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NSAIDS: Making safer treatment choices

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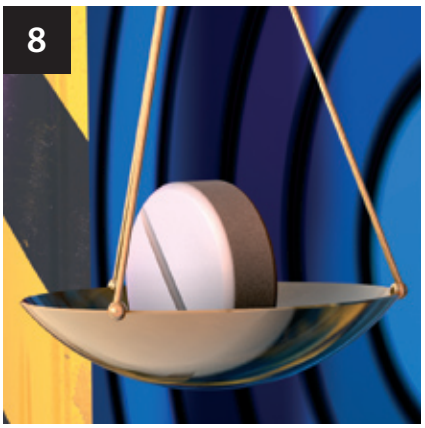

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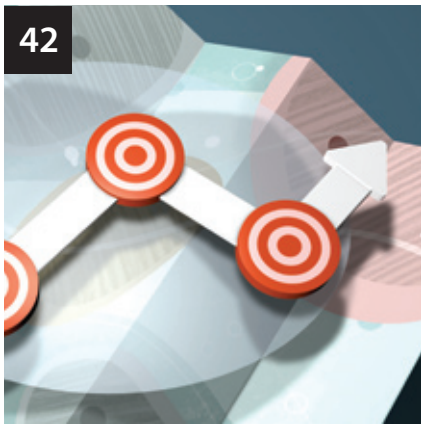

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The elite athlete-patient: a fresh clinical challenge

Contributed by Associate Professor David Gerrard

Associate Professor David Gerrard is a sports physician at the Dunedin School of Medicine, University of Otago. He gives an insight into the challenges faced by clinicians when providing care to elite athletes. When considering treatment options, it is important to be aware of which medicines are subject to restrictions under the World Anti-Doping Agency list of prohibited substances.

Elite athletes are a unique bunch, deserving no less attention than we provide to any patient, despite our occasional difficulties in reconciling their seemingly trivial clinical demands. Obsessive-compulsiveness is a common pre-requisite for contemporary high performance sport, and an athlete's innate desire for an accelerated return to physical activity can make them a clinically challenging prospect.

This editorial comment is not written with the intention of advising doctors how best to treat their patients – this responsibility appropriately resides with the clinician. The aim of this article is to raise awareness of the international "Code" for duty of care, which is unique to sport.[1] It is important that clinicians who provide care for high performance athletes familiarise themselves with these obligations, and consider them as no different as the protocols followed, for example, for an occupational health check or an insurance medical examination.

Doping and drug testing in sport

One particularly perplexing area in sports medicine relates to the use of a group of restricted medicines, defined in sport as "prohibited substances". This is especially challenging when these medicines are also the usual recommended treatment for particular medical conditions. Some physicians vigorously object to the intervention of an external authority that restricts valid therapeutic options when patient wellbeing is the doctor's primary responsibility. In principle there is no argument with this opinion. However, in sport at the highest levels, certain decisions about the use of prohibited medicines are non-negotiable.

Prohibited substances in sport

The internationally agreed List of Prohibited Substances in Sport was established to address the misuse of drugs for purposes of performance enhancement.[1] The list, containing common therapeutic medicines, is formulated and reviewed annually by an international committee of experts appointed by the World Anti-Doping Agency (WADA).[1]

To qualify for consideration of list inclusion, a particular drug must meet two of the following three criteria defined by WADA:

a) The potential for performance-enhancement in sport
b) The potential for harm when used for "non-clinical" purposes
c) Being in violation of "the spirit of sport" as defined in the Code

The ethics of the misuse of drugs in sport

Disgraced cyclist Lance Armstrong was legendary for his survival from testicular cancer and his unprecedented success in seven consecutive Tour de France races. However late in 2012, the widely publicised Report of the United States Anti-Doping Agency (USADA) was the final straw for Armstrong.[3] This document provided unequivocal evidence that his Tour de France successes were enhanced through the use of autologous blood transfusions and an expensive intravenous cocktail that included recombinant erythropoietin, testosterone and corticosteroids. These drugs were administered and closely monitored by medical associates who cunningly circumvented routine drug-testing procedures. Armstrong's undoing was arguably sports greatest "drug-bust" but it provided clear confirmation of medical complicity and the "athlete entourage", and raised concerns for the disregard of ethical clinical practice.[4] Dr Michele Ferrari, the Italian physician implicated with Armstrong, was linked to trafficking, possession and assisting doping. He has received a lifetime sports ban from WADA and the final opinions of the medical jurisdiction are awaited.

Pehaps the most distasteful experiment in the use of performance-enhancing drugs in sport was demonstrated by the government of the former German Democratic Republic (GDR) during the period of the 1960s to 1980s. East German physicians, scientists and coaches collaborated in systematic drug administration to athletes, under the sanction of the GDR Ministry for State Security (Stasi). This clandestine programme of experimentation involved athletes, predominantly females, who received high dose potent drugs without concern for moral or ethical principles.[5 – 9] Under the pretence of research, thousands of "subjects" were implicated in "…one of the largest pharmacological experiments in history… running for more than three decades…". [5]

The consequences of this era in East German sport and politics were profound and far-reaching. Young, female athletes, to whom excessive doses of anabolic androgenic steroids had been administered, suffered long-term consequences. The true facts of this horrendous "experiment" were not made public until the unification of Germany in 1989 when official Stasi documents became available for scientific scrutiny.[5, 8, 9] The world of clinical medicine and sport science still reels from the revelations. In this contemporary human experiment, "…government policy, measured in gold medals, gave scant regard to human suffering and permanent disability."[10]

An increasingly vocal body of contemporary medical opinion has declared the misuse of drugs in sport as an unethical and illegal practice and the Medical Council of New Zealand (MCNZ) has added its support.[11] In 2010 an updated statement entitled "Prescribing performance-enhancing medicines in sport" was posted on the MCNZ website. It states: [11]

> *"Any doctor who knowingly prescribes, administers, traffics, supplies or otherwise assists in the use of prohibited substances, for the deliberate purpose of enhancing sports performance and helping a sports person to cheat, may be subject to disciplinary proceedings and may be liable to a charge of professional misconduct."*

Elite athletes are under the scrutiny of anti-doping authorities and are closely monitored and subjected to testing both in- and out-of-competitive sport. To the public this may appear draconian and a major intrusion of privacy. But to those familiar with contemporary sport, these practices have become "stock-in-trade" to a generation of competitors. These athletes also have an obligation to disclose their status as a tested athlete to their doctor. In New Zealand, athletes in the drug-testing pool will carry a small "wallet-card" provided by Drug-Free Sport New Zealand (DFSNZ), with relevant identification and information for the doctor. However, despite the vigilance of anti-doping agencies and the acceptance by the majority of athletes of strategies to minimise drug misuse, high profile cases provide a stark reminder that the temptation to cheat by using banned, performance-enhancing substances is ever present.[2]

Therapeutic use of prohibited drugs in sport

When, on justified occasions, there is no alternative but to use a listed, prohibited substance to treat an athlete-patient this can be done under the Therapeutic Use Exemption (TUE) process.[12] This is a means by which athletes with genuine medical conditions have the justification for receiving valid, essential treatment. The TUE process protects the athlete from any punitive sanction arising from the presence of a banned substance detected by the analysis of their urine or blood. However, in the interests of consistent application and international integrity, the TUE process is subject to certain pre-requisites, including the provision of adequate diagnostic evidence and specialist endorsement to meet the criteria for a successful TUE application.

The international committee of WADA responsible for establishing TUE Standards, has provided guidelines for several conditions that commonly require the use of prohibited substances.[1] Examples include chronic inflammatory bowel disease (systemic glucocorticosteroids), attention-deficit hyperactivity disorder (methylphenidate or amphetamine), hypogonadal hypogonadism (testosterone) and type 1 diabetes (insulin). The WADA website has instructions for physicians managing these conditions in elite athletes subjected to doping control.

"Retroactive" therapeutic exemption would always be endorsed where the management of any life-threatening episode necessitates the use of a prohibited substance, such as in an emergency department or acute surgical setting. Cases of athletes requiring urgent surgical intervention or treatment for acute asthma or anaphylactic shock are examples frequently encountered in this category. However, the attending physician still remains responsible for ensuring that a complete record is kept of any prohibited substances used and a clear note of their clinical indication is provided to the athlete to substantiate the TUE application.

– David Gerrard

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Providing health care for an athlete: frequently asked questions

Q: What obligations do athletes have in terms of drug testing?

A: Elite-level, New Zealand athletes are constantly under scrutiny by our National Sports Anti-Doping Agency, Drug-Free Sport New Zealand (DFSNZ). These profiled athletes must adhere to doping control procedures in accordance with their obligations to the World Anti-Doping Code established by WADA. This may require the witnessed collection of a urine sample for analysis following an event ("in-competition testing") or without prior notice, involving a sample being collected at a training venue, a residence or elsewhere ("out-of-competition testing"). Athletes may also be required to undergo blood sampling as part of the "athlete biological passport".

Q: How do I know if a patient is a tested athlete?

A: It is the responsibility of individual athletes to inform their doctor of their status as a listed athlete who may be tested for prohibited substance use. In New Zealand, athletes in the testing pool will usually carry a small "wallet card" provided by DFSNZ, with relevant identification and information for the doctor. It is also important to be aware of an athlete who is not currently subject to drug testing in sport, but who may be called in to compete at very short notice.

The testing that the athlete undergoes may be both at the time of competition and at random. It is important then, that clinicians do not assume that a medicine will only be in the body for a short time and can be used in between competitions. Most prohibited substances are prohibited at all times.

Q: What obligations does a doctor have when treating an elite athlete?

A: When providing care to a patient who is an elite athlete, it is necessary to become familiar with the requirements for sports anti-doping. Before administering or prescribing medicines to an athlete who might be subjected to doping control, it is important to first clarify whether the intended medicine is included on the WADA Prohibited List.

If the medicine is prohibited, and no permitted alternative is available, then it is necessary to apply for Therapeutic Use Exemption (TUE) on the athlete's behalf.

Q: How do I know which medicines are prohibited?

A: The list of substances prohibited by the World Anti Doping Agency (WADA) is large. Substances are classified under four categories: substances prohibited at all times for all sports, substances prohibited during competition, substances prohibited from specific sports and limited-use substances.

Many of the prohibited medicines are not routinely prescribed in general practice. However, some prohibited medicines are very commonly used in the community, such as insulin, oral corticosteroids, beta-2 agonists (therapeutic use via inhaler is permitted) and diuretics.

Q: How do you access the WADA List of Prohibited Substances?

A: Check the medicine in the New Zealand Formulary. If a medicine has restrictions on its use based on the current WADA list, it is indicated as "restricted in sport" under Cautions.

For further information on the medicine, visit the DFSNZ website (www.drugfreesport.org.nz); click on "check your medications online" to search for individual medicines, or phone 0800 DRUGFREE, or text the name of the medicine or active ingredient to 4365 (texts cost 20 cents) for full details of its status.

MIMS resources display 'athlete' or an athlete logo next to each medicinal substance, to indicate a permitted medicine or medicine that is permitted with restrictions.

The full 2013 Prohibited List is also available from the World Anti Doping Agency (WADA), see:
www.wada-ama.org/en/Resources

Q: What is the process of Therapeutic Use Exemption?

A: The TUE process protects all athletes and their medical advisors in situations where, in the athlete's best health interests, the use of a prohibited drug is indicated.

Ideally the application should be made before treatment begins. However, the TUE process also allows retroactive approval to be granted in some situations, e.g. treatment in emergency situations, and exceptional circumstances such as the accidental prescription of prohibited substances. The requirements of TUE are included on the application form available on the DFSNZ website. It is necessary to demonstrate a clear diagnostic process and specialist endorsement, especially where the drugs used have a high potential for performance enhancement, e.g. the use of anabolic androgenic agents or potent stimulants.

Further information on TUE and a downloadable application form is available from:
www.drugfreesport.org.nz

For assistance with the TUE process,
phone: 0800 DRUGFREE.

Q: Can athlete patients be prescribed the usual medicines for asthma?

A: The inhaled beta-2-agonists currently permitted in sport (WADA, 2013) are salbutamol (maximum 1600 micrograms over 24 hours), formoterol (maximum delivered dose 54 micrograms over 24 hours) and salmeterol (recommended therapeutic regimen as per medicine datasheet).

Beta-2-agonists by any other method than inhalation are prohibited.

Inhaled corticosteroids are permitted. Oral, IM or IV corticosteroids are prohibited.

A TUE must be applied for if an athlete requires a prohibited medicine (or dose) for control of their asthma.

Q: What can athlete patients be prescribed for pain and inflammation?

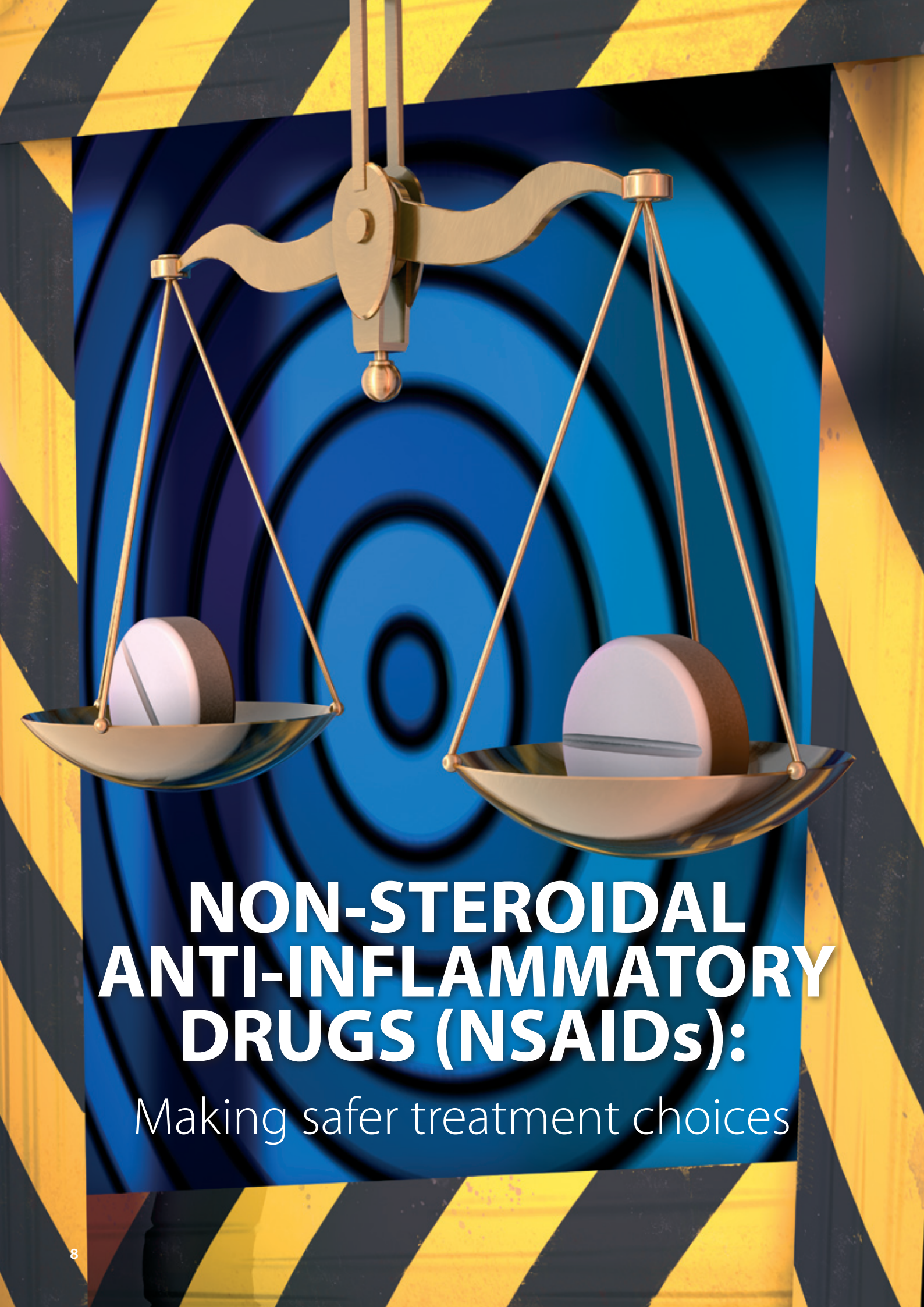
A: Pain and inflammation are common in people competing professionally in sport. Mild analgesics and anti-inflammatories, for general treatment of pain, inflammation or headache are permitted options. For example, paracetamol, non-steroidal anti-inflammatory agents, codeine and tramadol are all permitted medicines on the WADA list. Strong opioids, such as oxycodone and morphine, are prohibited during competition.

