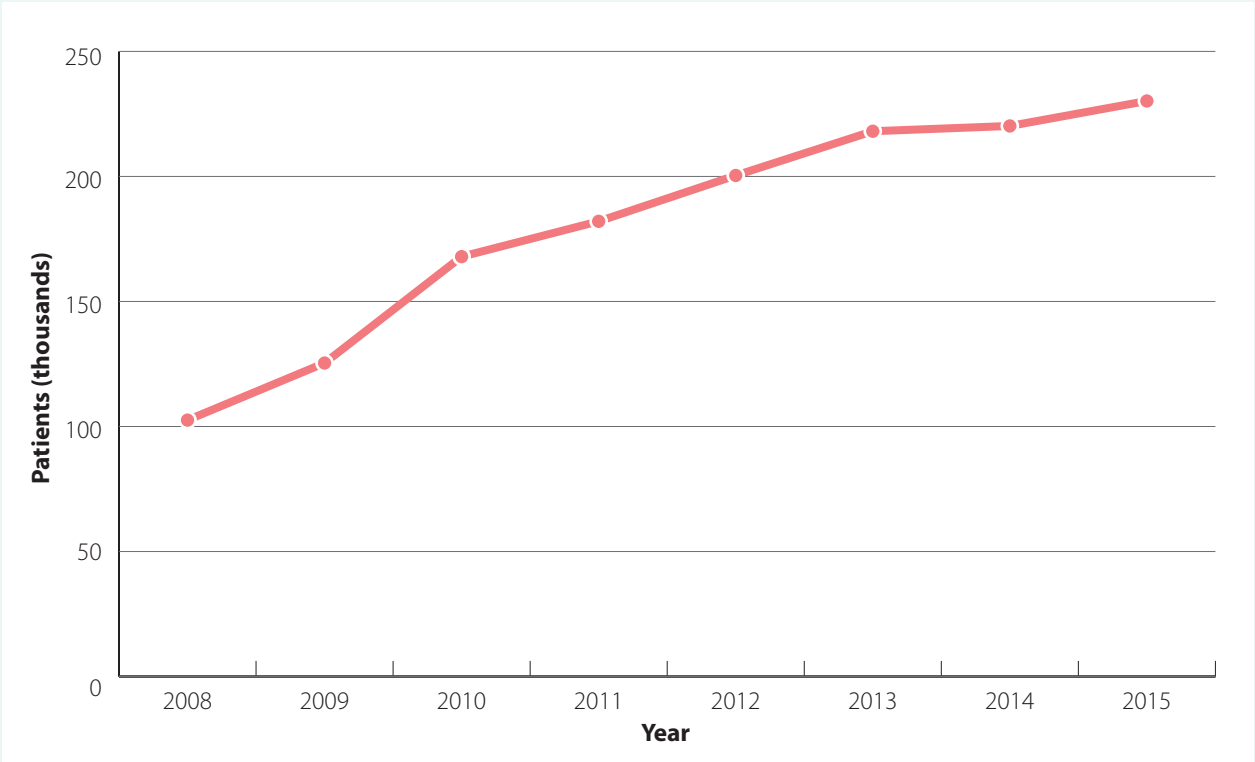

Figure 1: Number of patients dispensed subsidised vitamin D supplements in New Zealand (2008 – 2015).[5]

The benefits of supplementation on bone health and falls prevention have been overstated

More than 50 meta-analyses have examined the effects of vitamin D on falls or fractures.[6] This research now confirms that vitamin D supplementation for the general population provides no benefit and is a waste of resources. Key findings from studies include:

- The United States Preventative Services Task Force concluded, in 2013, that daily supplementation with 400 IU (10 micrograms) of vitamin D_3 and 1000 mg of calcium has no effect on fracture incidence in post-menopausal women.[7]
- A meta-analysis involving more than 50 000 participants concluded that vitamin D taken without calcium has no effect on fracture incidence and that vitamin D taken in combination with calcium has weak and inconsistent effects on fracture risk; benefits were restricted to frail, older females living in institutions.[8]
- Analyses of randomised controlled trials involving almost 30 000 participants found that vitamin D with or without calcium has no effect on the risk of falls.[8]

Adverse effects associated with vitamin D supplementation have been reported

Vitamin D taken at recommended doses, i.e. 1.25 mg per month or 10 – 20 micrograms (400 – 800 IU) per day, is generally well tolerated and considered to be safe. There is no evidence of toxicity at doses of vitamin D_3 below 25 micrograms (1000 IU), daily, however, hypercalcaemia and hyperphosphatemia can occur at substantially higher doses, e.g. 50 000 IU daily.[10] Vitamin D supplementation in combination with calcium supplements is reported to increase the risk of renal tract stones.[7]

In a randomised controlled trial it was found that single high doses of colecalciferol, e.g. 12.5 mg (500 000 IU) given annually, were associated with an increased risk of falls and fractures in older women who were considered at high risk of fracture (see: "High and low levels of vitamin D can cause bone weakness").[9]

Inconclusive research has created confusion

In addition to preventing osteomalacia, there are a plethora of health claims associated with vitamin D supplementation. This has created confusion both for patients trying to make informed treatment decisions and for clinicians guiding their care.

Numerous studies have examined associations between vitamin D deficiency and a range of conditions including: cardiovascular disease, cancer, autoimmune and inflammatory diseases, neurodegeneration, cognitive impairment and mood disorders.[10] Association does not equate to causation, however, and randomised controlled trials show that vitamin D supplementation has little or no effect on the non-skeletal illnesses studied; the meta-analyses reported also do not support the observational findings.[11] It is more likely that vitamin D deficiency is a marker of reduced health, rather than a cause of it.[11]

High and low levels of vitamin D can cause bone weakness

Vitamin D is thought to affect bone mineralisation by regulating circulating calcium.[12] If levels of circulating calcium are low, this is rectified through the stimulation of osteoclasts which cause bone resorption via secondary hyperparathyroidism, thereby reducing bone mineralisation.[12] High levels of vitamin D can also cause bone weakness by stimulating osteoclasts directly.[12] These two mechanisms explain why high and low levels are both associated with bone weakness.

When to consider vitamin D supplementation

Vitamin D supplementation is only beneficial for people at risk of deficiency such as frail older people, those with dark skin and women who are veiled; supplementation of the general population is not recommended.[1] Vitamin D and calcium supplements are indicated for patients treated for osteoporosis if their dietary calcium intake is inadequate (see below).[13]

See: "Vitamin D supplementation during pregnancy and infancy" for guidance on prescribing vitamin D to women who are pregnant or breast feeding.

Risk factors for vitamin D deficiency

Groups considered to be at high risk of vitamin D deficiency and who may benefit from supplementation include people:[1]

1. With very dark skin pigmentation
2. Who completely avoid the sun for medical reasons, e.g. they have had skin cancer or are using photosensitising medicines long-term
3. With reduced mobility who are frail or housebound and at risk of musculoskeletal pain and osteomalacia

People who completely cover their skin with clothing or veils will be at greater risk of vitamin D deficiency.[1] Living in southern regions means that transitory vitamin D deficiency is more likely to occur between the months of May and August.[1]

The symptoms of vitamin D deficiency

In children, vitamin D deficiency is associated with delayed tooth eruption and rickets.[14]

In adults, severe vitamin D deficiency causes osteomalacia with symptoms of bone pain and muscle weakness.[14]

Physiological changes consistent with osteomalacia in adults who are vitamin D deficient include:[14]

- Elevated alkaline phosphatase levels; often the earliest finding
- Low calcium levels
- Elevated parathyroid hormone levels, i.e. secondary hyperparathyroidism
- Low phosphate levels

Vitamin D testing is only indicated if severe deficiency is suspected

Vitamin D supplementation can be initiated in people at risk of deficiency without the need for testing.[1] Testing of vitamin D levels is usually only indicated in patients with features of severe deficiency.[1] This includes patients who may have:[15, 16]

- Metabolic bone disease or features such as unexplained fractures or bone pain
- Unexplained raised alkaline phosphatase, low calcium or phosphate levels
- Chronic kidney or liver disease
- Osteoporosis secondary to endocrine disorders, e.g. Cushing syndrome
- Malabsorption of dietary fat, due to conditions such as coeliac disease, previous intestinal surgery or gastric bypass

When vitamin D testing is requested serum 25-hydroxyvitamin D (vitamin D) is measured as it is a stable metabolite with a plasma half-life of three weeks.[2] The optimal serum vitamin D level is contentious: a serum level ≥ 50 nmol/L is generally considered to be sufficient to maintain adequate bone health,[2] and levels below 25 nmol/L are considered to be deficient.[1] Day-to-day variations in serum vitamin D are small (5%), although levels may decrease by as much as 20 nmol/L over winter compared to measurements taken during summer.[2] Where severe symptomatic vitamin D deficiency is suspected serum calcium, phosphate and alkaline phosphatase should also be tested.[1]

There is limited clinical value in testing vitamin D levels in patients without symptoms of deficiency because the results of testing are difficult to interpret, as the optimum level of vitamin D is unknown and levels can vary substantially between seasons.

Prescribing vitamin D for those at risk of deficiency

Colecalciferol is the recommended form of vitamin D for patients at risk of deficiency,[13] who are unlikely to meet sun exposure recommendations.[1]

Vitamin D undergoes hydroxylation in the kidney to its active form, therefore hydroxylated derivatives alfacalcidol or calcitriol should be prescribed for patients with renal failure.[13]

Contraindications for colecalciferol include patients with hypercalcaemia, hypervitaminosis, metastatic calcification, and renal osteodystrophy with uncontrolled hyperphosphatemia.[13] The current subsidised brand of colecalciferol contains soya oil in the gel capsule and is contraindicated in patients with soy allergy.[17] People with a history of peanut-induced anaphylaxis should also avoid this formulation as they may react to soya oil.

For mild to moderate vitamin D deficiency prescribe:[13]

- 1.25 mg (50 000 IU) colecalciferol, once a month

For moderate to severe vitamin D deficiency prescribe an initial loading dose of one capsule daily for up to ten days. Vitamin

Vitamin D supplementation during pregnancy and infancy

During pregnancy the same risk factors for vitamin D deficiency and recommendations for sun exposure apply as for the general population.

In general, testing vitamin D levels is not recommended in either asymptomatic women who are pregnant or infants.[15] Supplements should be prescribed based on the risk of vitamin D deficiency.[15]

The same colecalciferol regimen subsidised for adults who are at risk of vitamin D deficiency, i.e. colecalciferol, 1.25 mg, monthly, may be beneficial for women who are pregnant and vitamin D deficient, or at high risk of deficiency; this is not recommended for all women who are pregnant due to a lack of safety data.[15] Women who are pregnant who are at a lower risk of vitamin D deficiency may benefit from lower daily dosing, i.e. 10 micrograms per day of vitamin D, especially during the third trimester.[15] There is no 10 microgram vitamin D supplement subsidised in New Zealand but this quantity of vitamin D is included in ante-natal multivitamin tablets that can be purchased over-the-counter.

Supplementation during infancy

Infants who are exclusively breastfed or who receive less than 500 mL of milk formula per day may benefit from vitamin D supplementation if they also have one or more of the following risk factors:[15]

- Dark skin
- A mother who is vitamin D deficient or is at increased risk of becoming deficient
- A sibling diagnosed with rickets or hypocalcaemic seizures
- Being born preterm with a body weight less than 2.5 kg (see NZFC: **www.nzfchildren.org.nz/nzf_5385**)

Vitadol C, containing vitamins A, D and C is the recommended supplement in New Zealand for infants.[15] This can be given as ten drops (0.3 mL, approximately 10 micrograms of colecalciferol) once per day.[15] Due to the high vitamin A concentration in Vitadol C this formulation is not appropriate for infants who are not deficient.[15] It is reasonable to wait until breastfeeding is well established in full-term babies before introducing vitamin D supplementation, e.g. at six weeks of age (See NZFC: **www.nzfchildren.org.nz/nzf_70283**).[15]

Further information on vitamin supplementation during pregnancy or infancy is available from: **www.health.govt.nz/system/files/documents/publications/companion-statement-vit-d-sun-exposure-pregnancy-infancy-v3.pdf**

D taken at these doses is associated with few adverse effects, however, it may raise concentrations of calcium and phosphate in the plasma and urine,[13] and increase the risk of renal tract stones and arterial deposits.

Patients with vitamin D deficiency due to malabsorption or liver disease often require higher maintenance doses and consultation with an endocrinologist is recommended.[13]
Hypervitaminosis D from excessive supplementation has non-specific symptoms resulting from hypercalcaemia, including: dehydration, vomiting, decreased appetite, irritability, constipation, fatigue and muscle weakness.[1]

Optimising calcium intake

Increasing dietary calcium is preferred over oral calcium supplementation for patients prescribed vitamin D supplements; both are associated with increases in bone mineral density of 1 – 2%,[18] although calcium supplementation is associated with some adverse effects (see below). It should be noted, however, that modest changes in bone mineral density of this magnitude are unlikely to result in a reduced fracture risk for most patients.[18]

Dietary sources of calcium

The recommended daily intake of calcium in New Zealand is:[19]

- 1000 mg for men and women aged 19 – 70 years
- 1300 mg for men and women aged over 70 years

Dairy products are the richest source of calcium and two to three serves, e.g. a cup of milk, a pottle of yoghurt or two slices of cheese, per day will maintain adequate calcium intake.[19]

Oral calcium supplements may be associated with adverse effects

Serum calcium levels are slightly elevated in the short term by taking oral calcium supplements.[7] People who ingest an equivalent amount of calcium from their diet do not experience the same elevations in serum calcium.[7] Since vascular calcification is an established risk factor for cardiovascular disease it has been suggested that calcium supplementation may increase cardiovascular risk.[7]

Calcium supplementation is known to be associated with increased rates of:[20]

- Renal tract stone formation
- Constipation
- Gastrointestinal symptoms
- Cardiovascular events, including myocardial infarction

A 2015 meta-analysis concluded that due to the limited benefits of calcium supplementation and the increased risk of relatively serious adverse events, calcium supplements should not be recommended for individuals or at a population level.[20]

The final word

It has become clearer since 2011 that the proportion of the population who are likely to benefit from vitamin D supplementation is relatively small and restricted to frail older patients and those at risk of deficiency. The prescribing of vitamin D to nearly one-quarter of a million people in New Zealand therefore may not be justified. When discussing new or ongoing supplementation with patients who do not have a clear indication for treatment, an evidence-based conversation about the likelihood of benefit may be helpful.