Beware of combination products and supplements

There have been many cases of athletes who have unknowingly taken prohibited substances which have been "hidden" in a product. Dietary, nutritional and sport supplements and herbal products are not manufactured to the same standard as medicines, and may contain substances that are prohibited in sport.

Labelling standards for supplements manufactured in New Zealand and overseas do not always require a complete list of components on the product label. Therefore, it is often not possible to guarantee the status of a supplement that is used in sport. Elite athletes need to be aware of this risk, and be cautious about the use of supplements; reputable products should be chosen, and the ultimate responsibility that they do not contain prohibited drugs remains with the athlete.

"Cough and cold" preparations have been implicated in cases of use of prohibited substances, but this is less common now since pseudoephedrine (prohibited in sport) was removed from over-the-counter cough and cold products. Pseudoephedrine is now only available on prescription (as a single product), and is a controlled medicine.



NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs):

Making safer treatment choices

Non-steroidal anti-inflammatory drugs (NSAIDs) are successfully used to treat a wide range of painful conditions. However, NSAIDs should be prescribed with caution as courses of just a few days, even at doses within prescribing recommendations, can be associated with serious adverse effects in susceptible patients. In primary care, paracetamol is recommended in preference to NSAIDs, where appropriate. If a patient is likely to benefit from NSAID treatment naproxen or ibuprofen are recommended first-line, at the lowest effective dose, for the shortest possible time. Patients taking NSAIDs who are at increased risk of complications require regular monitoring.

How NSAIDs work determines their risk and guides their use

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medicines for analgesia in primary care, after paracetamol.[1] However, NSAID use can be associated with a range of serious adverse effects including: cardiovascular events, gastrointestinal complications, renal failure and hypersensitivity reactions. Even if the risk of an individual patient experiencing an NSAID-related adverse event is relatively low, the frequent use of NSAIDs within the community means that the potential for NSAID-related adverse events to occur is a concern. NSAID use therefore requires careful consideration of individual patient risk factors. To maximise patient safety it is recommended that clinicians consider the following points before prescribing an NSAID:[2]

- Prescribe all NSAIDs with caution, in all patient groups, even over short periods of time
- Prescribe the lowest effective NSAID dose, for the shortest possible time, and review the need for continued use at each consultation
- Older patients, patients with increased cardiovascular risk, patients with type 2 diabetes, and patients with reduced renal function or a history of renal problems are at increased risk of NSAID-related complications and should be advised about adverse effects and regularly monitored when taking NSAIDs
- Naproxen (up to 1000 mg per day) or ibuprofen (up to 1200 mg per day) are the recommended first-line choices for adults based on our current knowledge of NSAIDs and cardiovascular risk; ibuprofen is the most appropriate NSAID for children
- Avoid prescribing long-acting formulations of NSAIDs, where possible, as these are associated with an increased risk of gastrointestinal adverse effects

How NSAIDs work, the patient's age and the condition being treated also need to be taken into account when these issues are discussed with patients.

NSAIDs and cyclo-oxygenase (COX) selectivity

The cyclo-oxygenase-1 (COX-1) and COX-2 enzymes produce prostaglandins following the metabolism of omega-6 polyunsaturated fatty acid (arachidonic acid).[3] Prostaglandins are chemical messengers that mediate inflammation, fever and the sensation of pain.[3] The analgesic and anti-inflammatory effects of NSAIDs are produced through the prevention of prostaglandin production by inhibition of COX activity. The clinical effects and the risk profiles of the different NSAIDs are largely determined by their differential ability to inhibit the COX-1 and/or COX-2 enzymes and their half-lives.

COX-1 is widely distributed in the body but is concentrated in cells of the stomach, kidney, endothelium and in platelets.[4] Prostaglandins catalysed by COX-1 activity control renal perfusion, promote platelet aggregation and provide gastroprotection by regulating mucous secretion.[4] Inhibition of COX-1 can cause adverse gastrointestinal effects.[4]

COX-2 is induced by inflammation and it is present in macrophages, leukocytes, fibroblasts and synovial cells.[4] Prostaglandins formed via COX-2 activity mediate pain, inflammation, fever and inhibit platelet aggregation.[3]

NSAIDs that inhibit both COX-1 and COX-2 enzymes are termed non-selective NSAIDs, while NSAIDs which predominately inhibit COX-2 enzymes are termed COX-2 inhibitors.

NSAIDs and COX inhibition

Ibuprofen, naproxen and diclofenac are non-selective NSAIDs. However, diclofenac inhibits COX-2 relatively more than COX-1.[5] Many of the NSAIDs available in New Zealand have

similar indications, e.g. musculoskeletal pain and inflammation, therefore these three medicines account for 97% of all NSAID prescribing.[1] Other non-selective NSAIDs indicated for specific conditions include: tenoxicam (inflammatory arthropathy, dysmenorrhoea, post-operative pain and acute gout), tiaprofenic acid (inflammatory arthropathy), ketoprofen (inflammatory arthropathy), mefenamic acid (dysmenorrhoea and menorrhagia) and sulindac (inflammatory arthropathy).[6]

Meloxicam is currently the only subsidised (Special Authority) COX-2 inhibitor in New Zealand. At low doses meloxicam mainly inhibits COX-2. As the dose of meloxicam increases COX-1 is increasingly inhibited. For example, there is an increased rate of serious gastrointestinal adverse events at a dose of 15 mg per day, compared to 7.5 mg per day.[7]

Celecoxib and etoricoxib COX-2 inhibitors are also available in New Zealand, but are not subsidised.

Check the New Zealand Formulary or Pharmaceutical Schedule for the subsidy details of NSAIDs

COX selectivity and cardiovascular risk

COX-2 inhibitors were initially developed on the rationale that selective inhibition of COX-2 might replicate the anti-inflammatory and analgesic effects of non-selective NSAIDs while reducing gastrointestinal adverse effects. However, it was later discovered that COX-2 activity inhibits platelet aggregation, therefore NSAIDs that block COX-2 promote thrombosis and events such as myocardial infarction become more likely (see: "Cardiovascular risk in people taking NSAIDs", Page 12).[3] It is now thought that the relative degree to which different NSAIDs inhibit both COX-1 and COX-2, and the effect that this has on platelet aggregation, determines the likelihood of each NSAID causing cardiovascular events.[8] For example, if COX-1 is weakly inhibited and COX-2 is strongly inhibited then the risk of thrombosis will be increased.

Naproxen use (up to 1000 mg per day) does not appear to be associated with increased vascular risk, based on current evidence.[8] This may be because COX-1 inhibition by naproxen is sufficiently prolonged and intense to effectively block platelet activation and counterbalance the prothrombotic effect of COX-2 inhibition.[8]

NSAID half-life also influences treatment choice

NSAIDs can be divided into short-acting NSAIDs with half-lives less than six hours and long-acting NSAIDs. NSAIDs with a short half-life, e.g. ibuprofen, have a relatively quick onset of action and are better suited for the treatment of acute pain. NSAIDs with longer half-lives, e.g. naproxen, or in long-acting formulations are more suited for the treatment of chronic conditions, as they require only once or twice daily dosing. However, persistent exposure to NSAIDs is an independent determinant of gastrointestinal effects therefore NSAIDs with a long-half life, or NSAIDs in a slow-release formulation, are associated with an increased risk of gastrointestinal adverse events (see: "NSAIDs and gastrointestinal complications", Page 13).[9]

Choosing an analgesic regimen

The WHO analgesic ladder recommends paracetamol and/or an NSAID first-line for pain management. The relative efficacy of paracetamol and NSAIDs depends on the underlying condition causing the pain. Specifically, NSAIDs are more effective than paracetamol in the treatment of inflammatory conditions, such as gout or rheumatoid arthritis, and in the treatment of dental and menstrual pain.[3, 10] For tension headache or following orthopaedic surgery paracetamol is reported to provide equivalent analgesia to NSAIDs.[10]

Paracetamol and codeine may have variable efficacy

The effectiveness of paracetamol and codeine may vary depending on a person's level of expression of the CYP2D6 enzyme. People deficient in this enzyme are unable to convert codeine to morphine and may not receive pain relief from its use. Conversely, people who are ultra-fast metabolisers of codeine are at increased risk of opioid toxicity, even at low doses. This can result in respiratory depression. It is estimated that among Europeans up to 10% of people will be either ultra-fast or slow metabolisers of codeine.[14] The prevalence of fast and slow metabolisers of codeine among Māori and Pacific peoples is not known.

Paracetamol is safer than NSAIDs for most conditions

Paracetamol is considered to be a safer treatment choice than NSAIDs in people at increased risk of NSAID-related adverse effects, e.g. children or older patients, patients with cardiovascular or renal co-morbidities or diabetes, or patients with a previous history of gastrointestinal symptoms or NSAID hypersensitivity (see: "Hypersensitivity to NSAIDs", Page 16). Paracetamol is also recommended by United Kingdom guidelines for the long-term treatment of back pain and degenerative conditions, such as osteoarthritis, due to its superior tolerability.[3]

Compared to NSAIDs, paracetamol has:[3]

- Minimal gastrointestinal toxicity
- Little effect on blood pressure
- No association with myocardial infarction
- No interaction with the antiplatelet effect of aspirin

Paracetamol can be given for mild to moderate pain in adults at the recommended dose of 0.5 – 1 g, every four to six hours, to a maximum of 4 g per day.[6] The major adverse effect associated with paracetamol is liver damage due to overdose and it should not be prescribed to patients with liver disease.[6]

Consider adding codeine to paracetamol in select patients

If the risk of NSAID-related adverse events is high, it may be appropriate to consider adding codeine to paracetamol, in preference to NSAID treatment.[11] For example, an older patient with osteoarthritis, diabetes and chronic kidney disease (CKD) may be particularly susceptible to the nephrotoxic effects of NSAIDs (see "NSAIDs and renal function", Page 14).

An appropriate starting dose of codeine in combination with paracetamol for mild to moderate pain in adults is 15 mg, every four hours, as required.[6] Codeine can be given in doses up to 60 mg, if required, but the total dose should not exceed 240 mg per day.[6] The main adverse effects of codeine are gastrointestinal disturbance and potential respiratory depression.[6] The effectiveness of codeine may vary between individuals due to genetic differences in metabolism, and it may not be an appropriate choice for all patients (see: "Paracetamol with codeine may have variable efficacy", previous page).

Combining paracetamol with NSAIDs may be appropriate

The combination of paracetamol with NSAIDs may provide more effective analgesia for some patients, e.g. for post-surgical pain, than either medicine alone.[12] This combination treatment may allow the dose of NSAID required to achieve analgesia to be reduced (compared to NSAID treatment alone) therefore reducing the amount NSAID-related risk the patient

Combination paracetamol and ibuprofen

There are an increasing number of products being marketed to the public that contain both paracetamol and ibuprofen. It is uncertain whether the concomitant use of paracetamol and ibuprofen significantly improves analgesia compared to the use of NSAIDs alone. Studies have produced mixed results and outcomes may be influenced by the cause of the pain being studied. It is also not clear whether the combined use of paracetamol and ibuprofen increases the risk of adverse effects.

A Cochrane review of the analgesic efficacy of paracetamol and ibuprofen in the treatment of post-operative pain, concluded that combinations of paracetamol plus ibuprofen provided better analgesia than either medicine alone.[12] It was also concluded that the combination treatment reduced the need for additional analgesia to be administered and reduced the risk of adverse events occurring.[12] A study of approximately 900 patients using paracetamol or ibuprofen, or a combination of the two, for the treatment of osteoarthritis of the knee found significantly more patients achieved pain control at ten days and at 13 weeks with the combination treatment compared to paracetamol alone, but there was not a statistically significant difference compared to using ibuprofen alone.[15] In contrast, a small study of 90 patients randomised to one of three treatment groups in an emergency department setting found that combination treatment with paracetamol and ibuprofen did not provide more effective pain relief following musculoskeletal injury compared to either medicine alone.[16]

A large British study funded by a pharmaceutical company reported that compared to the use of the paracetamol and ibuprofen alone, the combined use of the two medicines did not increase the number of adverse effects.[17] However, in the treatment of osteoarthritis of the knee a trend towards increased dyspepsia, diarrhoea and blood loss was reported in patients using a combination product.[15]

The lack of a demonstrated strong synergistic analgesic effect between paracetamol and ibuprofen, suggests that the two medicines may have similar modes of actions and their effects may not be additive.[18] The lack of clear evidence of improved analgesia has led some experts to question the value of combination products containing paracetamol and ibuprofen.[18]

is exposed to.[12] However, this approach does not appear to be effective for all conditions (see: "Combination paracetamol and ibuprofen", Page 11). If a combination of paracetamol and NSAIDs is used to treat pain, consider titrating the NSAID dose downwards as pain becomes more manageable, while continuing treatment with paracetamol at the same dose. The NSAID can then be withdrawn, before paracetamol, and treatment with paracetamol continued, as required.

Review and intensify lifestyle modifications to manage pain

Long-term pain, as with any chronic condition, requires continual review and ongoing lifestyle modifications to prevent a decline in the quality of the patient's life. For example, a person with osteoarthritis is likely to benefit from intensifying exercise and weight loss programmes.[13]

Reducing the risk of NSAID use

If it is decided that NSAID treatment is appropriate, having weighed the risks versus benefits of treatment, ensure the patient's history is known before an NSAID is prescribed. In particular:[3]

- Ensure the patient is aware which over-the-counter (OTC) products contain NSAIDs and that they know that they should not take any other NSAID-containing products while they are being treated with an NSAID
- Determine if the patient has any co-morbidities that may increase the risk of NSAID treatment, e.g. cardiovascular disease, CKD, diabetes, hypertension or duodenal ulcer
- Query if the patient is taking any medicines that may interact with NSAIDs, e.g. angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), diuretics, clopidogrel, warfarin, dabigatran or aspirin
- Discuss any history of NSAID-related adverse effects with the patient. Their preference may affect the dosing regimen. Some patients may prefer to tolerate adverse effects if a higher dose is likely to result in improved symptom control, while other patients may take the opposite view.

Naproxen (up to 1000 mg per day) or ibuprofen (up to 1200 mg per day) are recommended first-line choices if NSAIDs are required, due to the lower risk of cardiovascular events occurring when these medicines are taken at these doses, compared to other NSAIDs.[2] N.B. The recommended maximum dose of ibuprofen is 2400 mg/day;[6] this higher dose may be necessary, and appropriate, for some patients, but is associated with increased cardiovascular risk.

Diclofenac (75 – 150 mg, daily, in two or three divided doses) is indicated for acute pain and inflammation, in inflammatory arthropathy and other musculoskeletal disorders.[6] However, diclofenac at doses of ≥ 150 mg per day is associated with an increased risk of cardiovascular events (see below). Diclofenac use is contraindicated in patients who have had a myocardial infarction in the previous 12 months.[6]

When prescribing NSAIDs following muscle injury, short courses, i.e. three to seven days, are preferable to longer term use.[19]

Cardiovascular risk in people taking NSAIDs

Prescribe long-term NASIDs with caution to people with an elevated cardiovascular risk, particularly if they have had a previous cardiovascular event. All non-selective NSAIDs and COX-2 inhibitors are associated with increased cardiovascular risk - except naproxen up to 1000 mg per day or ibuprofen up to 1200 mg per day.[2, 20] This increased risk begins within the first week of treatment and translates to an additional three major vascular events per 1000 patients, per year.[8, 21]

NSAID use has also been found to approximately double the risk of hospital admission due to heart failure and increase systolic blood pressure by an average of 2 – 3 mmHg.[3, 8] The effect NSAIDs have on blood pressure may be more dramatic in people with pre-existing hypertension and in people taking antihypertensives (see: "NSAIDs and renal function", Page 14).[3] Blood pressure should be monitored in patients with hypertension and older patients within the first month of initiating long-term NSAID treatment, and then routinely monitored as part of ongoing management.[3]

NSAIDs increase cardiovascular risk across all patient groups

A large study found that there was a relative increase in cardiovascular risk, mainly attributed to coronary events, of approximately 33% in patients using high-dose diclofenac (> 150 mg), COX-2 inhibitors (celecoxib, rofecoxib, etoricoxib and lumiracoxib) and high-dose ibuprofen.[8] Importantly, the trial found that there was no statistical difference in this risk between patient groups with low or high predicted five-year cardiovascular risk.[8] The significance of this study to primary care in New Zealand is that an increased cardiovascular risk has been an under-recognised concern in many patients taking non-selective NSAIDs.