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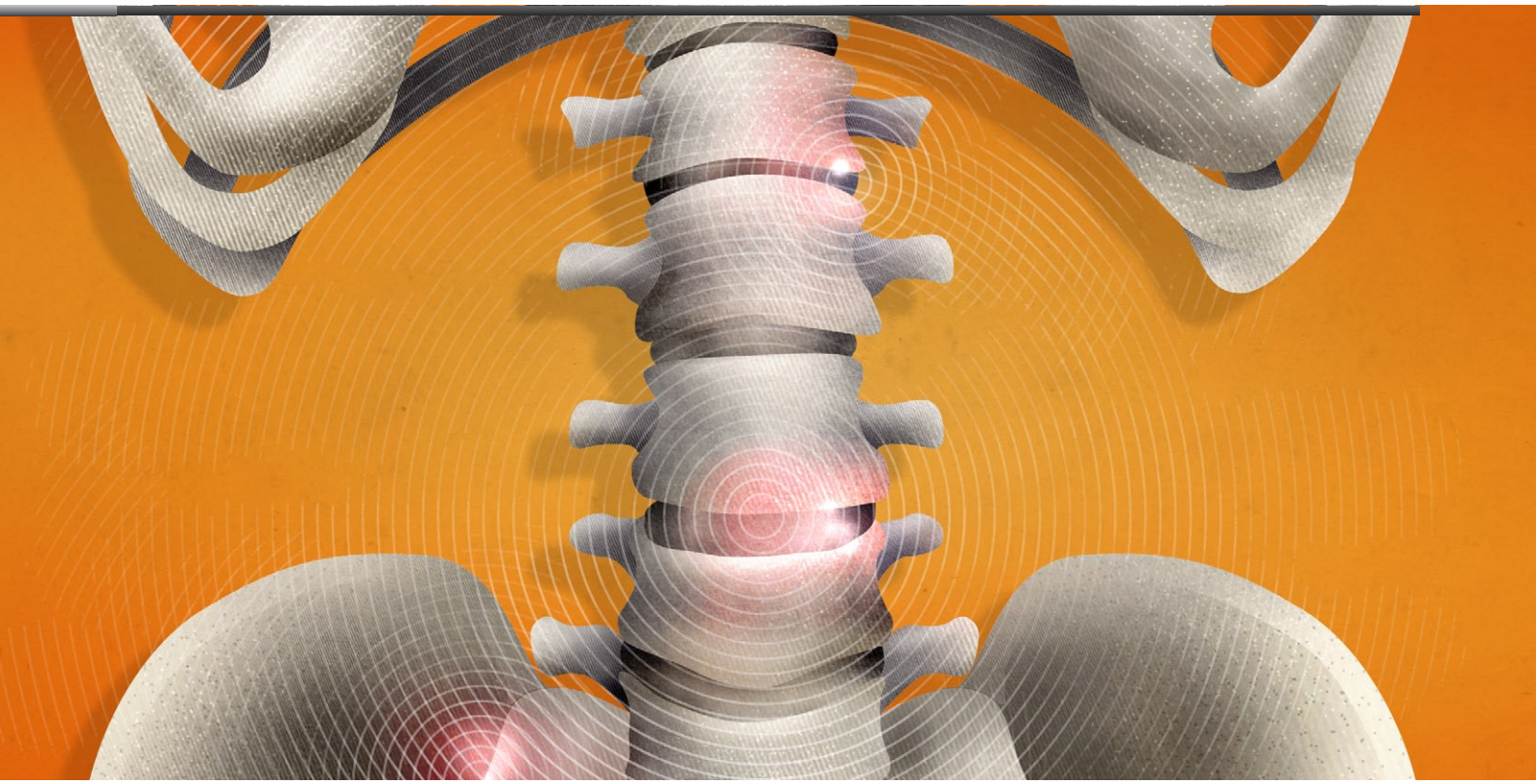


Diagnosis and management of axial spondyloarthritis in primary care

KEY PRACTICE POINTS:

- Axial spondyloarthritis is relatively uncommon and is likely to be the cause of long-term back pain in only 5% of patients
- Axial spondyloarthritis is characterised by a slow onset of back pain in the absence of injury, onset before the age of 45 years, improvement with exercise rather than rest, back stiffness in the morning resolving with movement, pain or stiffness which wakes the patient and pain that responds well to non-steroidal anti-inflammatory medicines (NSAIDs)
- Diagnosis is aided by a family history, clinical examination, CRP, HLA-B27 testing and radiographic imaging. Imaging is usually reserved for patients with back pain of at least three months duration
- Early diagnosis and treatment is beneficial
- Many patients can be effectively managed in primary care with exercise, physiotherapy and NSAIDs
- Patients with ankylosing spondylitis who do not benefit from NSAIDs usually benefit from tumour necrosis factor (TNF) inhibitors initiated in secondary care

Ankylosing spondylitis is a relatively uncommon inflammatory cause of long-term back pain which can result in radiographic changes in the spine and sacroiliac joints. Ankylosing spondylitis is part of a spectrum of interrelated conditions collectively termed spondyloarthritis. Patients with axial spondyloarthritis have predominantly spinal symptoms and some will develop classical ankylosing spondylitis. Axial spondyloarthritis is an insidious disease and difficult to diagnose; patients have an average delay of eight years from the onset of symptoms to diagnosis. Recent evidence suggests early treatment with exercise, physiotherapy and pharmacological treatments may delay disease progression and therefore improve outcomes.

A new way of thinking about spondyloarthritis

Spondyloarthritis is a collective term for a group of diseases including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and arthritis associated with inflammatory bowel

disease.[1] There is considerable overlap between the symptoms, signs and genetic risk factors for these diseases and patients may have more than one of these conditions (Table 1). Although these have historically been defined as separate conditions they are now thought to be a single disease with different phenotypes.[2]

Classifying spondyloarthritis

Spondyloarthritis is classified as axial or peripheral, depending on whether patients primarily experience symptoms in the spine, sacroiliac joints, hips and ribcage (the axial skeleton), as seen in patients with ankylosing spondylitis, or peripheral joints, as seen in those with psoriatic arthritis.[5]

Axial spondyloarthritis is a continuum

Axial spondyloarthritis is now viewed as a continuum of disease which can lead to ankylosing spondylitis (Figure 1). In patients with ankylosing spondylitis, inflammatory changes eventually affect the spinal and sacroiliac joints, leading to spinal fusion, reduced mobility and an increased risk of spinal fractures. Various diagnostic criteria have been used for ankylosing spondylitis, with all relying on evidence of radiographic damage as a criterion for diagnosis.[6]

It is now recognised that patients in earlier stages of disease do not have radiographic changes, but share similar symptoms and signs, family history and genetic risk factors, and can experience disability as severe as some patients with a confirmed diagnosis of ankylosing spondylitis.[5]

Table 1: Overlap between ankylosing spondylitis and other forms of spondyloarthritis.[3,4]

Percentage of patients with ankylosing spondylitis who also have:			
Peripheral arthritis	Acute anterior uveitis	Psoriasis	Inflammatory bowel disease
50%	26%	9%	7%

Patients in the early stage of disease are classified as having "non-radiographic axial spondyloarthritis". Follow-up studies report that among patients diagnosed at this early stage, 6% develop ankylosing spondylitis after five years, 17% after ten years and 26% after 15 years.[7] Therefore, some patients may never develop ankylosing spondylitis, while others may live with inflammatory back pain for a considerable time before developing ankylosing spondylitis.

Early diagnosis and treatment may improve patient outcomes

Research suggests that early diagnosis of axial spondyloarthritis improves patient outcomes, resulting in less pain and functional limitation, and may avoid unnecessary testing, treatment or referral.[9] Although long term studies are lacking, limited evidence associates early treatment with reduced skeletal damage on radiography.[10]

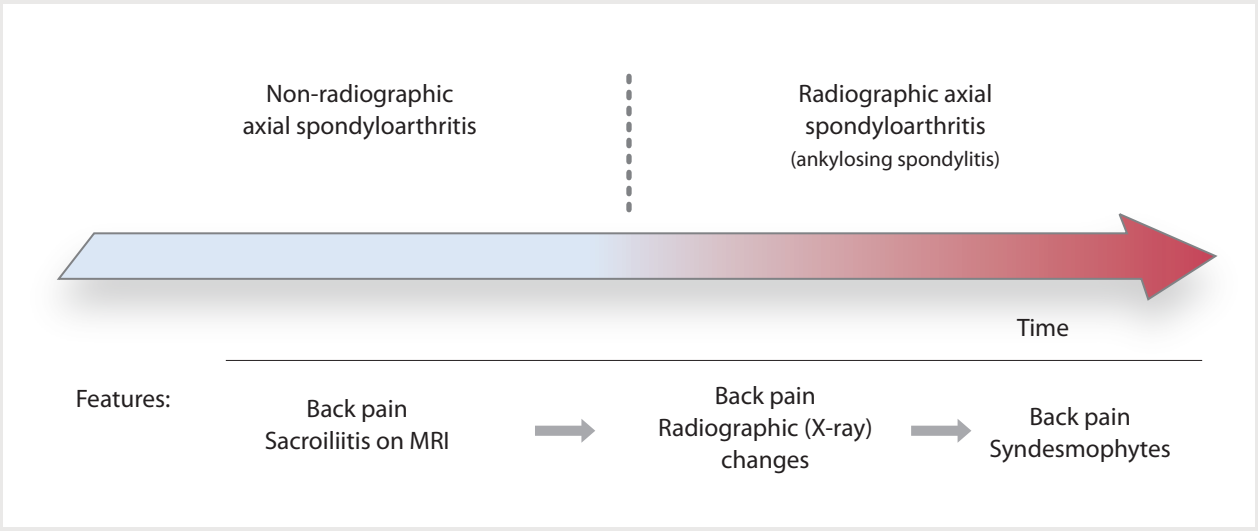


Figure 1: Axial spondyloarthritis is a continuum of disease. Adapted from Rudwaliet *et al*.[8]

Evaluating patients with suspected axial spondyloarthritis

Low back pain lasting longer than three months is a common symptom in primary care; **spondyloarthritis is estimated to be the cause in only 5% of these patients**.[3]

In patients with complex histories, e.g. previous injuries, diagnosing spondyloarthritis can be challenging and the diagnosis may need to be revisited after other causes have been excluded. The clinical picture may be further complicated by co-morbidities such as depression which can compound pain and functional limitation.