Short-term and long-term use of NSAIDs is associated with increased cardiovascular risk. Advise patients who have had a previous cardiovascular event that even one or two doses of

ibuprofen or diclofenac may increase their risk of a recurrent event. A study of over 83 000 patients with prior myocardial infarction found that NSAID use increased the risk of recurrent myocardial infarction or death by 1.45 times during the first seven days of treatment and this risk persisted throughout the course of treatment.[21] The greatest risk was associated with diclofenac which increased the risk of myocardial infarction and/or death by 3.26 times at day one to seven of treatment.[21] Naproxen was not associated with an increased risk of myocardial infarction or death during the 14 week study duration.[21]

NSAIDs and gastrointestinal complications

Gastrointestinal adverse events are increased two to four-fold by the use of all NSAIDs and this increase is dose dependent. Gastrointestinal complications associated with NSAID use include: dyspepsia, gastrointestinal bleeding, peptic ulcers and perforations of the upper gastrointestinal tract.[3, 9] This is because inhibition of the COX-1 enzyme reduces the production of protective gastric mucous. In general NSAIDs that have a long half-life or are taken in a long-acting formulation have a greater risk of gastrointestinal adverse effects.[9] Gastrointestinal symptoms are less common in people taking COX-2 inhibitors, however, the risk is increased in patients who are concurrently taking aspirin.[8]

Risk factors for gastrointestinal adverse effects associated with NSAID use include:[3]

- Age over 65 years
- Previous adverse reaction to NSAIDs
- The use of other medicines that may exacerbate any gastrointestinal adverse effects, e.g. anticoagulants, selective serotonin reuptake inhibitors (SSRIs) and corticosteroids
- Liver disease
- Chronic kidney disease (CKD)
- Smoking
- Excessive alcohol consumption

Use of non-selective NSAIDs and COX-2 inhibitors in people with ulcerative colitis and Crohn's disease may cause an exacerbation of symptoms.[3]

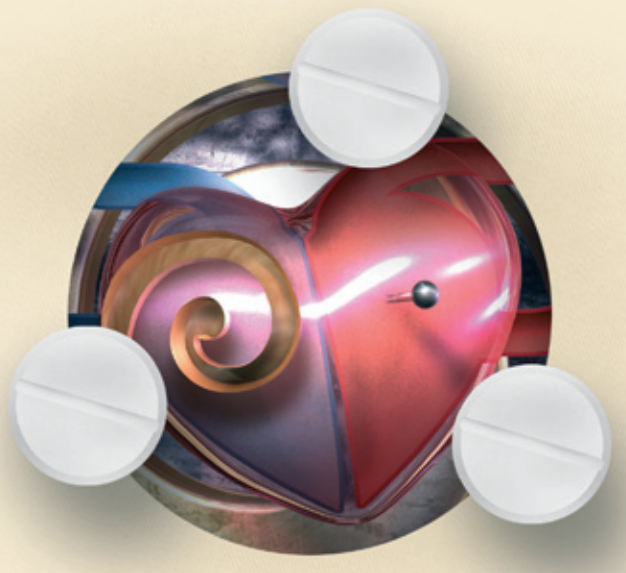
Paracetamol is generally better tolerated than NSAIDs in people at increased risk of gastrointestinal adverse effects. Diclofenac and COX-2 inhibitors appear to be the least likely NSAIDs to cause upper gastrointestinal perforation, obstruction or bleeds, while the risk is likely to be increased for patients taking ibuprofen and naproxen.[8]

Aspirin and cardiovascular risk

It is unknown if aspirin use, which irreversibly inhibits COX-1, influences the apparently neutral cardiovascular effects of naproxen. A large study has found evidence that aspirin may confer a cardioprotective effect in patients taking COX-2 inhibitors, but not in patients taking ibuprofen.[23] Further studies are required to characterise the cardiovascular effects of aspirin in people taking naproxen.

A practical approach to the issue of a possible interaction between NSAIDs and aspirin prescribed for cardioprotection is to minimise the combined use of these medicines in patients with elevated cardiovascular risk. The use of aspirin for the primary prevention of cardiovascular disease is controversial. Current evidence only justifies the use of low-dose aspirin for primary prevention in patients with a five-year cardiovascular risk of greater than 15%.[24] Furthermore, patients with a high cardiovascular risk should not be routinely prescribed long-term NSAIDs, if possible. Finally, patients with increased cardiovascular risk are likely to be older and may have other co-morbidities that increase the risk of NSAID-related adverse effects. Therefore the number of patients whose cardiovascular risk is clinically affected by any interaction between aspirin and NSAIDs in primary care is likely to be small when NSAID use is carefully managed.

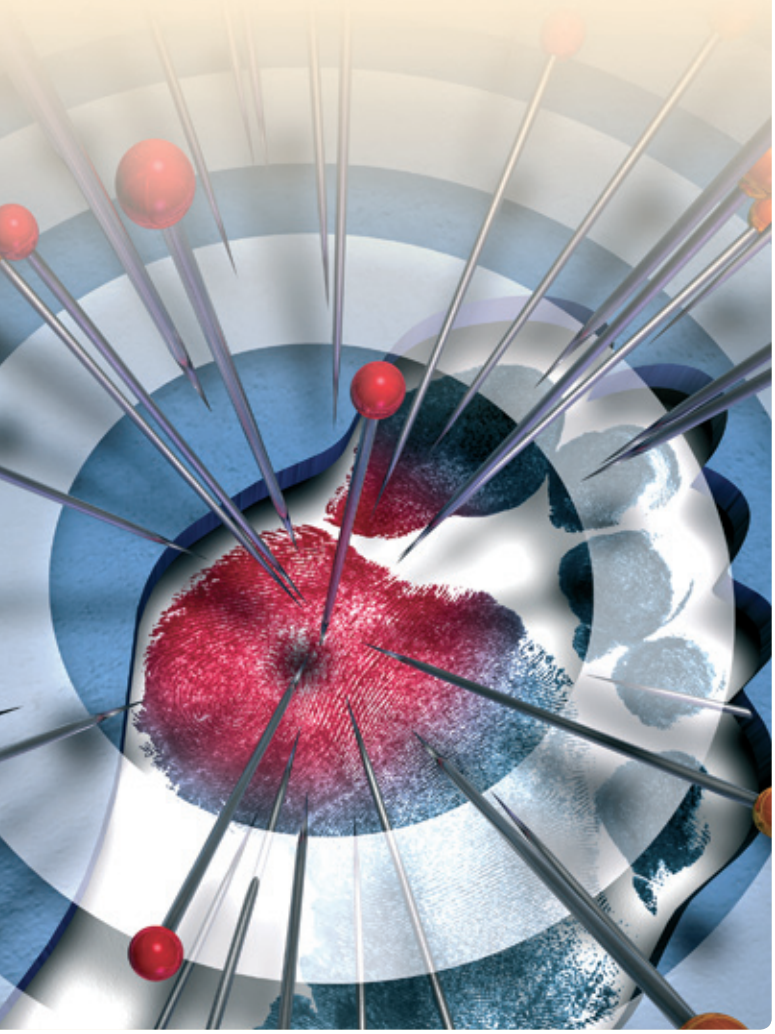
For further information see: "The use of antithrombotic medicines in general practice: A consensus statement", BPJ 39 (Oct, 2011).



Reducing NSAID-related risk in Māori

NSAIDs are often used in the management of gout. Gout is more prevalent among Māori males (11.7%) compared to European males (3.7%).[22] Māori are also more severely affected by gout and are therefore more likely to be using NSAIDs to manage acute flares than non-Māori.[22] As Māori are approximately twice as likely as non-Māori to die of cardiovascular disease, the use of NSAIDs in this population requires added caution. Prescribers should be aware of the elevated cardiovascular risk amongst Māori when prescribing NSAIDs for gout and monitor for adverse effects accordingly. In addition, management of gout among Māori patients should be intensified to reduce the likelihood of flares occurring and reduce the need for NSAID treatment. Corticosteroids (oral or intra-articular) or colchicine may be considered as treatment alternatives to naproxen for acute gout flare.

For further information see: "An update on the management of gout", BPJ 51 (Mar, 2013).



Reducing the risk of gastrointestinal complications

Advise patients to take NSAIDs with milk or food so the stomach is not empty and irritation is reduced.[3] Consider co-prescribing a proton pump inhibitor (PPI) prophylactically in people aged over 45 years if NSAIDs are being used long-term in the treatment of osteoarthritis, rheumatoid arthritis or lower back pain.[2] PPIs should be taken daily, rather than "as needed" because PPIs require approximately three days to achieve steady state inhibition of acid secretion and ulceration or bleeding of the gastrointestinal tract can often occur in the absence of dyspepsia.[3, 25]

A Cochrane review found that both PPIs and histamine-2 receptor antagonists, e.g. ranitidine, were effective at preventing chronic NSAID-related gastric and duodenal ulcers.[26] Omeprazole for the prevention of NSAID-related ulcers can be initiated in adults at 20 mg, once daily, for four weeks and continued for another four weeks if gastrointestinal symptoms have not completely resolved.[6] Ranitidine can be initiated in adults, for protection against NSAID-related ulcers, at 150 mg, twice daily, or 300 mg at night, for up to eight weeks.[6] Misoprostol is no longer routinely used in primary care for the prevention of NSAID-related ulcers as it is associated with diarrhoea and occasionally more severe adverse effects, even at low doses.[6, 26]

If a patient develops gastrointestinal symptoms during NSAID treatment another type of NSAID can be trialled, an alternative class of analgesic trialled, or a PPI prescribed.

In patients with a high risk of developing gastrointestinal complications who require long-term NSAID treatment:[3]

- Prescribe a PPI and advise the patient to discontinue the NSAID and contact a health professional if they notice any gastrointestinal symptoms, e.g. black stools
- Monitor haemoglobin levels for the first month of treatment. Long-term haemoglobin monitoring is recommended if bleeding is an ongoing clinical concern.
- If gastrointestinal adverse effects do develop, consider switching to another NSAID

NSAIDs and renal function

All medicines which block COX-2 are potentially nephrotoxic because they can reduce blood flow to the kidney by preventing prostaglandin-mediated vasodilation. This is particularly true in patients who are dehydrated. NSAIDs can also cause immune mediated acute kidney injury (AKI), e.g.

acute interstitial nephritis. In New Zealand over 40% of all renal adverse reactions reported to the Centre for Adverse Reactions Monitoring (CARM) were associated with diclofenac.[27] The risk of AKI in patients taking NSAIDs and other potentially nephrotoxic medicines is greatest at the start of treatment, therefore even short courses of NSAIDs should be avoided, if possible, in patients at increased risk.[28]

All people with CKD should avoid NSAIDs where possible. CKD is a risk factor for AKI and one-quarter to one-third of all people aged over 64 years have CKD.[29] Acute illness and/or hypovolaemia, even if mild, further increases the risk of AKI occurring in people with CKD who are taking NSAIDs. Patients with CKD who are taking NSAIDs should be advised to discontinue use if they develop an acute illness, especially if they become dehydrated. Patients who have had a previous acute decline in renal function should have their notes flagged and be identified as at risk of NSAID-related AKI.

People with type 2 diabetes should avoid NSAIDs where possible. Reduced renal function and albuminuria are both risk factors for micro and macrovascular complications that have increased prevalence in people with diabetes.[30] Preservation of renal function to prevent the development of CKD and to reduce cardiovascular risk is an essential part of the management of patients with type 2 diabetes.

NSAID nephrotoxicity can be exacerbated by ACE inhibitors or ARBs as these medicines impair the regulation of blood flow leaving the kidney. Renal function can be compromised even further if a patient is also taking a diuretic. The combined potential effect of these three medicines has been referred to as the "triple whammy". This can result in hyponatremia or hyperkalemia, AKI and cardiac failure.[3, 31] The risk of this occurring is greatest in the first 30 days of use.[28] This combination of medicines should be prescribed with caution, particularly in people with CKD or diabetes. If patients develop an acute illness it may be appropriate to discontinue or reduce the dose of these medicines.

In patients with reduced renal function who are taking NSAIDs, or in patients at increased risk of renal toxicity, serum creatinine and potassium should be measured after one to two weeks of treatment and then monitored regularly.[3]

For further information see: "Acute-on-chronic kidney disease: Prevention, diagnosis, management and referral in primary care", BPJ 46 (Sep, 2012).

Topical analgesics

Topical NSAIDs are not subsidised in New Zealand, however, they are readily available over-the-counter (OTC) and are frequently purchased for the treatment of soft tissue injuries, e.g. sports injuries. Topical NSAIDs, in combination with paracetamol, are recommended before oral NSAIDs or codeine in United Kingdom guidelines for the treatment of osteoarthritis.[13] Topical NSAIDs are also preferred to oral NSAIDs by some clinicians for patients aged over 75 years.[3]

Topical NSAIDs are considered to be as safe as placebo in the treatment of acute pain and therefore can be safely used by patients who are at risk of developing complications associated with oral NSAIDs.[35] Blood concentrations of NSAIDs after applying topical products are typically less than 5% of those reached by using oral NSAIDs.[35] Approximately six or seven patients out of ten will experience successful pain control with topical NSAIDs.[35] However, a large proportion of this effect is because sprain-type injuries tend to improve without treatment.[35]

Topical capsaicin is also often used as an adjunctive treatment for osteoarthritis of the knee or hand.[13] Topical capsaicin is currently subsidised for patients who have osteoarthritis that is not responsive to paracetamol and where oral NSAIDs are contraindicated. Topical capsaicin is an irritant and should not be applied to the eyes, mucous membranes or broken skin.[6] Hands should be washed immediately after applying this medicine.[6]

Hypersensitivity to NSAIDs

NSAID/aspirin hypersensitivity is characterised by symptoms ranging in speed of onset from anaphylaxis and bronchospasm to delayed skin and systemic reactions occurring over weeks.[32] The reaction is due to COX-1 inhibition and is not mediated by IgE, therefore it is not a true allergy.[32] NSAID hypersensitivity is reported to affect 0.5 – 1.9% of the general population.[32] However, reports of prevalence among adults with asthma are as high as 21% if aspirin provocation testing is used.[32] In children the prevalence of NSAID hypersensitivity is lower and reported to be 0.3% – 5% as assessed by provocation.[32] Cutaneous hypersensitivity reactions are relatively infrequent and affect 0.3% of the population.[32]

NSAIDs can be routinely prescribed to patients with asthma who have no previous history of NSAID-associated symptoms. However, the possibility of NSAID use increasing asthma severity should be discussed with the patient first. Patients with asthma and nasal polyps or recurrent sinusitis are more likely to experience hypersensitivity to NSAIDs.[33] People who have had a hypersensitivity reaction to a NSAID should avoid all non-selective NSAIDs as the reaction is likely to be a class effect.[32]

NSAID use in women who are pregnant is not recommended

Paracetamol is preferred to NSAIDs in women who are pregnant because NSAID use in the first trimester doubles the risk of spontaneous abortion.[3] Later in pregnancy NSAID use is associated with premature closure of the ductus arteriosus blood vessel, which can result in structural birth defects, preterm delivery or low birth weight.[34] NSAIDs may also delay the onset of labour and increase blood loss during childbirth.[3]

Breast feeding while taking paracetamol or NSAIDs is considered safe due to the low concentrations of these medicines in breast milk.[34] However, aspirin use during lactation has been associated with significant adverse events in infants.[34] Repeat doses of codeine should be avoided wherever possible in women who are breast feeding, as severe toxicity has been reported in infants whose mothers are ultra-fast metabolisers (see: "Paracetamol and codeine may have variable efficacy", Page 10).[6]

Use of NSAIDs in children

Ibuprofen is generally the preferred NSAID for use in children. Naproxen is not indicated for the short-term treatment of pain and fever in children, but may be prescribed for rheumatoid arthritis in children aged over five years.[6] Diclofenac is the only other NSAID available in New Zealand for the treatment of pain and inflammation in children aged under 12 years, but it is rarely prescribed for this purpose in primary care.

Fever and NSAID use in children

Febrile illness accounts for a large proportion of childhood presentations to primary care. Between 20 – 40% of parents report an occurrence every year.[36] Paracetamol (children aged over one month, 15 mg/kg per dose, every four hours, up to four times daily, maximum 1 g per dose and 4 g per day) or ibuprofen (children aged under 12 years, 20 mg/kg in divided doses, to a maximum of 500 mg per day in children under 30 kg) are both indicated for the treatment of pain and fever in children.[6, 36] However, before prescribing ibuprofen for the treatment of febrile illness consider emerging evidence that suggests the use of NSAIDs in children may be associated with an increased risk of AKI, especially in children who are obese (see below).