Key features of spondyloarthritis

Symptoms of spondyloarthritis generally begin in early adulthood. Males and females are equally affected in the early stages, but males are two and half times more likely to progress to ankylosing spondylitis.[1, 2]

Key features which help identify patients with axial spondyloarthritis include back pain consistent with inflammation and a positive family or personal history of inflammatory diseases (see: "Criteria to assist the diagnosis of axial spondyloarthritis in primary care", below).[11]

Criteria to assist the diagnosis of axial spondyloarthritis in primary care

In patients with back pain lasting more than three months beginning before age 45 years, the presence of two or more of the following criteria has a sensitivity of 100% and specificity of 60% for identifying patients with axial spondyloarthritis, compared to diagnosis by a rheumatologist:[5, 11]

- Inflammatory back pain*
- Peripheral manifestations, such as arthritis, dactylitis or enthesitis, especially of the Achilles tendon or plantar fascia
- Psoriasis, inflammatory bowel disease or a history of uveitis
- A family history of spondyloarthritis or related spectrum disorders†
- Back pain which improves after 24 – 48 hours of treatment with an NSAID
- Elevated C-reactive protein (CRP), where causes such as spinal infection or cancer have been excluded. Patients with axial spondyloarthritis or ankylosing spondylitis may have CRP levels ranging from > 6 mg/L (slightly elevated) to 20 – 30 mg/L.[12]
- Positive HLA-B27 test
- Sacroiliitis on X-ray or MRI

* At least four out of the five criteria from "Differentiate inflammatory back pain from pain due to other causes"

† A first-degree or second-degree relative with ankylosing spondylitis, psoriasis, uveitis, reactive arthritis or inflammatory bowel disease

Differentiate inflammatory back pain from other causes

Inflammatory back pain is a hallmark of axial spondyloarthritis, although it is not specific; patients with diseases such as rheumatoid arthritis may also have inflammatory back pain. Back pain in patients with axial spondyloarthritis typically has a gradual onset, without any specific injury, before the age of 45 years.

Features consistent with back pain due to inflammation include:[13]

- Improvement with exercise
- No improvement with rest
- Pain at night, including early morning
- Morning stiffness
- Pain which alternates between buttocks

Patients with four of these criteria are likely to have pain caused by inflammation rather than mechanical or other causes.[13]

Important differential diagnoses and their features include:[14, 15]

- **Muscle pain** from poor posture and core muscle weakness – may be exacerbated by injury
- **Fracture** – risk factors include older age, osteoporosis, osteopenia or the use of corticosteroids
- **Herniated disc** – characterised by leg pain with lower lumbar nerve root distribution
- **Spinal stenosis** – results in radiating leg pain, more common in older adults
- **Referred pain** – causes include abdominal aortic aneurysm, pelvic inflammatory diseases, endometriosis, prostatitis, renal or gastrointestinal disease
- **Vertebral infection** – assess whether patients have fever, have had a recent infection or have used intravenous drugs
- **Cauda equina syndrome** – features include urinary retention, motor deficits in the lower limbs, faecal incontinence and "saddle" anaesthesia – the most frequent finding is urinary retention, which has a sensitivity of 90%; the probability of cauda equina

syndrome without urinary retention is approximately 1 in 10,000 patients

- **Cancer** – consider in patients with history of cancer, unexplained weight loss, older age or ongoing back pain for more than one month
- **Other** – Scheuermann's disease of the spine, most commonly occurring during adolescence and treated conservatively,[16] and Diffuse Idiopathic Skeletal Hyperostosis (DISH); a severe form of degenerative thoracic and lumbar spondylosis which is more common in patients with diabetes.[17]

Assess whether patients have a family history of a spondyloarthritis

Spondyloarthritis is highly heritable. A family history of inflammatory bowel disease confers a three-fold increased risk of ankylosing spondylitis. A family history of psoriasis, recurrent uveitis or reactive arthritis are also risk factors.[5, 18]

Look for symptoms and signs in peripheral joints, the skin, eyes and gut

People with axial spondyloarthritis often have symptoms in peripheral joints and extra-articular features as inflammatory processes can cause damage in other organs. Most often this involves the eyes, skin, gastrointestinal and urogenital tracts.[1] Reactive arthritis can develop in response to a recent episode of gastroenteritis due to *Yersinia*, *Salmonella*, *Shigella*, and *Campylobacter*; symptoms typically begin two to ten days after onset of gastroenteritis. *Chlamydia* infections resulting in genitourinary symptoms are also a common trigger.[19]

Musculoskeletal system: examine patients for the presence of:[3]

- Achilles tendinitis and plantar fasciitis
- Chest wall pain, which can be caused by intercostal enthesitis
- Dactylitis (inflamed finger joints and swelling of the whole finger or toe, also referred to as "sausage digit")

Eyes: acute anterior uveitis (iritis) occurs in approximately one-quarter of patients with ankylosing spondylitis.[4] In patients with acute anterior uveitis, 20 – 25% can be expected to have spondyloarthritis.[20] Patients who present with acute anterior uveitis should be referred for ophthalmology assessment. HLA-B27 is highly prevalent in patients with recurrent anterior uveitis patients and is independently associated with recurrent anterior uveitis even in the absence of musculoskeletal symptoms.[20]

For further information on the diagnosis of acute anterior uveitis, see: **www.bpac.org.nz/BPJ/2013/August/redeye.aspx**

Skin and nails: check for psoriasis in the scalp line, behind the ears, extensor surfaces of elbows and knees, natal cleft and umbilicus. Examine nails for signs of psoriasis.

For further information on diagnosing and treating psoriasis, see: **www.bpac.org.nz/BPJ/2009/September/psoriasis.aspx**

Gastrointestinal tract: ask patients about bowel habits and any changes consistent with inflammatory bowel disease or a recent gastrointestinal infection. Approximately 60% of patients with ankylosing spondylitis have mucosal inflammation detectable on colonoscopy, and up to 30% of patients with ankylosing spondylitis will report bowel symptoms if questioned.[3, 21]

For further information on inflammatory bowel disease, see: **www.bpac.org.nz/BPJ/2008/September/crohns.aspx**

Genitourinary symptoms: patients may have ongoing urethritis following resolution of an infection, or a history of *Chlamydia* infection.[19]

Consider laboratory or imaging investigations

Testing CRP and HLA-B27 is appropriate for patients where there is a strong suspicion of axial spondyloarthritis. In cases with less certainty ordering CRP and HLA-B27 tests may not be helpful as the results are non-specific. An elevated CRP is associated with more aggressive disease and a worse prognosis.[2]

Radiographic imaging can detect changes consistent with ankylosing spondylitis, however, patients without radiographic changes may still have back pain due to early stage axial spondyloarthritis.

The HLA-B27 gene is the strongest genetic risk factor

Testing for HLA-B27 can assist diagnosis and a negative HLA-B27 may help rule out axial spondyloarthritis, but it is not a definitive test. HLA-B27 risk alleles are relatively common in the population; approximately 9% of New Zealand Europeans and 6–7% of Māori have HLA-B27 risk alleles.[22] People with the HLA-B27 risk allele are approximately 60 times more likely to develop ankylosing spondylitis.[23] However, other genetic and environmental factors play a role in the development of disease as only 5% of people with risk alleles develop ankylosing spondylitis.[3] Therefore HLA-B27 testing should not be used to screen asymptomatic people.

Radiographic imaging: to order or not to order?