A paracetamol dosage calculator for children is available from:
www.bpac.org.nz/resources/other/bmi_calc/bmiCalc.html

Management of fever in children should aim to improve comfort rather than reduce body temperature.[37] Points to consider when prescribing medicines specifically for fever in children include:[36]

- Mild fevers (<38°C) do not need to be treated
- Paracetamol or ibuprofen should not be given for the sole purpose of reducing body temperature (see: "The benefits of inflammation and fever")
- Medicines for fever should only be prescribed for as long as the child is in discomfort. If discomfort is not alleviated before the next dose is due, then switching, e.g. changing from paracetamol to ibuprofen, may be considered. Also consider medical review.
- Do not give paracetamol and ibuprofen at the same time
- Paracetamol and ibuprofen do not prevent febrile convulsions and should not be prescribed specifically for this reason

Ask if the child has taken any medicine for their current illness when assessing their condition. A failure to respond to prior

treatment may indicate a more serious illness. Advise parents of the need for children with fever to receive regular fluids.[36] Small quantities of water offered frequently are best, or breast milk if the child is being breast fed. Parents should not give NSAIDs to children who may be dehydrated, e.g. vomiting, sunken eyes, tears or urine absent or if skin turgor is diminished. Tepid sponging is not recommended for the treatment of fever, and children with fever should neither be over-wrapped nor under dressed.[36] Discussing the benefits of fever with parents may help to reduce parental distress.

NSAIDs and acute kidney injury in children

NSAIDs should be prescribed with caution in children with acute illness and/or volume depletion.[38]

Children aged under five years and children who are obese may be at greatest risk of NSAID-induced AKI. One study of children admitted to hospital with AKI found that at least 2.7% of all instances were due to NSAID use, with NSAID use likely to be a contributing factor to additional cases of multi-factorial AKI.[39] The majority of presentations occurred within the first seven days of treatment and doses were generally within recommended prescribing guidelines.[39] Vomiting (74%) was the most frequent symptom followed by abdominal pain (67%) and decreased urine output (56%).[39] Children aged under five years were most likely to require intensive treatment and stay in hospital for longer.[39] Obesity may be an important risk factor for NSAID-induced AKI in children as almost half of the patients admitted were at or above the 95th percentile for body mass index (BMI) or weight:length ratio.[39]

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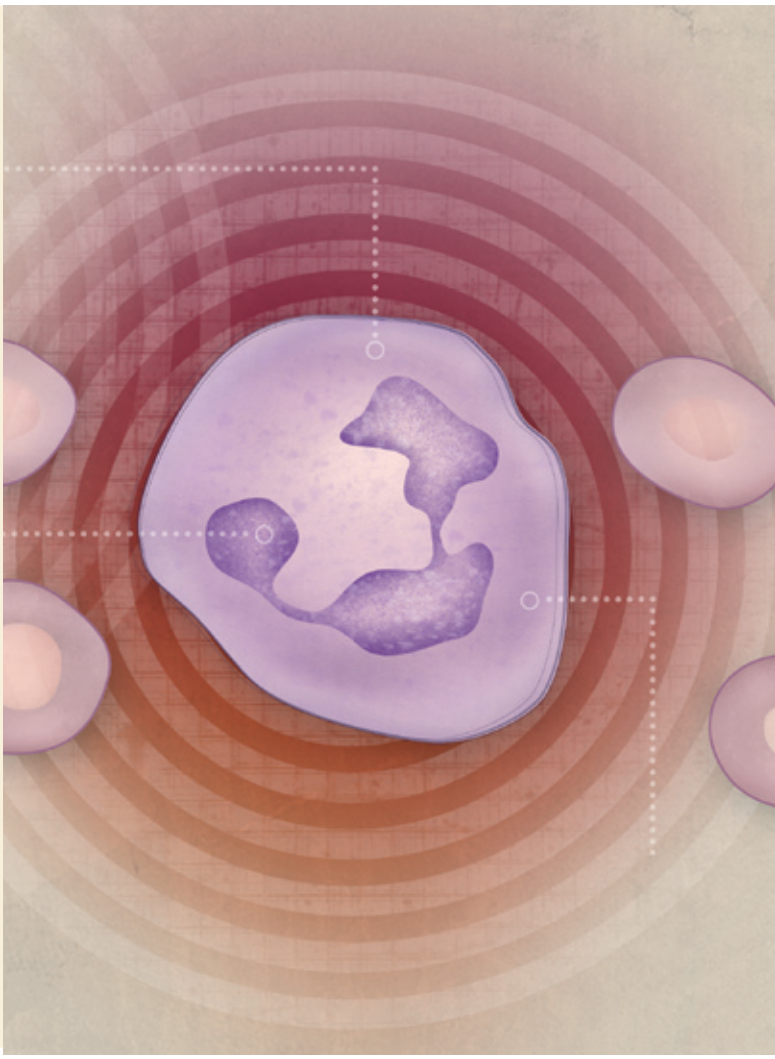
The benefits of inflammation and fever

The inflammatory response is triggered by damaged or infected cells releasing pro-inflammatory proteins. These signals cause local capillaries to increase in size and capillary membranes to become permeable, resulting in swelling as fluid accumulates locally. Attracted by the chemical signals, white blood cells pass through the capillary membranes and invade the area, attacking pathogens and consuming dead and infected cells. The increased body temperature acts to suppress bacterial growth, viral replication and therefore reduces the duration of infections.



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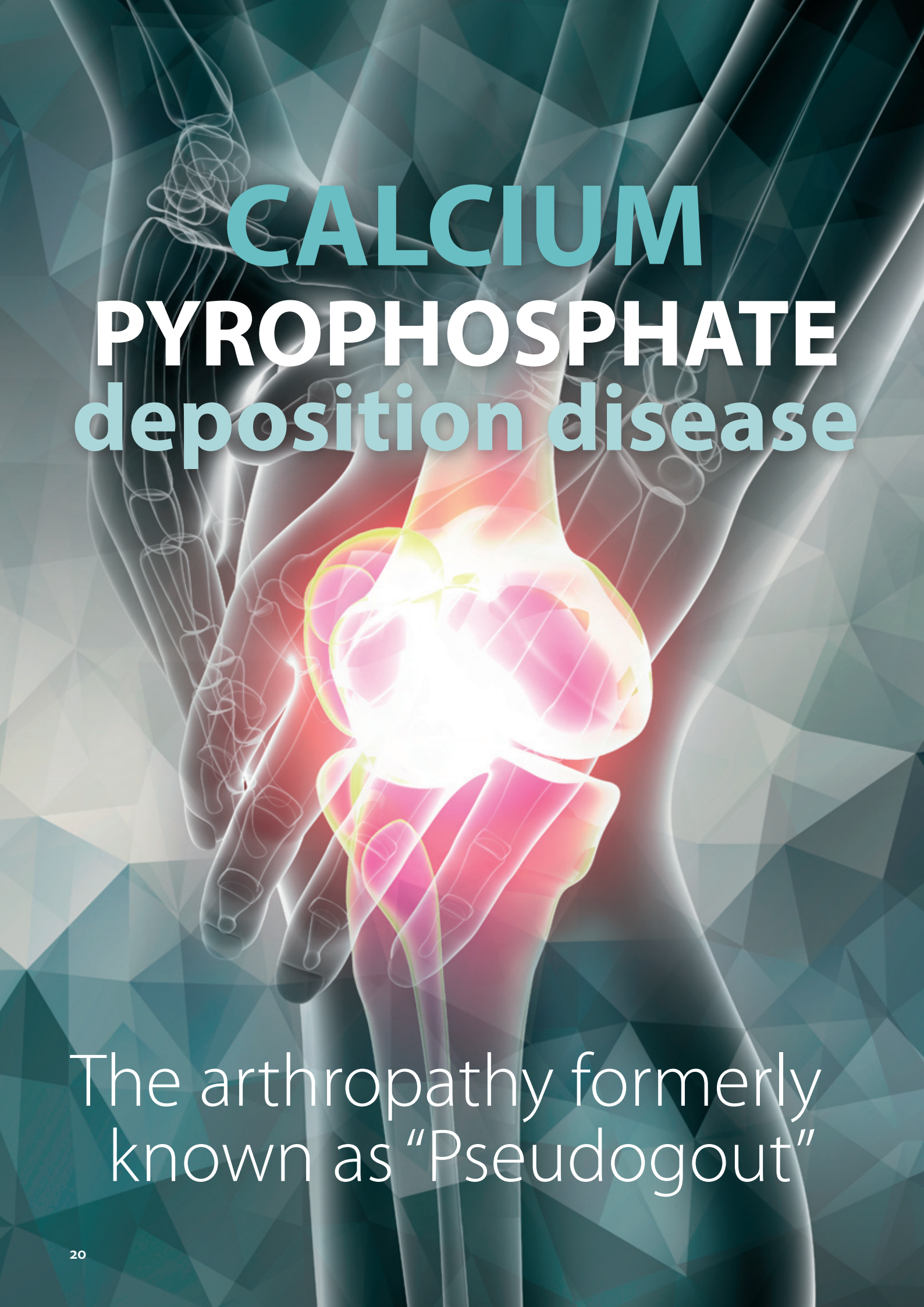

CALCIUM PYROPHOSPHATE deposition disease

The arthropathy formerly known as "Pseudogout"

A number of clinical syndromes are associated with the precipitation of calcium pyrophosphate dihydrate crystals in and around joints. These syndromes have previously been referred to by terms such as "pseudogout" or "pseudo-osteoarthritis", but these terms are no longer favoured. Instead, the syndromes are grouped under the umbrella term calcium pyrophosphate deposition (CPPD) disease. The deposition of calcium pyrophosphate crystals results in an inflammatory reaction within the joint in a similar way that precipitation of monosodium urate monohydrate crystals does in patients with gout, and can contribute to significant chronic degenerative change in joints. Patients with CPPD disease can be asymptomatic or present with a range of symptoms and signs similar to gout or other forms of inflammatory arthritis, making an accurate clinical diagnosis difficult. In addition, unlike for gout, there is a relative lack of evidence-based research on the syndromes caused by CPPD and there is no specific medicine that can decrease the concentration of crystals. Management is therefore targeted at symptomatic relief only.

The prevalence of CPPD disease

There is little research into the prevalence of symptomatic calcium pyrophosphate deposition (CPPD) disease. Chondrocalcinosis, which is calcification of the articular cartilage, most often caused by CPPD, is estimated to affect 5% of the general population, and prevalence increases with age.[1, 2] CPPD disease may be more prevalent in females than males, but evidence is conflicting.[1, 3] There is currently no evidence available regarding ethnic differences between the prevalence of CPPD disease in Māori, Pacific peoples and New Zealand Europeans. However, there is some evidence that people of Asian descent may have a lower prevalence of CPPD disease than people of European descent.[4]

Risk factors for CPPD

Risk factors for the development of CPPD include:

- Increasing age – after age 50 years, the risk of developing CPPD approximately doubles every decade.[1] In people aged under 50 years, CPPD is rare and if diagnosed in this age group it is likely that there is a familial association or a predisposition to a metabolic disease.
- Prior joint injury or surgery
- A history of gout – it is estimated that 20% of patients with CPPD disease also have hyperuricaemia and 25% of these patients will develop gout[5]
- Hereditary/familial predisposition to CPPD – patients may present at a younger age and are more likely to have polyarticular involvement (see: "Deposition of CPP crystals, Page 23)
- A history of an endocrine or metabolic condition such as haemochromatosis, primary hyperparathyroidism, hypophosphatasia, hypomagnesaemia – metabolic changes that occur as a result of these conditions are thought to promote calcium pyrophosphate (CPP) crystal deposition by inhibiting pyrophosphatases or by a direct effect on cartilage.[1, 6]

The association between CPPD and osteoarthritis is complex. The two conditions have risk factors in common, such as increasing age and previous injury, and CPP crystal deposition is increased in the presence of damaged cartilage.[1] However, CPPD also appears to initiate and worsen existing osteoarthritic damage in joints.[1, 5] CPP crystals are found in approximately one-third of cases where samples are taken from the knees of patients with osteoarthritis who are undergoing arthroscopy.[5]

The clinical presentation of CPPD disease

Patients with CPPD disease can be asymptomatic (with the changes detected incidentally on x-ray) or may present with a range of symptoms and signs similar to those found in patients with gout or other forms of inflammatory arthritis (e.g. rheumatoid arthritis) or septic arthritis. It can be difficult to distinguish CPPD disease clinically from these other conditions affecting joints. CPPD may also co-exist with gout, osteoarthritis and joint infection, and may not always be the condition that is causing the patient's symptoms.[9]

The deposition of CPP crystals results in an inflammatory reaction within the joint in a similar way that precipitation of monosodium urate monohydrate crystals does in patients with gout. Acute symptoms of CPPD disease therefore, include pain, swelling, stiffness, erythema, loss of function and marked tenderness of the affected joint(s).[10] Patients with CPPD disease may also present with systemic features, such as neck pain, headache and fever (estimated to occur in up to 50% of people with CPPD),[6] which may make it more difficult to differentiate between infection and inflammation.

CPPD disease often affects the large joints, most commonly the knee. Other joints likely to be involved are the wrist, ankle, elbow, toe, shoulder and hip.[5] CPPD disease is polyarticular in approximately two-thirds of patients,[6] and it often occurs in an asymmetric pattern. CPPD disease, however, can mimic rheumatoid arthritis or polymyalgia rheumatica, and patients may present with symmetrical joint involvement. Rarely, there may be deposition of CPP crystals in other parts of the skeleton, e.g. in the spine, symphysis pubis or temporomandibular (TMJ) joint.[3] CPPD in the neck can cause crowned dens syndrome, a rare cause of acute neck pain.[11] CPPD can also be associated with tendinitis, tenosynovitis and bursitis.[1, 10]

Clinical syndromes associated with CPPD

Asymptomatic CPPD – patients may have incidental x-ray findings consistent with CPPD (chondrocalcinosis) but have no apparent clinical consequence. It has been suggested, however, that if a fuller history is taken, many of these patients do have a history of joint symptoms, especially of the knee or wrist.[5]

Making the terminology crystal clear

Many terms, e.g. pseudogout, pseudo-osteoarthritis, pseudo-rheumatoid arthritis, have been used to describe the wide range of clinical syndromes associated with the deposition of calcium pyrophosphate dehydrate crystals in joints. The term "pseudogout" was adopted in 1962 following the first description of calcium phosphate crystals found in the synovial fluid of affected joints in patients with a normal serum urate level.[7] The term was chosen to reflect a discrete type of crystal-induced synovitis that resembled an acute attack of gout. Subsequently it has been found that deposition of CPP crystals in joints is not only responsible for acute synovitis, but associated with a wide range of clinical syndromes.

Within the literature there is debate about which terms should be used and there has been a recent attempt to clarify the nomenclature. The European League against Rheumatism (EULAR) CPPD Task Force has agreed on a uniform terminology with the aim of reducing confusion and the inconsistent use of terms such as "pseudogout". Their recommendations are that the following terminology be accepted into clinical research and practice:[1]

- CPP crystals – the simplified term for calcium pyrophosphate dihydrate crystals
- Calcium pyrophosphate deposition; CPPD – the "umbrella term" for all conditions associated with the deposition of CPP crystals:
  - Asymptomatic CPPD – CPPD without any apparent clinical consequence, most often an incidental finding on x-ray
  - Acute CPP crystal arthritis (formerly pseudogout) – referring to an acute, self-limiting synovitis with CPPD
  - Osteoarthritis with CPPD (formerly pseudo-osteoarthritis) – CPPD that occurs in a joint that has pre-existing degenerative changes due to osteoarthritis
  - Chronic CPP crystal inflammatory arthritis (formerly pseudo-rheumatoid arthritis) – chronic inflammatory arthritis associated with CPPD
- Chondrocalcinosis – calcification of the articular cartilage identified on an x-ray. Chondrocalcinosis is usually caused by CPPD, however, it may be present in a joint that otherwise appears normal, or in association with structural changes consistent with osteoarthritis. The term "chondrocalcinosis" should be reserved for describing the radiologic changes of cartilage calcification rather than used to describe a clinical situation in a patient.

Acute CPP crystal arthritis – an acute onset of a painful swollen joint (or joints) reflecting a self-limiting synovitis with CPPD. An acute episode of CPPD disease may occur spontaneously or develop after trauma, surgery or a severe medical illness, in a similar way to an attack of gout. Recurrent, acute attacks of CPPD disease can cause progressive damage to the joint. The term "pseudogout" was traditionally used for this acute condition because of the similarity to an acute attack of gout, although it is estimated that only approximately 25% of patients have this classic pattern of disease.[5]

Compared to patients with acute gout, acute attacks in patients with CPPD disease are generally:[5]

- In the knee rather than the first metatarsophalangeal (MTP) joint
- Less painful
- Slower to reach their peak intensity
- Slower to resolve even with symptomatic treatment, e.g. three months

Osteoarthritis with CPPD – CPPD that occurs in a joint that has pre-existing degenerative changes due to osteoarthritis. Both osteoarthritis and CPPD disease as isolated conditions often involve the knee joint, however, patients who have osteoarthritis with CPPD tend to have:[1]

- Pain that is more intense (than in osteoarthritis alone)
- Marked tenderness of the affected joints
- Systemic symptoms, e.g. fever
- An atypical distribution of affected joints – osteoarthritis alone does not usually involve joints such as the wrist, elbow, shoulder or ankle joint[6]

Chronic CPP crystal inflammatory arthritis – chronic inflammatory arthritis associated with CPPD, often with a symmetrical distribution to affected joints. This may be more frequently seen in younger patients (age < 50 years) who have a familial form of CPPD.[6]

History and examination may not always result in a definitive diagnosis

CPPD disease can mimic most other forms of inflammatory arthritis, gout and joint infection.[5] History and clinical examination may help the clinician to distinguish CPPD disease from these other conditions, however, the clinical picture is usually not sufficiently distinct enough to allow a definite diagnosis to be made on clinical grounds alone.

Deposition of CPP crystals

The factors contributing to CPP crystal deposition and joint damage remain uncertain, however, research has contributed to the understanding of how CPP crystals are formed. Changes in cartilage as a result of ageing, trauma, genetic factors and metabolic or biochemical processes are known to contribute to the development of CPPD.[3, 6] There appears to be increased production of inorganic pyrophosphate and decreased levels of pyrophosphatases (enzymes that break down pyrophosphate).

Enhanced activity of enzymes that break down adenosine triphosphate (ATP) produces an increase in extracellular inorganic pyrophosphate. The inorganic pyrophosphate binds with calcium to form CPP crystals which are then deposited in the cartilage and synovium of joints.

A mutation in a gene that encodes a protein involved in the transport of pyrophosphate is now known to have a key causative role in the familial forms of CPPD and is also likely to be involved in the non-familial forms.[8] The gene has been identified as ankylosis protein homolog human gene (ANKH) and is located on chromosome five.[8] A familial form of the disease should be considered in a symptomatic person aged less than 50 years who is found to have CPPD disease.

Ask patients about:[6, 10]

- The number and site of affected joints
- The speed of onset and the severity of the pain
- The presence of systemic symptoms, e.g. fever – up to 50% of people with acute CPPD disease will have a fever, and rarely, older patients may present with delirium
- Any acute injury to the joint
- If there has been a past history of pain, trauma or surgery in the affected joint(s)
- Any history of a recent severe illness (e.g. significant infection, cardiac failure) or recent surgery (in particular parathyroidectomy). These conditions can cause a rapid decrease in serum calcium which may precipitate an attack.
- A family history of episodes of polyarticular joint pain in young relatives, particularly if the patient themselves is younger (age < 55 years)
- Co-morbidities, specifically haemochromatosis or parathyroid disease

Investigations can often confirm a clinical suspicion of CPPD disease

It is important to initially consider the possibility of septic arthritis, particularly if the patient presents with a single affected joint.

Exclude septic arthritis

If a single joint is involved, septic arthritis should be excluded, however, infection may also occur concurrently with underlying CPPD disease. If the joint is able to be aspirated, synovial fluid should be obtained and sent for microscopy and culture. There may also be a high leukocyte count (predominantly neutrophils) in the synovial fluid, however, this can occur with both infection and CPPD disease.

Whether a joint can be aspirated depends on a number of factors, including the skill of the clinician, which joint is affected (some joints are easier to aspirate than others) and any contraindications, including cellulitis overlying the affected joint, the presence of a joint prosthesis or a bleeding disorder. The use of oral anticoagulants is a relative contraindication and a decision to aspirate an affected joint should be made on an individual patient basis.[12]

Identification of CPP crystals from synovial fluid is the gold standard for diagnosis

The gold standard for a definitive diagnosis of CPPD disease is the identification of CPD crystals in synovial fluid.[1] The characteristic crystals found in CPPD disease are generally rectangular, square, rhomboid or rod-shaped and can be seen using polarised light microscopy.[5, 6] Other types of crystals, e.g. monosodium urate, may also be visible.

Blood tests

A number of blood tests may be requested but none have as much diagnostic value as synovial fluid analysis. Consider requesting:[5, 10]

- FBC – this may show an increased white blood cell count, however, this is often not particularly useful in distinguishing between infection and inflammation
- CRP – similar limitations exist with the interpretation of a raised CRP result
- Serum urate levels – a normal result reduces the likelihood of gout, however, serum urate can be normal in some patients with acute gout and up to 20% of patients with CPPD may have an elevated serum urate. Urate levels should be taken when joint symptoms are not evident to ensure increased accuracy.
- Creatinine and electrolytes – particularly if the use of an NSAID is being considered

Patients aged less than 55 years and those who present with florid, polyarticular joint involvement should be assessed for an underlying metabolic disease, such as hypomagnesemia, hyperparathyroidism or haemochromatosis.[1, 3] Additional investigations may include parathyroid hormone, calcium, phosphate, magnesium and iron studies.

The role of radiology

Plain x-rays can help to confirm a clinical suspicion of CPPD, particularly if synovial fluid is not able to be obtained to look for CPP crystals. X-ray may also reveal the extent of degeneration within the joint. Chondrocalcinosis (linear or punctate calcification of the hyaline and fibrocartilage) is the characteristic finding on plain x-ray that is associated with CPPD.[13] However, the absence of chondrocalcinosis on x-ray does not exclude CPPD disease.[1] If plain x-rays are requested, the recommended joints to be imaged are the knees, wrists and an anteroposterior view of the pelvis. An x-ray of the knees alone is likely to result in a significant number of patients with CPPD being missed.[14]

Other forms of imaging, e.g. ultrasound, CT and MRI, have a relatively limited role in the majority of patients with CPPD disease, however, they can be useful in patients with atypical or rare presentations of the disease.[13] Ultrasound, for example, can be useful to guide joint aspiration in some patients or may

identify calcium deposits within articular cartilage.[13] CT and MRI scanning may be requested in secondary care to assess CPP crystal deposition at atypical sites such as in the neck (crowned dens syndrome) or in other areas of the spine where it may cause spinal cord compression.[10, 13]

Treatment of CPPD disease

Unlike in gout, there is currently no effective treatment that reduces or removes CPP crystals from a joint.[6, 15] Treatment therefore is not indicated for patients found to have asymptomatic chondrocalcinosis on x-ray. Treatment for an acute attack provides symptomatic relief, but it does not modify the course of the disease. If untreated, an acute attack of joint pain due to CPPD disease may last from a few days or up to a month.[6] If CPPD disease is a result of an underlying condition, e.g. haemochromatosis, primary hyperparathyroidism, this should be managed as appropriate, although there is little evidence that this improves arthropathy due to CPPD in patients with these conditions.[5] Many patients will have associated osteoarthritis and general measures used to manage this will also be of value, including education, exercise and weight loss, joint supports and mobility aids to maintain joint mobility and reduce pain and stiffness.

There is limited evidence supporting the use of any of the medicines used in the treatment of CPPD disease, in particular, a lack of randomised controlled trials. Recommendations for the management of CPPD disease tend to be based on expert opinion or extrapolated from research on the treatment of gout.[15]

Treatment of an acute attack

Treatments to reduce the pain and swelling associated with an acute attack of CPPD disease include:[3, 15]

- Ice or cool packs
- Temporary rest of the affected joint
- Joint aspiration
- Oral NSAIDs
- Low dose colchicine
- Corticosteroids (intra-articular injection or oral)

Ice or cool packs and rest of the affected joint are likely to provide temporary relief from pain and can reduce swelling.

Aspiration of an affected joint not only provides fluid for confirmation of the diagnosis and exclusion of infection, it can give temporary relief from pain due to a reduction in the fluid volume within the joint. An intra-articular injection of corticosteroid can be very effective in reducing symptoms in patients who have a single affected joint that is easily accessed.

If appropriate, an oral NSAID (with PPI cover if necessary) or low dose colchicine can be effective in reducing acute symptoms.[15] Recommendations for the dose of colchicine for the management of CPPD vary. For relief of acute symptoms, EULAR recommends colchicine 0.5 mg, up to three to four times daily, with an optional loading dose of 1 mg.[15] The duration of treatment depends on symptom relief and adverse effects.[15] The use of both colchicine and NSAIDs will be limited by individual patient factors such as age, renal function, other co-morbidities and the risk of adverse effects or toxicity.

If NSAIDs or colchicine are unable to be used, a short tapering course of oral corticosteroids (e.g. prednisone 0.5 mg/kg, daily, with a rapid taper) may also provide relief from acute symptoms, especially in patients with severe polyarticular attacks.[3, 15]

Treatment of chronic CPPD disease

The choice of medicines used for patients with chronic CPPD is based primarily on evidence for treatments used to manage gout and osteoarthritis, and on expert opinion.[15] The following treatments may be trialled as appropriate (in order of preference), in patients with chronic CPPD disease:[15]

- NSAIDs (with PPI protection)
- Low dose colchicine, e.g. 0.5 – 1 mg daily
- Low dose oral corticosteroids – no specific dose recommendation given; usual maintenance dose is between 2.5 mg – 15 mg daily[16]

Long-term use of these medicines is associated with various adverse effects; patients should be monitored appropriately. Patients taking colchicine should immediately report any gastrointestinal symptoms. Consider the need to monitor renal function, FBC (for leukopenia and thrombocytopenia) and creatinine kinase (for colchicine-induced myotoxicity). Also be aware of potential medicine interactions.

For further information on prescribing NSAIDs, see: "NSAIDs: Making safer treatment choices", Page 8.

For further information on prescribing long-term steroids, see: "Polymyalgia rheumatica – Practical considerations when prescribing long-term corticosteroids", BPJ 53 (Jun, 2013).

There have been some small trials of other medicines, such as methotrexate and hydroxychloroquine, in patients with chronic,

severe CPPD that has not responded to usual treatment, however, there is limited evidence of their effectiveness.[15, 17] Referral to a Rheumatologist is recommended for patients with chronic symptomatic CPPD disease where other treatments have been unsuccessful.

Chronic disease or recurrent acute attacks of CPPD disease can cause progressive damage to the joints. Patients with CPPD in joints that have deteriorated significantly, often in combination with osteoarthritis, should be assessed for joint replacement surgery in the same way that patients with osteoarthritis alone are.

Medicines used for prophylaxis of recurrent attacks

There is some evidence that low dose colchicine (0.5 mg, once or twice daily) may be effective in reducing the number of attacks in patients with frequent recurrent episodes, but no evidence on the use of NSAIDs.[15] Either of these medicines can be prescribed in an attempt to reduce the frequency of acute attacks, however, the appropriateness for an individual patient must be considered and the patient monitored for adverse effects such as gastrointestinal disturbances (bleeding, diarrhoea), changes to renal function, myopathy and cardiovascular events.

Potential future treatments for CPPD disease

There have been suggestions that some medicines and dietary changes may theoretically work to inhibit the formation or increase the dissolution of CPP crystals, but more research is required. The treatments being studied further include: anti interleukin 1 therapy, glucosamine, magnesium, probenecid, a diet rich in vitamin C and a low cysteine diet.[3, 5, 15]

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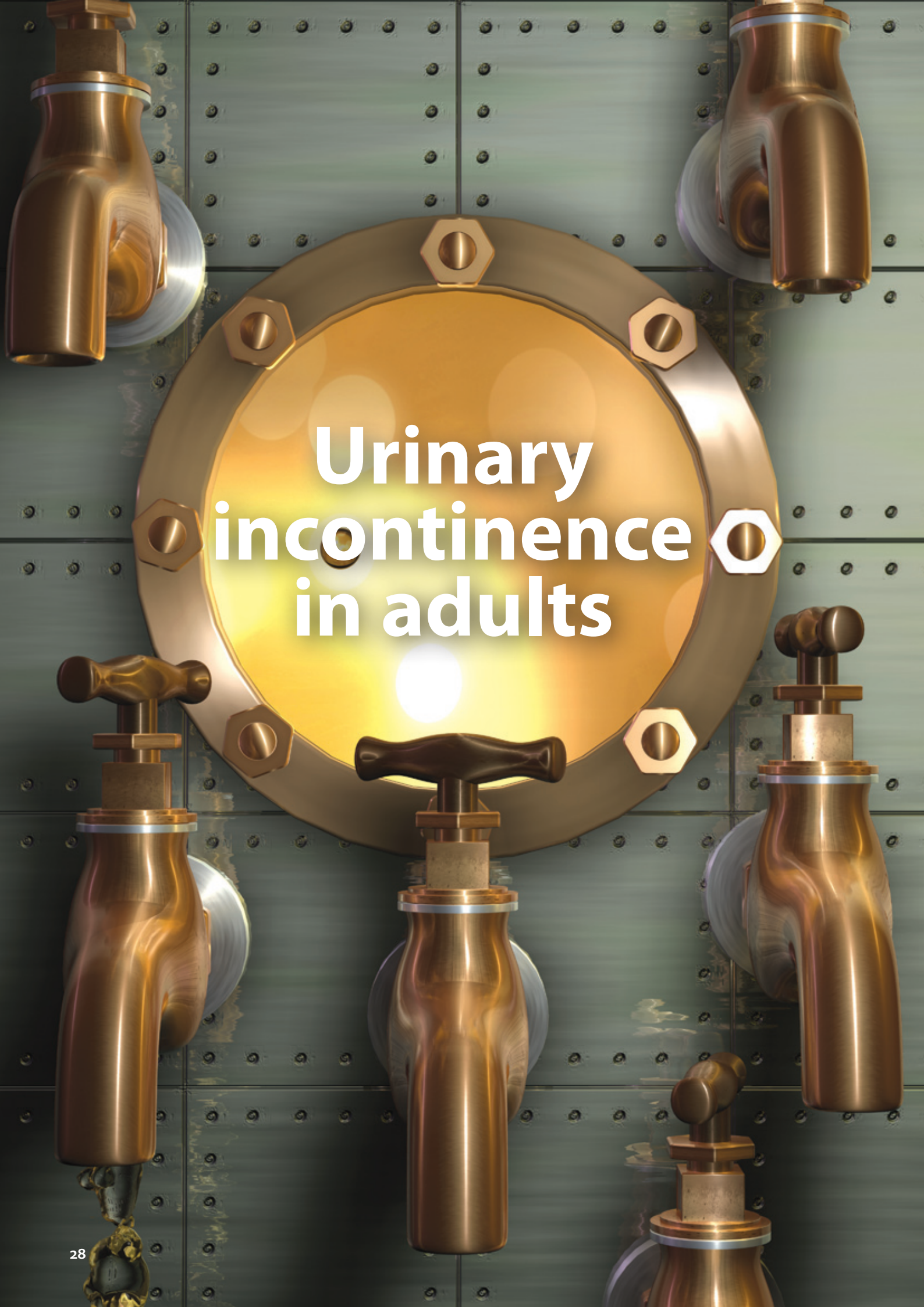

Urinary incontinence in adults

Managing urinary incontinence goes beyond just treating the medical condition. For the patient, the social and psychological impact of incontinence can far exceed the extent of the clinical problem. Incontinence can lead to depression, sexual dysfunction and social isolation. Once the type, cause, severity and impact of the patient's incontinence are determined, management involves exercise programmes and lifestyle changes. Pharmacological and surgical interventions are then considered if lifestyle intervention is insufficient.

General practice plays an important role in managing urinary incontinence

Urinary incontinence is defined as self-reported involuntary leakage of urine.[1] Incontinence is usually associated with ageing, childbirth or menopause. However, incontinence can occur secondary to conditions such as heart failure, stroke, multiple sclerosis and diabetes; as a result of trauma or after surgery; and as an adverse effect of some medicines, such as loop diuretics.

Approximately 10% of people experience urinary incontinence at some point in adulthood, and incidence increases with age.[1] Incontinence is approximately six times more common in females than in males.[1] This means that incontinence is often viewed as a condition exclusive to females. However, incontinence is prevalent in certain groups of males, such as those who have undergone any prostate surgery.