Radiographic investigations can be reserved for patients with back pain for three months or more, or who meet criteria suggestive of axial spondyloarthritis.[24] If radiological investigations are indicated, initially request anterior-posterior lumbar X-rays which include the sacroiliac joints.[15]

The benefits of X-rays include:

- Changes in the spine or sacroiliac joints identified by radiography are required for a definitive diagnosis
- Radiography can demonstrate disease progression or identify prognostic factors, e.g. hip arthritis is associated with a poorer prognosis[3]

Factors which favour delaying or not requesting X-rays include:[15, 24]

- Early imaging, e.g. for back pain of six weeks or less, does not improve patient outcomes or rates of diagnosis
- Plain X-ray imaging cannot detect early disease
- Management may not be influenced by radiography as first-line treatments for all patients with axial spondyloarthritis include exercise and NSAIDs
- Radiographic changes are slowly progressive; imaging is recommended at intervals of at least two years even in patients with a definitive diagnosis

MRI is able to detect inflammatory changes in the axial spine and sacroiliac joints at an earlier stage of disease than plain X-ray. Consultation with a rheumatologist may be appropriate for patients where there is clinical suspicion of axial spondyloarthritis but no evidence of disease on X-ray.[3]

When should patients be referred to a rheumatologist?

For patients where there is a strong suspicion of axial spondyloarthritis, discussion with or referral to a rheumatologist is recommended as most will benefit from specialist assessment. After diagnosis, many of these patients can be managed in primary care with first-line treatments.

Patients with radiographic changes and a high burden of symptoms (see: "The BASFI and BASDAI scores") may be candidates for TNF inhibitor use (see: "Beyond NSAIDs") and should be reviewed by a rheumatologist.

Treatment of patients with axial spondyloarthritis

Treatment of patients with axial spondyloarthritis aims to improve quality of life and preserve spinal mobility by reducing inflammation.

Patients who are recently diagnosed require education and advice on living with spondyloarthritis, see: "Resources for patients with axial spondyloarthritis".

Assessing patients for inflammation and impairment

Ask patients about their ability to carry out tasks such as dressing, their level of fatigue and any problems they have sleeping. Driving can be an issue for patients with advanced ankylosing spondylitis as fusion of the cervical spine makes neck rotation difficult. The patient may need driving advice, extra mirrors or a reversing camera.

A patient's symptoms are the most reliable marker of whether they have active disease. Symptoms can be assessed and monitored using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores:[6]

- The BASDAI score covers common features of pain and discomfort experienced by patients with axial spondyloarthritis. Special Authority criteria for TNF inhibitor medicines requires this score.
- The BASFI assesses patient impairment and monitors disease progression

CRP levels are not elevated in all patients with axial spondyloarthritis but are an additional marker for follow-up visits for patients with previously elevated levels.

Smoking cessation, exercise and physiotherapy are the cornerstones of treatment

Smoking is associated with an earlier age of onset of axial spondyloarthritis, high levels of disease activity, functional impairment and radiographic damage; smoking cessation should be strongly recommended.[25, 26] Some, but not all, studies suggest smoking is associated with worse prognosis, and current smoking has been reported to reduce the effect of TNF inhibitor treatment.[25, 26]

For further information on smoking cessation, see: **www.bpac.org.nz/BPJ/2014/October/smoking-cessation.aspx**

Encourage regular exercise

Regular exercise can improve pain, function and mood.[27] Patients should be referred to a physiotherapist to improve muscle relaxation, flexibility, strength, breathing and posture.[28] Other treatment options include walking, swimming or pool-based exercises or non-exercise options such as massage and the use of a spa pool.[28] Encourage patients to attend group-based classes as supervised group activity may be more beneficial and result in greater adherence than exercises conducted alone.[27]

Exercises should be tailored to the patient's mobility and flexibility. High impact exercises should be avoided as these may exacerbate spinal pain and inflammation.[28] Patients with advanced ankylosing spondylitis are at increased risk of spinal fractures due to changes in spine biomechanics. For these patients the safety of exercise options becomes more important.

NSAIDs can be added to non-pharmacological approaches

NSAIDs produce modest improvements in axial spondyloarthritis. In clinical trials patients rated measures of pain, function and disease activity 9% to 22% lower after six weeks of NSAID use, compared to placebo treatment, with numbers-needed-to-treat (NNT) of 2 to 5.[29]

Naproxen has a long half-life and has not been associated with increased cardiovascular risk, making it an appropriate first choice NSAID, however, other NSAIDs may be preferred by some rheumatologists.

Suitable NSAIDs and doses for patients with axial spondyloarthritis include:[30, 31]

- Naproxen, 500 – 1000 mg, daily
- Diclofenac, 75 – 150 mg, daily
- Ibuprofen, 1200 – 2400 mg, in daily divided doses, or modified release tablets 1600 mg, as a single daily dose, preferably in the evening
- Ketoprofen, 100 – 200 mg daily

For patients with intermittent disease activity, NSAIDs can be used as required, but continuous use is preferred for patients with ongoing symptoms and disease activity, e.g. consistently elevated CRP; preliminary evidence suggests continuous use may reduce disease progression.[27, 29]

Recent studies suggest the incidence of upper gastrointestinal bleeding is very low in patients with spondyloarthritis, most likely because patients are young at diagnosis and seldom have co-morbidities.[29] For patients with an increased risk of gastrointestinal adverse effects a selective COX-2 inhibitor, such as celecoxib, 200–400 mg daily, or etoricoxib, 90 mg daily, could be used or a non-selective NSAID with a proton pump inhibitor.[29] Selective COX-2 inhibitors are unsubsidised.

Ask patients about any over-the-counter (OTC) pain relief and herbal supplements they are using, especially OTC NSAIDs.

For further information on prescribing NSAIDs, see: **www.bpac.org.nz/BPJ/2013/October/nsaids.aspx or www.nzf.org.nz/nzf_5476**

The BASDAI and BASFI scores[6]

The BASDAI consists of six questions. Patients score on a scale of zero (none) to ten (very severe) their degree of symptoms (with the exception of question 5b). Questions 5a and 5b assess two features of inflammatory back pain: these responses are averaged before combining results for the remaining questions:

1. How would you describe the overall level of fatigue or tiredness (since the last visit)?
2. How would you describe the overall level of neck, back or hip pain?
3. How would you describe the overall level of pain or swelling in joints other than the neck, back or hips?
4. How would you describe the overall level of discomfort from any areas tender to touch or pressure?

5a. How would you describe the overall level of morning stiffness from wakening?

5b. How long does morning stiffness last from wakening? (Scored from 0 to 10, where 10 equals two hours)

The overall BASDAI score equals the sum of questions 1–4, plus the average of questions 5a and 5b, then dividing the total by 5, resulting in a score from zero to ten. Patients with scores ≥ 6 may be eligible for TNF inhibitor treatment.

The BASFI scores on a zero to ten scale the difficulty patients experience in daily activities and is routinely used in secondary care.[6] BASFI can also be used to assess response to treatment. Zero is "easy" and ten is "impossible":

1. Putting on socks or tights without help or aids
2. Bending forward from the waist to pick up a pen from the floor without an aid
3. Reaching up to a high shelf without help or aids
4. Getting up out of an armless chair without using hands or any other help
5. Getting up off the floor from supine without help
6. Standing unsupported for ten minutes without discomfort
7. Climbing 12 to 15 steps without using a handrail or walking aid, with one foot at each step
8. Looking over shoulder without turning the body
9. Doing physically demanding activities, e.g. exercises, gardening, sports
10. Doing a full day's activities, whether at work or at home

The overall BASFI score is calculated as the average of the ten scores to give a value between 1 and 10.