The impact of urinary incontinence on a patient's quality of life can be significant. Most complications of incontinence are psychosocial, including depression, feelings of shame, loss of self-confidence, lower perceived sense of wellbeing, social isolation, sexual dysfunction and financial difficulties (due to the cost of pads, bedding, laundry and reduced ability to work).[2] Loss of sleep, and falls and fractures (due to hurrying to the bathroom) are also often reported.[2]

Treatment initially focuses on lifestyle changes and behavioural interventions, such as pelvic floor muscle exercises and bladder training. If these are ineffective, pharmacological treatments can be trialled, depending on the type of incontinence. Surgical options are available for some types of urinary incontinence, particularly stress incontinence, if conservative treatments are unsuccessful.

The prognosis for people with urinary incontinence depends on the type of incontinence, the severity, the underlying cause(s), any contributing factors and the individual's motivation for treatment. However, most incontinence can be substantially improved even where it cannot be "cured".

Urinary incontinence in females

Urinary incontinence in females is usually divided into: stress incontinence, urgency incontinence, mixed incontinence, overactive bladder and overflow incontinence. Stress and urgency incontinence account for 90% of all cases of incontinence in females.[2]

The most significant risk-factors for incontinence are older age and previous pregnancy with a vaginal delivery.[2] Obesity and having a family history of incontinence also increase the likelihood of developing incontinence.[2]

Types of urinary incontinence

Stress incontinence is defined as leakage associated with physical activity or increased intra-abdominal pressure, such as coughing, sneezing or rising from a chair.[5] It occurs in 25 – 45% of females aged over 30 years.[5] It is caused by atrophy or damage to the pelvic floor muscles, ligaments or fascia. This is usually associated with childbirth and menopause (See: "Pelvic organ prolapse", Page 33).

Urgency incontinence is leakage associated with, or immediately after, the sudden need to void (termed urgency). The volume of urine lost is variable, and total emptying of the bladder, known as complete incontinence, may occur. Urgency incontinence occurs due to detrusor muscle overactivity. This overactivity may be neurogenic, secondary to an underlying pathology or idiopathic. Neurogenic overactivity of the bladder can result from any condition that causes loss of neurological control, most commonly stroke, multiple sclerosis, spinal cord injury or spina bifida.[5] Secondary causes of incontinence include urinary tract infection (UTI), sexually transmitted infections (STI), interstitial cystitis, atrophic vaginitis, bladder diverticula or prior pelvic radiation or surgical treatment. Idiopathic overactivity is poorly understood, but occurs with ageing, and is closely linked with overactive bladder syndrome.

Overactive bladder syndrome is a largely idiopathic urological condition comprising urgency, frequency and, often, nocturia.[6] Urgency incontinence with no known cause is often referred to as overactive bladder. However, in people with overactive bladder, urgency and frequency can occur without any resulting incontinence. The frequency of voiding will generally be more than eight times per day.[2] The cause of overactive bladder is not well understood, but loss of neurological control of the detrusor muscle activity is thought to contribute to the condition.[6] Overactive bladder is managed in the same way as urgency incontinence.[2]

Mixed incontinence is defined as a combination of stress and urgency incontinence, and occurs in approximately one-third of females with incontinence.[1] Mixed incontinence becomes more common with age as multiple disease states begin to occur, e.g. idiopathic urgency incontinence begins to develop in a woman with a weak pelvic floor that is causing stress incontinence. Management should follow the individual management of each type of incontinence, but with a focus on the dominant type.[2]

Overflow incontinence occurs when there is obstruction at the bladder neck or an impairment of detrusor contractility, so that leakage occurs from an over-filled bladder, often without urgency. It is more commonly seen in males. Overflow incontinence can be caused by urethral obstruction, prolapse of the pelvic organs, neurological damage and conditions that can reduce sensation in the bladder, such as stroke, multiple sclerosis and diabetes.

Other forms/causes of incontinence include:

- **Functional incontinence** occurs when cognitive or physical impairments prevent the patient from voiding independently and appropriately
- **Post-void dribbling** is leakage occurring after voiding due to urine remaining in the urethra
- **Urogenital fistula**, where a passage opens between the bladder/urethra and the vagina, bypassing the urethral sphincter. Urogenital fistula can cause complete incontinence. Among women in the developed world, this occurs most often due to complications from gynaecological surgery, e.g. hysterectomy.

How does the bladder work?

The bladder is a muscular reservoir for urine that sits behind the pubic symphysis. A normal bladder in an adult holds between 300 – 600 mL of urine.[3] When healthy, bladder function is controlled by coordination between musculoskeletal and neurological inputs.[3]

Neurological control of the bladder is bi-phasic, operating like a switch: alternating between storage or voiding.[4] The neural pathways controlling voiding are complex and involve the brain, spinal column and peripheral ganglia. These pathways involve autonomic (sympathetic and parasympathetic) and somatic nerves (via the pudendal nerve). N.B. Acetylcholine is one of the neurotransmitters of the parasympathetic pathways which mediate detrusor contraction, so this is why anticholinergic medicines are used to stabilise the bladder.

Damage to any of these structures or neural pathways can lead to incontinence.[4] Afferent and efferent nerve fibres involving bladder control are mainly located at the S2–S4 spinal nerve levels (but also involve the T11–L2 spinal segments),[4] so spinal cord injuries at the sacral level often affect continence. The frontal lobes of the brain provide inhibitory input, suppressing inappropriate bladder voiding,[4] therefore incontinence can result from damage to the frontal lobes, such as in people who have had a stroke or with dementia. Surgical procedures involving the urogenital system, such as prostatectomy in males, may damage the adjacent external urethral sphincter or the urethra itself, leading to incontinence.

In healthy person, voiding is under conscious control, and relies on learned behaviours that develop during childhood.[4] Mechanical control of continence involves the muscles and connective tissue surrounding the bladder.[3] The bladder neck and pelvic floor musculature work together to increase outflow resistance to a point where it is greater than the outflow pressure created by the resting bladder.[3] Acute spikes of pressure also occur with daily activities, such as coughing, standing up and laughing. If the pelvic floor muscles have sufficient tone, the guarding reflex increases urethral pressure as outflow pressure increases, maintaining continence. If the outflow resistance is less than these spikes of pressure, such as when pelvic floor support is lost, leakage occurs. Outflow pressure also increases when the detrusor muscles contract. This occurs consciously during normal voiding, but may also occur unconsciously with overactivity in the bladder, causing incontinence.

History and examination

As urinary incontinence is initially diagnosed based on the patient's report of symptoms, the focus of the history and examination should be on assessing the patient to determine the type, underlying factors, severity and impact of their incontinence.

Red flags in patients with urinary incontinence are listed on Page 38.

Patient history

Enquire about the following factors when taking a patient history:[7]

- Frequency of voiding
- Frequency of leakage (how many times per day, how many days in a typical week) and the volume of urine leaked
- The triggers associated with leakage, i.e. does leakage occur when the patient laughs? When they are lying flat in bed?
- The use of pads or other protective devices
- Diet and fluid intake, including caffeine and alcohol intake
- Lower urinary tract symptoms, e.g. UTI symptoms, post-void dribbling, needing to urinate again immediately after voiding[1]
- Other genitourinary symptoms, e.g. urogenital or abdominal pain, discomfort, haematuria, other discharge
- Constipation and faecal incontinence/soiling*
- Sexual function (i.e. psychosocial effects of incontinence)
- Past history of: bladder surgery, hysterectomy, childbirth (including number of births and mode of deliveries), previous UTI, previous STI
- Medicine use (see: "Medicines that may cause incontinence", over page)
- Smoking status**

* The rectum and bladder share similar neural pathways, and dysfunction of one often leads to dysfunction in the other, either neurologically or mechanically.

** Cigarette smoking is associated with bladder overactivity, is thought to be a bladder irritant and causes chronic cough, which may weaken the pelvic floor over time, and will directly influence the severity of stress incontinence.[8]

Determining the type of incontinence

At this point in the assessment the type of incontinence is likely to be apparent.

The following incontinence types are more likely depending on when the leakage of urine occurred:[2]

- Stress urinary incontinence – when coughing, sneezing, laughing, lifting or exercising
- Urgency incontinence, with or without overactive bladder syndrome – sudden urgency, often accompanied by frequency and nocturia, particularly if the patient is in bed and lying still (i.e. there is no stress)
- Mixed incontinence – both types of symptoms are present

If incontinence is not associated with the above causes (which will be rare), consider:[2]

- Chronic urinary retention associated with bladder overflow incontinence or a bladder outlet obstruction – voiding difficulty (hesitancy, straining to void, poor or intermittent urinary stream, and post-void dribbling)
- Fistula (vesicovaginal, urethrovaginal or ureterovaginal – constant passive leakage of urine and often complete incontinence
- Urethral diverticulum – post-void dribbling, frequency, dyspareunia and dysuria, particularly in a woman with recurrent UTI

A urethral diverticulum is an out-pouching of the urethra of uncertain aetiology. It most commonly occurs in females aged 30 – 60 years. Urine stagnates in this pouch and can predispose the patient to recurrent infections. If the diverticulum is large, it may cause bladder outlet obstruction. Over time, chronic inflammation may lead to malignant transformation of the cells lining the urethral diverticulum.[12]

Examination

The physical examination should be aimed at identifying any underlying or contributory causes to the type of incontinence identified from the history, and include:[1]

- An assessment of the patient's general health status, particularly looking for impaired mental status (i.e. confusion, signs of dementia), obesity and reduced mobility/dexterity
- Consideration of the presence of systemic conditions that may be contributing to incontinence, e.g. uncontrolled diabetes

Medicines that may cause, contribute to or worsen incontinence[9, 10]

Medicine class	How it causes incontinence
Sympathomimetics, e.g. pseudoephedrine	Tightening of the urinary sphincter can cause urine to be retained, leading to overflow incontinence
Alpha blockers, e.g. doxazosin	Relaxes the urinary sphincter and urethra; potentially causing stress incontinence
ACE inhibitors, e.g. cilazapril	Can cause cough and worsen stress incontinence
Tricyclic antidepressants, e.g. amitriptyline	Anticholinergic effect can interfere with bladder contraction and cause constipation leading to urinary retention and overflow incontinence
Antihistamines, e.g. promethazine	Anticholinergic effect as above
Antipsychotics, e.g. haloperidol, risperidone, quetiapine	Anticholinergic effect as above, and can also reduce physical mobility and cause abrupt urgency incontinence
Calcium channel blockers, e.g. diltiazem	Interfere with bladder contraction and worsen constipation leading to urinary retention and overflow incontinence
Diuretics, e.g. furosemide	Increase urine production, potentially worsening all types of incontinence
Vitamin and mineral supplements, particularly iron	Can cause constipation and urinary retention leading to overflow incontinence[11]
Opioids, e.g. oxycodone	Can interfere with bladder contraction and worsen constipation leading to urinary retention and overflow incontinence
Sedatives, e.g. diazepam	Can slow mobility and cause urgency incontinence

- Abdominal examination for masses, including an enlarged bladder (suggests potential urinary retention)
- Cough stress test (if stress incontinence is present)
- Pelvic examination – perineum and external genitalia including tissue health, signs of oestrogen deficiency, vaginal examination with a speculum for pelvic organ prolapse, bimanual pelvic and anorectal examination for pelvic masses and pelvic floor muscle function and tone

Cough test for stress incontinence

Stress urinary incontinence in females should ideally be confirmed with examination. To assess whether stress incontinence is present, ask the patient to lie flat on their back and cough. Observe the external urethral meatus for leakage during the first cough. The absence of leakage does not rule out stress urinary incontinence.

Pelvic examination

Perform a visual and digital examination of the vagina to assess for masses, structural abnormalities and for evidence of pelvic organ prolapse, using bivalve and Sims speculums (See: "Pelvic organ prolapse").[2] During the digital examination, feel for a soft, tender mass on the anterior vaginal wall and look for urethral discharge or tenderness, which may indicate urethral diverticulum.

The patient's pelvic floor musculature should ideally be assessed.[2] Insert a finger into the vagina and ask the patient to tense their pelvic floor muscles: assess both the strength and endurance of the muscle tone. This can give a baseline from which to measure the effectiveness of treatment. It is also useful to ensure that the patient is contracting the correct muscles, if they are going to begin pelvic floor muscle exercises while waiting for referral to a specialist physiotherapist or nurse.

Clinicians who are experienced with assessing incontinence may grade muscle tone using a scale such as the Oxford Grading system. Further information about this is

available from: **http://cks.nice.org.uk/incontinence-urinary-in-women#!scenarioclarification**

Additional examination

Further examination may be carried out as indicated by the patient's symptoms and signs. A focused neurological examination may be appropriate to assess the likelihood of a neurological condition causing incontinence, e.g. recent stroke, multiple sclerosis.

Investigations

Dipstick urinalysis should be performed to assess for haematuria, glycosuria and signs of infection.[2]

Serum creatinine is usually not necessary, but may be considered if the patient has recurrent UTI, urinary retention or renal obstruction is suspected.

The patient should be asked to keep a bladder diary.[2] The diary should cover three days and document the amount and types of fluids consumed, how frequently they void, any episodes of urgency, any episodes of incontinence and pad/clothing changes.[2] A bladder diary has been shown to be a reliable method of quantifying frequency, incontinence and measuring response to treatment.[2]

The normal volume of urine passed in each voiding is between 200 – 400 mL, and the generally accepted average voiding frequency is four to eight times daily, including one void per night.[2]

An example of a bladder diary is available from: **www.continence.org.nz.**

Further testing (below) may be necessary once the bladder diary is completed, at a follow-up consultation. Some of these tests may need to be carried out in a secondary care setting.

Post-void residual bladder volume should be assessed in patients with significant voiding symptoms, recurrent UTI, symptomatic pelvic organ prolapse (See: "Pelvic organ prolapse") or bladder distension.[1, 7] This should be done with a bladder ultrasound, which will require referral for those practices without a bladder scanning device (bladder scans may not be routinely available in some regions).[7] In-out catheterisation may also be used to measure residual urine volume in bladder, but should only be considered where bladder scanning is unavailable, or if urinary retention is noted during the examination.[7]

Pelvic organ prolapse

Pelvic organ prolapse is a frequent cause of urinary incontinence. It usually occurs following pelvic floor damage in childbirth, but can be multi-factorial, resulting from loss of support from the vagina, the pelvic floor musculature and connective tissue, as well as damage to the involved neurological system.[13]

Traditional terms for describing pelvic organ prolapse (e.g. cystocoele, urethrocoele, rectocoele, enterocoele) have generally been replaced. This is because the older terms imply a level of certainty about the structures causing the vaginal bulge, particularly in females who have had previous pelvic organ prolapse surgery. Current practice is to use terminology that divides the pelvis into anterior, posterior and middle or apical compartments.[13]

These terms refer to:[14]

- Anterior – the front wall of the vagina has herniated inward, usually caused by the bladder or/and urethra shifting position and placing pressure on the vaginal wall. This term includes the possibility of a cystocoele, urethrocoele and cystourethrocele.
- Posterior – weakening of the musculature and connective tissue or damage to the rectovaginal septum causes the rectum to herniate into the vagina. This term includes the possibility of a rectocoele or enterocoele.
- Apical – the tissue supporting the uterus weakens and the uterus slips downward, placing pressure on the vagina; usually associated with trauma in childbirth
- Vaginal vault prolapse – the roof of the vagina collapses, usually following hysterectomy (will also have an enterocoele present)[13]

Any pelvic organ prolapse is then staged based on the maximum prolapse descent seen when the patient performs a Valsalva manoeuvre. To clarify where the prolapse originates, a Sims speculum examination should be used. Referral to a Gynaecologist or Urologist is likely to be necessary for further evaluation and treatment.

Urodynamic testing may be used in secondary care.[7] Urodynamic testing measures how well the bladder and urethra store and release urine. The test usually records flow rate, residual urine, capacity and can identify involuntary spasm prior, during or after voiding that leads to leakage.

Pad testing, Q-tip testing, Bonney and Fluid-Bridge tests are not recommended for assessing urinary incontinence.[7]

Managing urinary incontinence in females

Women with most types of incontinence are initially managed with pelvic floor muscle exercises and lifestyle modifications. Pharmacological and surgical treatments then differ based on the type of incontinence.

General advice for all females with incontinence

The first step should be to recommend and offer support for weight loss for any patient with a BMI of ≥ 30 kg/m^2, as there is evidence of improved continence following weight loss.[2]

Other lifestyle advice focuses on reducing modifiable factors that may contribute to incontinence, such as:

- Avoid excessive fluid intake and drinking late at night. N.B. Some patients may overcompensate or try to control incontinence by reducing fluid intake below a normal level, which should be discouraged.
- Reduce caffeine and alcohol intake – as both have a diuretic effect and may increase frequency
- Avoid constipation by eating a varied diet and ensuring an adequate fibre intake (prescription of psyllium husk powder may be useful) – constipation and faecal incontinence can exacerbate urinary incontinence.
- Stop smoking (this may have the additional benefit of reducing coughing)
- Increase physical activity, starting with very light exercise in individuals with stress incontinence – increased cardiovascular fitness has been shown to reduce incontinence in some females[8]

Managing stress incontinence

As almost all stress incontinence in females is due to poor muscle tone in the pelvic floor muscles, exercises to strengthen these muscles are an essential part of treatment.[2] If this is ineffective or inappropriate, surgical options may then be considered. Pharmacological treatments are not routinely used for stress incontinence.

Pelvic floor muscle exercises are first-line

Pelvic floor muscle exercises are an effective treatment for stress incontinence. Females undergoing these exercises are more likely to report cure or improvement, better quality of life, fewer leakage episodes per day and have less urine leakage.[15]

Referral to an appropriate practitioner (such as a Continence Adviser, Nurse Specialist in urogynaecology or Physiotherapist specialising in women's health) for an assessment of the appropriateness of a supervised programme of pelvic floor muscle exercises is recommended. This programme should last for at least three months, be individualised and include instruction on correct technique and a programme of at-home exercise.[2]

The patient may be given advice on how to start the exercises while they wait for their referral (see: "Pelvic floor muscle exercises").

After twelve weeks of exercises the patient's pelvic floor muscle tone and the impact on incontinence should be reassessed. Any patient who shows benefit should be encouraged to continue the exercises two to four times per week.[2]

A list of continence health professionals by region is available from the New Zealand Continence Association: **www.continence.org.nz/pages/Continence-Service-Providers-for-adults-and-children/20**

Surgical and medical interventions

If the initial treatment with regular pelvic floor muscle exercises is unsuccessful, consider referral to an Urologist, Urogynaecologist or Gynaecologist for urodynamic investigations and potential surgery.[2]

Surgical interventions for females with stress incontinence include:[2]

- Mid-urethral slings – a mesh tape is placed under the urethra through two to three small incisions in order to support the urethra and "replace" the patient's pelvic floor muscles. The tape increases sub-urethral support and may help artificially recreate the pubo-urethral ligaments.
- Intramural urethral bulking agents – bulking materials are injected into the urethra and bladder neck, closing the lumen of the urethra, to increase the tissue's mass and increase outflow resistance. However, evidence about the effectiveness and durability of this treatment is limited.[16]

All surgical and medical interventions are associated with some adverse effects, such as increased voiding frequency and urgency incontinence.

Pharmacological treatment with duloxetine may be considered, although this medicine is not subsidised, and is considered second-line to surgical treatment. Pharmacological treatment is only given to women who decline or are not suitable for surgical treatment. Duloxetine can be effective in the short term, but there is no evidence of long-term efficacy or safety data for use in women with incontinence, and the medicine is associated with a range of adverse effects.[2, 17]

Managing urgency incontinence and overactive bladder

Urgency incontinence and overactive bladder can be initially managed with interventions for urgency and frequency, pelvic floor muscle exercises and bladder training.

Pharmacological interventions can also be trialled, followed by surgical interventions where medicines are ineffective or not tolerated.

Pelvic floor muscle exercises

Pelvic floor muscle exercises are used to strengthen the muscles under the uterus, bladder and bowel. They are used in both males and females who have problems with urinary incontinence or bowel control, and following pregnancy and childbirth in females. When performed correctly over several months, with good patient compliance, they can be effective in reducing stress incontinence for most people with mild to moderate stress incontinence.[7]

Most pelvic floor muscle exercise interventions will be designed and initiated under the supervision of a Physiotherapist or Continence Nurse.[2] An individualised programme of exercises is usually developed for each patient.[7] Where referral is not possible or where the wait time for referral will be significant, an exercise regimen may be initiated in primary care.

Pelvic floor muscle exercises can be described to the patient as tensing the muscles used to hold in urine. Advise the patient that next time they are voiding to attempt to stop the flow in order to "visualise" the muscles that should be tensed. Attempting to stop the flow of urine should only be used to assess whether the correct muscles are being contracted and not as part of the exercise programme itself. Unless the technique is correctly demonstrated, some females may do a Valsalva manoeuvre instead of contraction when they try to perform pelvic floor muscle exercises. If there is concern that the patient is performing the technique incorrectly, muscle contraction can be assessed with a digital examination (see Page 32).

Strengthening exercises are performed by tensing, holding and then relaxing the muscles. The exercise programme should comprise three sets of eight contractions, daily.[2] Each contraction should be held for approximately ten seconds. Between each contraction, the pelvic floor muscles are relaxed for several seconds. During contractions, it is important to isolate the pelvic floor muscles. To do this, tell the patient to keep the gluteal and thigh muscles relaxed during each contraction and to breath normally throughout the exercise.

Initially the patient may find it easiest to do the exercise while sitting or lying down, but once comfortable with the exercise they can be done at any time, place or body position. In addition, advise the patient that it may be more comfortable to empty their bladder prior to doing the exercise.

A Physiotherapist or Nurse may also suggest the use of biofeedback, electrical stimulation or vaginal cones as adjuncts to exercise where appropriate, e.g. in females with an absent or very weak contraction, or to increase confidence that the exercise is being done correctly.[2]

Commercially available products, such as Kegel balls and pelvic toners, are advertised as being effective for preventing incontinence and strengthening the pelvic floor. It is difficult to quantify the efficacy of such products, and it is advisable to discuss their use with a Physiotherapist first.

Treat the cause and train the bladder

Urgency incontinence has a more varied underlying aetiology than stress incontinence, and in some females, incontinence will be secondary to an infection or systemic condition. Treat or appropriately manage any underlying conditions that may be contributing to incontinence, such as:[2]

- Lower urinary tract infection
- Sexually transmitted infection
- Neurological conditions, e.g. Parkinson's disease and multiple sclerosis
- Systemic conditions, e.g. congestive heart failure and diabetes mellitus
- Functional and behavioural disorders, e.g. impaired mobility and excess alcohol use
- Adverse effects of medicines, e.g. diuretics

Following this, pelvic floor muscle exercises and bladder training are used to manage the symptoms of incontinence and overactive bladder. Refer females with urgency incontinence or an overactive bladder to an appropriate specialist, e.g. Continence Advisor, Nurse Specialist or Physiotherapist, for assessment and consideration of bladder training. The patient should be asked to complete a bladder diary before starting bladder training. This is also useful in assessing response to treatment.

Bladder training involves the patient becoming more aware of their voiding and incontinence patterns, and then learning to control them.[18] Scheduled times are set for voiding and then the times between voiding are gradually increased. If urgency occurs, the patient may be encouraged to try to "hold-on" for a short time, e.g. ten minutes, before voiding.

Strategies to decrease urgency include: squeezing and holding the pelvic floor muscles or doing several squeezes quickly, distraction, leaning forward slightly, keeping still, squeezing the fists tightly or pushing the ball of the foot hard onto the floor.

Combined, these actions can reduce frequency and urgency.[2] The effectiveness of bladder training varies and there is currently insufficient evidence to assess the likelihood of cure or improvement with bladder training, however, a Cochrane study concluded that it may be helpful and is a safe, low cost option.[18, 19]

Pharmacological treatment

If bladder training is ineffective or further control is needed, consider a trial of **oxybutynin**, an anticholinergic medicine. Anticholinergic medicines are effective for treating urinary incontinence because they decrease muscular spasms of the bladder, therefore suppressing urgency and overflow. Oxybutynin has been shown to reduce the symptoms of urgency and increase bladder capacity.[2] It is generally only appropriate for females with presumed detrusor overactivity or overactive bladder with frequency, urgency and incontinence. It is used first-line in preference to newer anticholinergic medicines due to a long history of use, a large evidence base for efficacy and lower cost.[7] In addition, oxybutynin must be trialled before other options to meet Special Authority criteria for subsidy for these medicines (see below).

The recommended starting dose of oxybutynin for incontinence is 5 mg, once daily, slowly titrated upward until effective, generally 5 mg, three times daily. The maximum dose is 5 mg, four times daily.[2, 10] In older patients the initial dose should be 2.5 mg, twice daily, and only increased if necessary.[10] Oxybutynin is available fully subsidised as an oral tablet or liquid, and without subsidy as a twice-weekly transdermal patch. Oxybutynin is associated with several adverse effects, most notably dry mouth, constipation and sedation, which often affects patient compliance with treatment. Transdermal patches may have fewer adverse effects due to a slower release of oxybutynin. Oxybutynin is contraindicated in people with bladder outflow obstruction, which can present in a similar way to urgency incontinence in some people. Oxybutynin is also contraindicated in people with angle-closure glaucoma, toxic megacolon, ulcerative colitis or gastrointestinal obstruction.[10]

Elderly patients are particularly susceptible to the effects of anticholinergics, and should have their current medicines reviewed to avoid anticholinergic loading.[2] Anticholinergic loading occurs in people taking multiple medicines with anticholinergic effects; the combined effect of all anticholinergic medicines is additive and their adverse effects become increasingly severe with greater load.

If oxybutynin is not tolerated or effective, consider other anticholinergic medicines,[2] such as solifenacin succinate, 5 mg, once daily, or tolterodine tartrate, 2 mg, twice daily.[10] These medicines have a more favourable adverse effect profile than oxybutynin because solifenacin and tolterodine are more selective for the bladder than oxybutynin.[20] Both solifenacin and tolterodine are subsidised subject to Special Authority criteria that require the patient to have first trialled oxybutynin and found it to be intolerable or ineffective.[10]

Patients taking any anticholinergic medicine for incontinence should be reviewed after six weeks to assess the efficacy of the medicine and the presence and severity of adverse effects.[2]

Other treatments can also be considered, such as intravaginal oestrogen.[2] How oestrogen works to reduce incontinence is not well understood. Oestrogen receptors have been identified in the tissues of the vagina, bladder, urethra and muscles of the pelvic floor; the bladder in particular is strongly influenced by circulating oestrogen levels.[21] It is thought that intravaginal oestrogen administration may reverse or limit the long-term loss of muscle tone to the urethral, pelvic and bladder muscle that occurs after menopause.[21]

Surgical interventions

Surgical interventions for females with urgency incontinence and overactive bladder may be considered where more conservative treatments have been ineffective. This includes botulinum toxin injected into the bladder, sacral nerve stimulation, augmentation cystoplasty and, where all other treatments have been ineffective, urinary diversion.

Botulinum toxin, when injected into the bladder wall, can reduce the frequency and strength of muscle spasms. The injection, given under anaesthesia, can be effective for nine months to one year. It appears to reduce bladder spasm and incontinence in approximately 60% of patients.[22] Botulinum toxin is associated with some adverse effects, the most significant of which is temporary urinary retention.

Sacral nerve stimulation involves the implantation of a device that applies mild electrical stimulation to the sacral reflex pathway of the bladder.[2] Sacral nerve stimulation generally decreases urinary frequency and can reduce the number of incontinent episodes.[2]

Augmentation cystoplasty is a surgical procedure that increases the capacity of the bladder and reduces overactivity.[2] The procedure involves grafting a section of tissue, usually from the small intestine or stomach, onto the top of the bladder. It is a relatively uncommon procedure.

Urinary diversion surgery is a complex and invasive procedure that diverts urine away from the bladder, generally through an ileal conduit (a passage made from a segment of the small intestine) into an external storage device (urostomy bag). It is a "last resort" treatment and is generally reserved for people with continuous or complete incontinence, for whom all other treatments have been trialled and been ineffective.

The role of incontinence pads

Incontinence pads are used as an adjunct to temporarily manage symptoms in some people. Clinicians should ask older female patients in particular about pad usage, as direct-to-consumer marketing and the easy availability of the products has made their use common and it may deter patients from seeking appropriate treatment. People with well controlled incontinence will usually not require incontinence pads. However, they can be recommended for the following reasons:[2]

- To manage urinary leakage while awaiting assessment and treatment
- To contain leakage while waiting for a treatment response
- For people with severe cognitive or mobility impairment the makes further assessment or treatment impossible
- For the long-term management of people who have trialled and not responded to all other treatment options

Whenever continence products are used, a variety of options should be discussed and trialled, with product choice based on patient preference. A Cochrane review found that the design of the product affected its efficacy.[23] Nappy-style products (i.e. side opening) were found to be most effective for males and pull-ups (underwear-style products with a smaller absorbency volume) or disposable pads were most effective and acceptable for females.[23] Nocturnal incontinence was best managed by nappy-style products for both males and females.[23]

Referral to a Continence Nurse specialist may be useful where continence pads need to be trialled. In addition, funding for incontinence pads may be available from some district health boards (DHBs).

Red flags for referral in people with incontinence

Males and females with urinary incontinence and any of the following factors should be referred to an appropriate specialist (Urologist or Gynaecologist) within two weeks:[2, 5, 24]

- Macroscopic haematuria without a concurrent urinary tract infection (UTI)
- Unexplained microscopic haematuria if aged over 40 years
- Recurrent or persistent UTI associated with haematuria if aged over 40 years
- A pelvic mass arising from the urinary tract or pelvis, e.g. palpable mass
- Suspected prostatic malignancy (in males)

Consideration for referral to a Urologist or Gynaecologist should be given to patients with the following factors(with urgency of referral based on clinical judgement):[2, 5, 24]

- A bladder that is palpable on abdominal or bimanual examination after voiding and/or chronic urinary retention/voiding difficulties
- Pelvic organ prolapse (in females)
- Associated faecal incontinence
- New or worsening incontinence in a person with a neurological disease
- Symptoms of voiding difficulty
- Recurrent UTI
- Suspected or recurrent urogenital fistulae
- Recurrent or continued incontinence following a previous continence surgery
- Previous pelvic cancer surgery or radiation treatment

Urinary incontinence in males

The approach to investigation and treatment of urinary incontinence in males is similar to that for females.

Many males experience incontinence at some point in their lives. Incidence increases with age and with certain conditions, particularly those involving the prostate. In males, incontinence is usually a subset of "lower urinary tract symptoms" (LUTS), which includes post-void dribbling, obstruction and overflow, nocturia and urgency. The likelihood of a significant underlying cause of incontinence is higher in males, and investigation of the cause is always necessary. Urinary incontinence in males is usually related to either prostate abnormalities or a neurological condition. The most common cause of urinary incontinence in males is benign prostatic hyperplasia, which causes incontinence, frequency and other LUTS due to the enlarged prostate pushing against the bladder.[1] Prostatectomy and radiation treatment of the prostate are also significant contributors to male incontinence (84% of males who undergo radical prostatectomy will develop incontinence).[25] Neurological causes of incontinence include age-related changes that lead to bladder overactivity, diabetes and other systemic conditions that reduce nerve function and neurological disorders such as stroke. More rarely, incontinence can be due to renal or bladder conditions, such as malignancy or vesical calculi (bladder stones).[26]

The dominant types of incontinence in males are similar to those seen in females, i.e. stress, urgency and overflow incontinence and bladder overactivity.

History and examination

Red flags for urinary incontinence in males should be assessed and the patient referred if necessary (see: "Red flags for referral").

As with females, the patient history should be used to assess the likelihood of an underlying cause, the severity of the incontinence and the impact that the incontinence has on the daily life of the patient (see: "Patient history", Page 31).

The history should also include questions on previous prostate conditions or surgery.[7]

Determining the type of incontinence present in males is similar to females and should be based on when and why leakage occurs, e.g. if leakage occurs during exercise, stress incontinence is likely.

The general examination should focus on any non-genitourinary causes or conditions that may be contributing to incontinence, e.g. obesity, stroke.

The external genitalia should be examined for signs of phimosis (the foreskin cannot be fully retracted over the glans), balanitis (inflammation of the glans), hypospadias (a birth defect causing the urethral opening to be abnormally placed on the ventral, or underside, of the penis), hernias, signs of infection or other abnormalities.[26]

A digital rectal examination is then recommended. Assess the size and consistency of the prostate and examine for nodules, tenderness and any masses.[26] The patient's **pelvic floor musculature** should also be assessed at this point, using the proxy measure of the patient's anal tone. To do this, with the patient supine, insert a finger one to two centimetres into the rectum (with the finger pad toward the coccyx) and assess the resting tone of the sphincter before asking the patient to tense the muscles. This contraction should be held for five seconds. Assess the relative strength and endurance of the muscle contraction. As for females, a grading scale may be used for this, such as the Oxford grading scale. See Page 32.