Beyond NSAIDs

Referral or consultation with a rheumatologist may be required for patients who do not gain sufficient benefit from treatment with NSAIDs, exercise and physiotherapy. Additional treatments include:

Intra-articular corticosteroid injections which can assist with localised peripheral joint inflammation, however, oral corticosteroid treatment is not recommended.[27]

Disease-modifying anti-rheumatic drugs (DMARDs) are not recommended for the treatment of axial symptoms in patients with axial spondyloarthritis or ankylosing spondylitis, due to a lack of efficacy. However, DMARDs such as sulfasalazine may be considered for patients with ongoing peripheral symptoms. Consider consulting with a rheumatologist to assess whether initiation is warranted. Evidence supports the use of sulfasalazine in the treatment of peripheral symptoms over methotrexate.[27]

TNF inhibitors, adalimumab, etanercept and infliximab can be effective for patients with more advanced disease. These medicines are fully subsidised and must be initiated by a rheumatologist; renewal applications can be made by a general practitioner on recommendation from a rheumatologist. Patients need to fulfil various application criteria, including having:

- Ankylosing spondylitis for at least six months' duration with radiographic evidence of disease
- Back pain which is relieved by exercise but not rest
- A BASDAI score of ≥ 6
- Moderate to severe limitation of lumbar spine flexion or chest expansion
- Trialled two or more NSAIDs during a three month exercise regimen supervised by a physiotherapist

In trials of TNF inhibitors approximately half of patients achieved a clinical reduction in pain and improvement in function and wellbeing after six months, with an NNT ranging from 3 to 5. In addition, approximately one in five experienced a partial remission, with an NNT of 3 to 11.[32]

General practitioners caring for patients taking TNF inhibitors should be aware of the safety issues associated with these medicines (see: "Special precautions for patients taking TNF inhibitors" and Table 2).

Follow-up in primary care

Treatment success is based on improvements in the patient's pain, and mobility. Patients requiring follow-up are likely to fall under one of two categories:

1. Patients with early disease who are being managed in primary care
2. Monitoring of patients managed in secondary care

Patients managed in primary care

Self-reporting questionnaires, e.g. BASDAI, BASFI, can be used to track disease activity and patient wellbeing. There is no benefit from routine radiographic imaging during follow-up. Monitoring of CRP levels can be an additional measure of disease activity for patients with active symptoms and previously elevated CRP levels.

Monitoring patients managed in secondary care

Patients managed in secondary care are more likely to have advanced axial spondyloarthritis and meet criteria for diagnosis of ankylosing spondylitis. Ankylosing spondylitis is associated with an increased risk of complications, either due to the disease itself or associated treatments.

Patients with ankylosing spondylitis have an increased risk of osteoporosis and spinal fractures.[27] Assessment of osteoporosis should consist of bone densitometry (DEXA) scans of the spine and hips, and an earlier age of testing may be appropriate depending on disease severity.[33] Management of osteoporosis is the same as for other patients due to a lack of trials in patients with both conditions to guide treatment recommendations.[27] Consultation with a rheumatologist is recommended where there is clinical uncertainty.

Patients with ankolysing spondylitis have an increased risk of cardiovascular disease, due in part to higher rates of smoking , as well as decreased mobility and inflammation.[34] It is recommended that patients with ankylosing spondylitis undergo more frequent evaluation of cardiovascular risk, e.g. every three years or more frequently for patients with greater disease activity.[34] Clinicians may also consider adopting a lower threshold for initiation of cardiovascular risk management.[34]

Patients with ankylosing spondylitis have an approximate two-fold increased risk of renal calculi, compared to the general population.[35]

Consultation with a rheumatologist and obstetrician may be appropriate if patients with ankylosing spondylitis become pregnant. Patients with ankylosing spondylitis may have a higher risk of preterm birth, small for gestational age babies and emergency caesarean section delivery.[36]

Special precautions for patients taking TNF inhibitors

Patients taking TNF inhibitors are at increased risk of infection, however, the overall risk of serious infection is low: a 2010 meta-analysis found that 257 patients would need to be treated for six months for one extra serious infection to occur.[37] Patients with spondyloarthritis are less prone to infection than those with rheumatoid arthritis, possibly because they are younger and generally healthier.[38] Table 2 provides precautions for clinicians treating patients with TNF inhibitors.

Do not administer live attenuated vaccines in patients

Table 2: Safety and monitoring of TNF inhibitor treatment.[39, 40]

	Potential issue or complication	Clinicians	Patients
Prior to initiation *	Activation of latent tuberculosis (TB) infection	Test for TB prior to initiation	–
	Avoid use during pregnancy	Exclude pregnancy. TNF inhibitors should not be used by females trying to conceive and are not recommenced until breastfeeding has finished; consultation with a rheumatologist and obstetrician is recommended if a patient becomes pregnant	Use adequate contraception and inform clinicians if planning a pregnancy or immediately if pregnancy occurs
During treatment	Increased risk of infection	Have a lower threshold for initiating antibiotics. Notify and consult with the initiating clinician if a severe infection occurs. Treatment may need to be withdrawn until the infection has resolved.	Have increased attention to food hygiene, and avoid foods containing unpasteurised milk, uncooked eggs or raw meat. Inform health professionals before major surgery about TNF inhibitor use. Withholding treatment for one to two doses may reduce infection risk.
	Possible increased risk of malignancy	Have a low threshold for investigating suspicious skin lesions for possible melanoma or non-melanoma skin cancers	Be "sun smart"

* TNF inhibitors are initiated by a rheumatologist and some tests may be conducted in secondary care

taking TNF inhibitors; other forms of vaccination may continue. If possible, vaccinate against influenza and pneumonia prior to starting treatment.[39, 40]

Common adverse effects experienced by patients taking TNF inhibitors include injection site reactions in 20–30% of patients which usually subside within 24 hours, and chills and nausea following a dose.[39]

Monitoring for adverse effects is conducted three months after initiating TNF inhibitor treatment, and every six months thereafter, including:[41]

- Full blood count
- Creatinine and electrolytes
- Liver function tests

Some patients develop anti-TNF inhibitor antibodies which reduce the efficacy of these medicines. Patients who fail to respond or have worsening symptoms during treatment may benefit from switching to a different TNF inhibitor.

For further information on TNF inhibitors, see: **www.bpac.org.nz/BPJ/2013/December/biologic.aspx**

For further information for patients using TNF inhibitors, see: **www.rheumatology.org/I-Am-A/Patient-Caregiver/Treatments/Anti-TNF**

Prognosis

The progression of axial spondyloarthritis is highly variable and complete spinal fusion is not inevitable. The majority of patients are likely to spend many years in early stages of disease with varying degrees of pain and impairment. During this time patients may benefit from treatment even if they do not meet the diagnostic criteria for ankylosing spondylitis. Untreated, patients with ankylosing spondylitis are less likely to be able to work and more likely to have disabling pain and depression.

Acknowledgement: Thank you to **Associate Professor Simon Stebbings,** Dunedin School of Medicine, University of Otago for expert review of this article.

Resources for patients with axial spondyloarthritis:

Information about ankylosing spondylitis and axial spondyloarthritis:

- **www.arthritis.org.nz/campaign/**
- **www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Spondyloarthritis**
- **www.arthritisresearchuk.org/arthritis-information/conditions/ankylosing-spondylitis.aspx**

Advice and guidance on appropriate exercises:

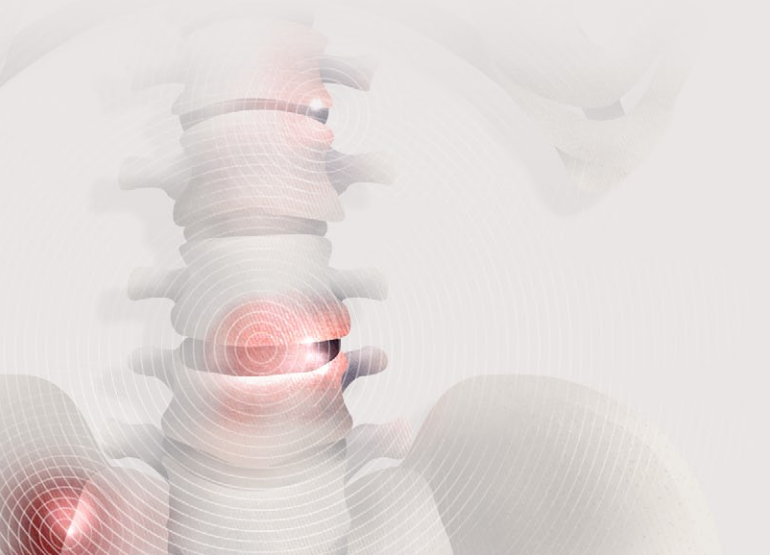
- **http://nass.co.uk/exercise/**

NZF patient information leaflets on NSAIDs:

- Naproxen: **www.mymedicines.nz/home/sheet/Naproxen**
- Ibuprofen: **www.mymedicines.nz/home/sheet/Ibuprofen**
- Diclofenac: **www.mymedicines.nz/home/sheet/Diclofenac**

Advice for patients using TNF inhibitors:

- **www.rheumatology.org/I-Am-A/Patient-Caregiver/Treatments/Anti-TNF**



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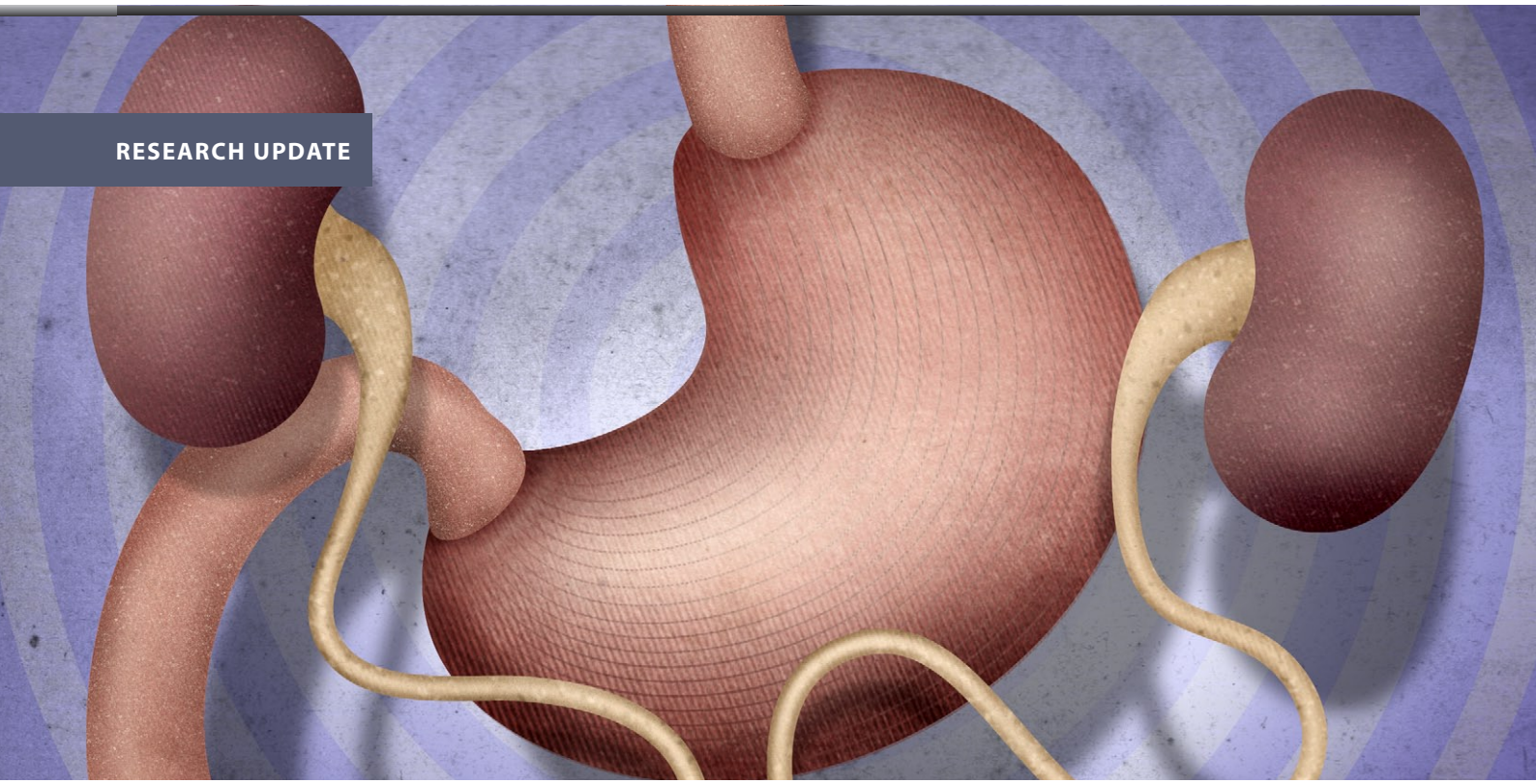
RESEARCH UPDATE



Proton pump inhibitors and the risk of acute kidney injury

KEY PRACTICE POINTS:

- The use of PPIs is associated with acute and chronic kidney injury
- When prescribing PPIs consider the patient's overall risk for kidney disease
- Maintain a high index of suspicion for kidney injury, especially during the first three months of PPI use; the risk diminishes quickly after cessation of treatment
- Features of PPI-induced acute interstitial nephritis are often non-specific and include malaise, anorexia and low grade fever in association with acute renal failure
- Prompt cessation of PPIs generally results in a full recovery of renal function, but delays in diagnosis can lead to the development of chronic kidney disease (CKD)
- PPI use should be reviewed regularly as dose reduction or withdrawal may be appropriate

Proton pump inhibitors (PPIs) are among the most frequently prescribed medicines in New Zealand. They are clinically effective and are widely believed to have few adverse effects. Recent research, however, has confirmed an association between PPI use and kidney injury. This article updates information on the safety of PPIs published in BPJ 61 (Jun, 2014).

See: **www.bpac.org.nz/BPJ/2014/June/ppi.aspx**

Proton pump inhibitors (PPIs): effective but not risk-free

Proton pump inhibitors are some of the most commonly prescribed medicines in New Zealand; omeprazole was the fourth most frequently prescribed medicine in the year to December, 2015.[1] The total use of PPIs in New Zealand is likely to be substantially higher than this as several are available over-the-counter without a prescription. This high level of use stems from their clinical effectiveness and relatively low risk of serious adverse effects. Post-marketing research reports, however, that PPIs may increase the risk of infection, fracture

and malabsorption of nutrients including vitamin B12 and magnesium.[2–4] In addition, recent research has confirmed an association between PPI use and kidney injury.[3, 5–7]

PPIs are associated with acute interstitial nephritis

Isolated case reports of interstitial nephritis in patients taking PPIs have triggered further investigation.[8] Research has now confirmed this association: patients who developed acute kidney injury (AKI), including acute interstitial nephritis (AIN), were at least twice as likely to have taken PPIs compared to those without renal disease.[6, 7] New Zealand research has also reported that patients currently using PPIs were four to five times more likely to experience AIN compared to non-users.[5] Patients over 60 years old were the most frequently affected, with approximately 20 patients in this cohort developing AIN each year per 100 000 patients taking PPIs.[5] PPI-induced AIN did not appear to be dose-dependent or related to duration of treatment.[5] This study did not report any significant relationship between interstitial nephritis and past PPI use.

Chronic kidney disease is also more common in patients taking PPIs

In addition to AKI, PPI use may cause chronic kidney disease (CKD) due to the secondary effects of AKI and hypomagnesaemia, which has been independently associated with declining kidney function.[9, 10] A large prospective cohort study in the United States reported patients taking PPIs had approximately 20–50% increased incidence of CKD compared to non-PPI users.[3]

Diagnosing acute interstitial nephritis in patients taking PPIs

Medicines are the most common cause of AIN, however, it may also be caused by infection or immunologic reaction.[6] Patients with AIN classically present with acute renal failure and a triad of fever, rash and arthralgia. This triad, however, occurs less often in PPI-induced AIN; patients are more likely to have non-specific symptoms such as malaise, anorexia and low grade fever.[6] Urine dipstick will typically show protein and white cells, and less commonly blood.[12] Laboratory investigations show acute worsening of renal function and in some cases, eosinophilia.[12]

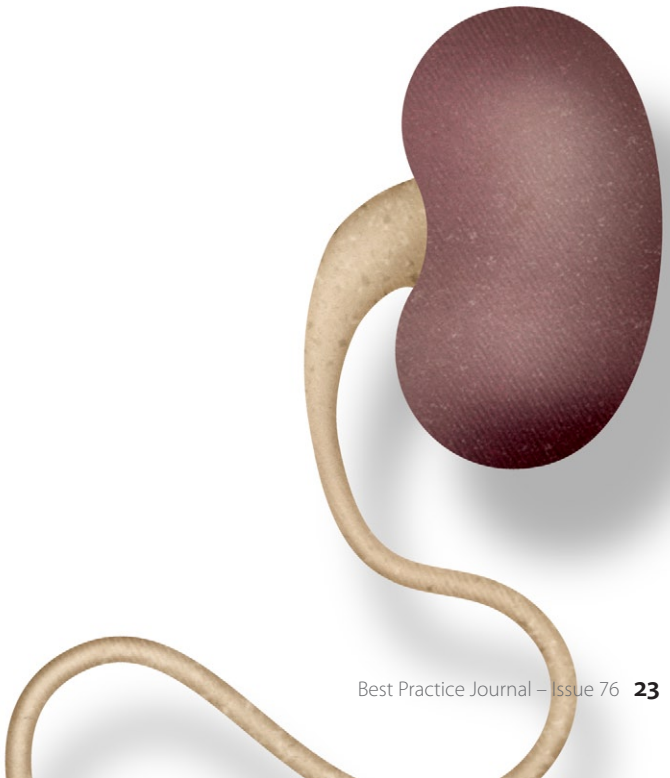
Early detection of AIN and cessation of the causative medicine is the most effective treatment.[12] Patients suspected of having AIN should be referred urgently to nephrology: 40% of these patients will require dialysis.[12] PPI-induced AIN may be less severe than AIN from other causes but recovery is often slower.[11]

Managing patients in the "real world"

While PPIs are associated with the development of both acute and chronic kidney injury, the risk is relatively low.[13] Many patients taking PPIs, however, are already at risk of renal disease as they may be older, taking NSAIDs and other nephrotoxic medicines, or have other risk factors for kidney injury. Clinicians should therefore maintain a high index of suspicion for AKI in patients on a PPI who have a rapid decline in renal function, especially during the first three months of use.[11] Baseline and monitoring of renal function may be appropriate in at risk patients.

Key features of PPI-induced AIN include non-specific malaise, anorexia and low grade fever in association with acute renal failure.[11] If AIN is suspected, request urine microscopy and renal function tests. The patient should be referred to a nephrologist for urgent review. AIN is confirmed by renal biopsy.

PPIs are widely considered to be overprescribed and this is supported by studies which show between 14 and 64% of patients using them long-term can discontinue treatment without adverse effects.[3, 14, 15] Patients may find "as required" use of PPIs sufficient to manage their symptoms. Patients taking PPIs long-term should be reviewed regularly for consideration of dose reduction or treatment withdrawal; ideally the goal of treatment is lifestyle control of symptoms with minimal reliance on medicines. Tapering is likely to be more successful than abrupt cessation, as it reduces the likelihood of rebound symptoms.[16]



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A general approach to managing infected wounds and when to remove sutures

Dear Editor,

I think the antibiotics guide is fantastic and use it very frequently. It is great the way it has first line, second line etc. It is a very useful guide.

I was wondering if you could add another part into the "skin" section. I feel wounds deserve their own section. I feel there is not a consensus among doctors in general in terms of the best approach for infected wounds. Or is it as simple as approaching it the same way as standard infected wound like cellulitis – unless it is a closed fist injury or on a diabetic foot.

I would also like to know what the policy should be on soft tissue wounds that have been sutured which then get infected. At what point do we remove the sutures? Is it as soon as infection is suspected or can you watch and wait and manage with antibiotics?

I struggled to find much evidence online on my article search. Most of the evidence was for surgical wound infections instead of soft tissue injuries.

I had a discussion with a patient today who had developed infection post-suturing. He came in previously with signs of infection on Day 3 (Day 1 = sutured) and was already on cephalexin for infection prophylaxis and was switched from that to flucloxacillin 1g four times daily. He was reviewed again on Day 5 and the doctor he saw advised him the sutures needed to be left in longer than normal.

I reviewed him on day 8 (today) and he still had the sutures in place in a wound that still looked red and infected but improved from previously. A colleague of mine who worked as an orthopaedic registrar, advised sutures need to be removed when infected and that's what I thought was standard practice.

However, I would very much appreciate your opinion on this given the lack of evidence I could find online.

Many thanks

Dr Nick Wilmore
Auckland

Response from the bpac^{nz} editorial team:

1. General guidance on wound management

Wounds comprise a diverse range of skin lesions. Wound management is guided by both the type of wound as well as patient characteristics which may delay wound healing, e.g. underlying medical conditions, older age, obesity, smoking, and poor nutrition. All open skin wounds are colonised by bacteria, however, this does not mean all wounds are infected. Inflammation occurs in all wounds during healing and minor

swelling, erythema and increased warmth at the site is normal and should not be confused with clinical infection. Similarly, sutures can provoke a local skin reaction; a small amount of redness and irritation around sutures is not necessarily indicative of infection.

There are four classes of wounds:[1]

- Clean
- Clean-contaminated
- Contaminated
- Dirty

Traumatic wounds are defined as contaminated if they are less than four hours old at time of medical review, and dirty if more than four hours old.[2] Some traumatic wounds, however, are more prone to infection than others: shearing force wounds, such as lacerations, tend to heal well, while avulsion injuries heal poorly and crush injuries both heal poorly and are prone to infection.[3] While clinicians need to consider each case individually, antibiotic prophylaxis is often recommended for contaminated and dirty wounds.[4]

Empiric antibiotic choices, for either traumatic or non-traumatic wounds, are guided by the type of wound, its location, potential pathogens and local antibiotic susceptibility. Susceptibility may differ by geographical area or location, e.g. MRSA is more common in some residential care facilities, and the prevalence of other multi-drug resistant organisms is increasing in New Zealand.[5] Laboratories may publish local antibiotic sensitivities, while the Institute of Environmental Science and Research Ltd (ESR) collates regional laboratory data and publishes this information quarterly.[6]

Flucloxacillin or cefalexin are the mainstays of empiric antibiotic treatment for skin infections, including wounds. Alternatives include erythromycin and co-trimoxazole (if MRSA is present).

Depending on the clinical circumstances, a wound swab may be required in addition to empiric antibiotics. It may be appropriate to change to a narrower spectrum antibiotic when swab results become available, especially if a long course of antibiotics is anticipated. Wounds failing to respond to empiric treatment should be swabbed, with the culture result guiding antimicrobial treatment; note any empiric therapy on the laboratory form.

2. Managing wounds with sutures

When considering wound infections, surgical and traumatic wounds are often grouped together as much of the advice is applicable to both types. Wound infections should be evaluated by severity; patients with mild infections may have increased redness, swelling and pain at the incision site. More severe infections may also have spontaneous drainage from the wound, as well as causing systemic symptoms of fever and tachycardia with associated lymphocytosis. In general, mild wound infections can be cleaned and observed, without suture removal.[2] Patients with moderately infected wounds should have the sutures removed and incisions opened and drained, while those with deep infections may require referral for washout in theatre.[4]

Wound infections do not always require antibiotics, and many wounds can be managed by cleaning, or suture removal and opening and drainage of incisions.[2, 4] Antibiotics are recommended for the treatment of infected surgical or traumatic wounds if the patient has systemic signs including a fever >38°C, tachycardia >110/min, erythema and/or induration > 5 cm from the incision, or necrosis.[4] Appropriate antibiotic therapy should be effective in treating wound infections as long as there is a good blood supply at the wound site. This may not always be the case, e.g. if necrotic tissue is present.

Written guidance cannot, however, replace evaluation of individual patients by an experienced clinician. If unsure, clinicians are advised to discuss their concerns with a senior colleague, an orthopaedic surgeon, or a wound care specialist.

The antibiotic guide is currently under review and will be updated later this year. The current version of the guide is available from: **www.bpac.org.nz/antibiotics**

For more information on wound management see: **www.bpac.org.nz/BT/2013/June/infected-wounds.aspx**

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