Investigations

Perform dipstick analysis of the urine in all males presenting with urinary incontinence to assess the likelihood of a treatable underlying cause, e.g. infection.[1, 26]

Request serum creatinine, as renal dysfunction or abnormalities may be a contributing factor, if any of the following are present:[26]

- Chronic urinary retention – this is suggested by overflow incontinence (e.g. bedwetting) or an enlarged bladder detected on abdominal palpation or percussion
- Recurrent urinary tract infection
- History of urinary tract stones

The patient should be asked to complete a bladder diary.[1] Further urodynamic testing such as flow testing (uroflowmetry) may be requested in secondary care.

Management

The management of urinary incontinence in males differs slightly from females as the likelihood of a significant underlying pathology is relatively high, particularly if there is no history of prostatic surgery or irradiation.

Management is based on the primary type of incontinence.

Managing stress incontinence in males

When stress urinary incontinence is caused by prostatectomy, patients should be referred to a Continence Nurse, Continence Physiotherapist or urology clinic for supervised pelvic floor muscle exercises.[26] Pelvic floor muscle exercises are very similar for both males and females. Exercises should be performed for at least three months before considering more invasive treatment options.[26]

For further information see: "Pelvic floor exercises", Page 35.

When stress urinary incontinence is not caused by prostatectomy, the patient should be referred to an Urologist for assessment to investigate the cause.[26] This is due to the potential for a significant underlying cause being present, such as prostate cancer or structural abnormalities.

Referral to an Urologist should still be considered in males with incontinence following prostatectomy, particularly if behavioural treatments are ineffective. Surgical interventions are available for males with stress incontinence. These are generally limited to male slings and artificial urinary sphincters.[26] For males with mild to moderate stress incontinence, male sling surgery has cure rates of 40 – 60%, with significant improvement in a further 10 – 40%.[25] The procedure is minimally invasive.[25] The artificial urinary sphincter is also highly effective, with complete continence achieved in 60 – 90% of males. However, this is a more invasive procedure and may be associated with greater adverse effects, such as urethral atrophy and mechanical failure of the device.[25]

Managing urgency incontinence and overactive bladder in males

First exclude or manage all treatable causes of urgency incontinence, such as benign prostatic hyperplasia, neurological conditions, current UTI or STI, vesical calculi or prostate or bladder cancer.[26] This may involve multiple consultations and temporary continence products can be offered while the cause of incontinence is being investigated (see: "Incontinence pads", Page 37).

Benign prostatic hyperplasia can be treated with alpha-blockers such as doxazosin or terazosin. Finasteride (Special Authority) may also be considered if alpha-blockers are not tolerated. N.B. Alpha blockers can potentially contribute to stress incontinence.

Where a preventable underlying cause is not identified, referral to a Physiotherapist or Nurse Specialist in incontinence for

bladder training is recommended.[26] Bladder training is similar for both males and females. For more information, see Page 36.

If symptoms persist despite bladder training, or where bladder training is not possible, consider a trial of oxybutynin (see Page 36).

If pharmacological treatment is ineffective, referral to an Urologist is recommended.[26]

Surgical and medical options for the treatment of urgency incontinence in males include botulinum injections into the bladder wall, sacral nerve stimulation and augmentation cystoplasty.[26]

Further resources

The New Zealand Continence Association (NZCA) has further information and resources for practitioners including templates of bladder diaries and examples on pelvic floor muscle exercise programmes. See: **www.continence.org.nz**

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How to increase the uptake of cervical screening: a profile of success

A cervical smear test is an effective method for the early detection of cervical cancer, and for reducing cancer mortality. However, testing rates fell in 2012, and the rate of screening among women in high need groups remains significantly lower than the total population. We interviewed managers and clinicians from three successful regional cervical screening programmes, and present their advice on how primary care can increase the uptake of cervical screening, especially for women in the high need group.

Cervical cancer screening needs a boost

There has been much work done in recent years to improve cervical screening rates in New Zealand. Screening rates for the total population reached 75% in 2011 (as measured by the PHO Performance Programme indicator for cervical cancer).[1] However, it is important to keep cervical screening "on the agenda" because the number of women who have been screened can still be improved.

In 2012, the percentage of women up to date with their cervical screening dropped from 74.8% to 73.9%.[1] Of the 35 PHOs in New Zealand, 28 had fewer women up to date than in the previous year, for the total population group.[1] In the high need group the uptake of screening was 66%, also dropping from the previous year's level.[1] The high need group for the PHO Performance Programme comprises Māori and Pacific peoples and people living in the lowest (NZDep 9 and 10) socioeconomic areas.[1] The National Cervical Screening Programme (NCSP) also identifies Asian women as having consistently lower screening rates than the total population group and includes them in their high need group.

Increasing the rate of uptake of cervical screening is essential. Cervical cancer has a ten to 20 year latency, and regular smear tests* can effectively identify the majority of pre-cancerous lesions.[2] The incidence of invasive cervical cancer and subsequent mortality rate has dropped by 50% in New Zealand since the implementation of the national screening programme.[2] An inadequate screening history is associated with increased rates of cervical cancer and cervical cancer mortality. This is particularly apparent among the high need group; Māori women are more than twice as likely to die from cervical cancer as European women.[3]

Although cervical screening rates have decreased overall, there are individual practices and clinicians around New Zealand who continue to achieve high rates of screening. The following article profiles three such groups, asking them why they have been successful and what other practices can do to increase uptake of cervical screening in their populations.

* A cervical screening test may be done by the conventional Papanicolaou smear method or by using liquid-based cytology. For brevity, we refer to both tests as a "cervical smear" in this article.

The PHO Performance Indicator: Cervical screening

The current PHO Performance Programme (PPP) indicator for cervical cancer screening aims to increase the number of women aged 20 – 69 years who are up to date with their smears. The Programme goal is to have 75% of all eligible women recorded as having a smear within the last three years. The indicator comprises 9% of a PHO's performance payment, with 3% for achieving the target in the total eligible PHO population and 6% in the high need population.[4]

The high need population for this indicator is Māori and Pacific women and women living in NZDep decile 9 and 10 socioeconomic areas.

The indicator is calculated by dividing the number of women aged between 20 – 69 years who have had a cervical smear within the past three years, by the total number of women aged 20 – 69 years within the practice population. The denominator for this indicator (the total number of women in the age range) is adjusted for the number of women expected to have had a complete hysterectomy.

The Panel:

Vivienne Back, Regional Manager and Ngahina Waretini, Māori Health Promoter, National Cervical Screening Programme (NCSP), Canterbury Region, CDHB. This group facilitates and provides health-promotion services to 143 practices across three PHOs, three independent service providers (He Waka Tapu, Pacific Trust and Family Planning), a Māori Health Promoter for the NCSP and Arowhenua Whanau Services, who in turn collectively provide screening services to over 140 000 women in the Canterbury region. The NCSP health promotion team comprises Māori, Pacific and Asian health promoters and a clinical team of seven nurses. They have faced a unique set of challenges recently with the Canterbury earthquakes, which have affected screening uptake rates and changed the health focus of many of the women in the region. **(CDHB)**

Jenny Cawston, Manager, Population Health Programme, Hawke's Bay DHB and Victoria Speers, Team Leader, General Practice Facilitation, Health Hawke's Bay PHO. This group provides overall management and support to the screening services offered by General Practice and other allied healthcare providers within the Hawke's Bay region. Using targeted funding, innovative IT support, professional development for Nurses and General Practitioners and social marketing, they have screened 80% of their total population, 80% of Pacific and Asian women and 74% of Māori women: exceeding the national average for all groups. **(Hawke's Bay DHB and PHO)**

Robyn Taylor, Nurse Manager, Karori Medical Centre, Wellington. Karori Medical Centre is a general practice facility that has developed and implemented a highly successful cervical screening programme. They have achieved the 75% threshold for their total patient population, and importantly, have also achieved the target in the high need group. Their focus is on providing cost effective alternatives to women in the high need group, being proactive in contacting women due or overdue for a smear and opportunistically offering smears to those women who are unable to be contacted but present for other reasons. In the future they aim to use more outreach resources and integrate screening into other existing initiatives, such as their immunisation programme, to provide smears to their remaining hard-to-reach women. **(KMC)**

What the panel had to say: a summary

The three interviewed groups had unique approaches to managing their cervical screening programme and increasing uptake in high need groups. This is largely due to the different population sizes in which they operate, e.g. across a DHB versus within a single General Practice, and the different barriers they face, e.g. the Canterbury earthquakes. However, when asked why they thought they had been successful or what other practices could do to improve screening uptake, there were many similarities in their answers.

Three points that were regularly reinforced were:

- Be proactive in contacting women for their smears, including:
  - The use of text, telephone and letters
  - Setting up alerts using the PMS
  - Making use of the NCSP register and register team to keep the practice's patient population database accurate
  - Contacting women prior to their 20th birthday to let them know that they now require regular screening (if they have ever been sexually active)
- Develop strategies to improve access to cervical screening services, including:
  - Making after-hours and weekend appointments available for screening where possible
  - Offering screening when women who are overdue for their smear present for any reason, i.e. opportunistic screening
  - Fully informing women of their options regarding screening services in the region, including their options for choice of screener
  - Providing educational resources to those women who are not yet ready to be screened
- Work with the community and with regional and national-level screening programmes, the NCSP promotion teams and independent service providers to ensure coverage

By using innovative ways to reach and communicate with women in the high need group, and making smears accessible and cost appropriate, the nationwide screening level should increase. As one of the interviewed groups summarised: "It's about taking a proactive approach for women, to know that they should 'take care, have a smear'. What's most important is that one size doesn't fit all".

Why is the high need group falling behind?

Women who are eligible for screening, particularly those in the high need group, face many potential barriers to receiving regular smears, such as:[5]

- Embarrassment/shyness/whakamā
- Cost
- Lack of transport
- Inability to take time off from work/family commitments preventing attendance
- Fear of the results
- Pain or discomfort from the smear
- Not knowing what to expect
- Not understanding the need to receive a smear

Health can be viewed differently by different groups of people and traditional attitudes toward medicine are often more prevalent among people of Māori, Pacific and Asian ethnicity. This is also true of sexuality, and the association between sexual activity, cervical screening and cervical cancer prevents some women from being comfortable presenting for a smear. Because of these differences, as well as a higher level of socioeconomic barriers, such as lack of transport and the cost of screening, levels are well below the desired level.

> "[The barriers we see are] outstanding debt with a practice, lack of transport, shyness, inability to attend during normal working hours due to work, home and personal commitments." — **Hawke's Bay DHB and PHO**

> "The same barriers are seen in each PHO – lack of awareness, lack of transport, lack of willingness to attend the medical centre." — **KMC**

> "We have an evaluation form that women fill out... the top barrier for women is cost." — **CDHB**

However, it is important to acknowledge that these barriers are not limited to the high need groups. Explaining to women that they do not qualify for free screening can be difficult. It is important to phrase the issue as one of reducing disparities within the New Zealand population, but to also approach the way the practice funds smears on a case by case basis.

> "Sometimes [the issue of funding] can cause quite a bit of a discussion. Imagine you're a woman and you're not part of that priority group; there can be discussion around 'how come these women are funded for smears but I'm not'... In addition, it can be difficult as there is no standard price for a smear [between practices in New Zealand]." -— **CDHB**

While many of these barriers are common to all types of health care, cervical screening faces an additional hurdle in that it is a "wellness" programme, performed in women who are asymptomatic, rather than a "sickness" programme where symptoms or reduced health are a strong motivating factor for women attending the practice. Preventative medicine is often low in the list of priorities for people in lower socioeconomic groups.[3]

> "It's a case of stretching that family budget. So it's food, it's a roof over their head, all those things they might need, and women will always put their smear test last." — **CDHB**

On a more technical level, accurate coding of ethnicity data was also identified as being important for ensuring that eligible women are able to access all of the available services. By correctly coding ethnicity, women in the high need group can access lower-cost or free smears from certain providers. In addition, funding for the clinic, through the PHO Performance Programme and other sources, better represents the make-up of the practice population if ethnicity coding is accurate. Women should be asked what ethnicity they identify with, when they present for a smear, and this can be checked for consistency with their coded ethnicity. In addition, accurate coding of other data, such as phone numbers and current address are important at a practice level to ensure that women are able to be contacted in the future.

> "Improving the quality of ethnicity data has positively impacted on screening coverage for Māori. Smear takers are encouraged to verify a woman's ethnicity and ensure it is recorded on the laboratory form." — **Hawke's Bay DHB and PHO**

> "At the regional service level, we receive hundreds of return-to-sender letters every week, for result letters, recall letters, contact letters, which are going out to women that no longer live at that address." — **CDHB**

How can general practice reach the high need groups?

Being proactive in contacting and making appointments for women in the high need group is likely to increase screening in the women at higher risk of poor cervical cancer outcomes. Each of the interviewed groups have implemented an active approach to reaching out to high need women, and attributed this as important to the relative success of their programmes. General practice should implement a systematic approach to find and contact women who have not received a smear within

the last three years. The following method may be used:

- Search patient records to identify the women aged 20 – 69 years in the practice population who have never had a smear or who have not had one within the last three years
- If the woman is not up to date, use the PMS to place an alert on her medical record so that a smear can be offered the next time they attend the general practice
- All women who are overdue for a smear should be contacted by text message, letter or telephone and encouraged to make an appointment for a smear
- If the woman cannot be contacted, contact the NCSP (0800 729 729) to verify their contact information and to check if a smear has been performed by another provider, such as Family Planning
- Those women who decline to have a smear in General Practice or are unable to, to should be offered referral to another provider based on their reason for declining, e.g. to a regional provider if they feel uncomfortable being screened by someone they know or wish to be screened by a culturally specific provider, or to a free provider if cost is an issue (if available)
- Women who still decline or wish to withdraw from the national register should have their details forwarded to the NCSP, so that they can be removed from the register. In addition, they should be regularly asked whether they wish to begin screening again, and any barriers to testing discussed.

Such an approach has proven successful for Karori Medical Centre:

> "We have designed the cervical screening programme to contact women for their three-yearly cervical smear by sending a recall letter just before they are due, followed up with a text or phone call (or second letter if no mobile phone number [has been recorded]) about two to three months later. If the patient still does not present, another letter is then sent and the recall moved on to start the process over again. The same process happens for women needing annual cervical smears but within a tighter timeframe." — KMC

Despite these measures, some women will still be missed. Taking the opportunity to offer a smear to women when they attend general practice for another reason can help to "capture" those women who are unable to be contacted or are unable to present for a smear.

> "Our high needs women can also have a cervical smear free of charge if they come in for another reason, e.g. with a child or for some other health reason. An alert/dashboard [on their medical record] will show they are overdue so they can be identified while at the practice." — KMC

To complement these approaches, regional providers (available in most regions through either the DHB or PHO and occasionally through non-government organisations) are able to help general practices maintain and stay current with their database of women requiring or overdue for a smear.

> "We also work alongside [Primary Care] practices to help with data matching of their register, if a practice needs to, they can provide us a complete list of their population, their overdue women, and we will take that back to the [National] register and update the information for them." — CDHB

What strategies can help general practice make screening more accessible and comfortable?

The major theme from the comments of each respondent was to encourage practices to make the screening process as simple and accessible as possible. Strategies to make screening easier generally focus on directly addressing barriers, and include:

- Normalise the procedure as routine, and explain that this is recommended for all women as part of maintaining their health
- Give women a choice of smear-taker (gender, ethnicity, anonymity)
- Make sure that low cost screening options are in place for women who cannot afford a full consultation, or that referral to a free screening provider (if one is available within the region) is offered for women who cannot meet the cost of being screened in general practice
- Consider running a nurse-led smear clinic after hours or at weekends, as this may increase uptake among patients with work and other commitments
- Provide advice and educational material about cervical cancer, the smear test and about what the results mean, i.e. an abnormal cervical smear result rarely indicates cancer

Such an approach was encouraged and used by all three respondents:

> "Give women a variety of service options – evening and weekend clinics, kaupapa Māori service providers, outreach smear clinics, female nurse smear-takers." — **Hawke's Bay DHB and PHO**

> "By having the clinics in the evening and on a Saturday, women who work could access the service… An extra project is then implemented six monthly to capture our remaining high need patients by offering open and booked clinics at no charge…The results were seen almost immediately with a strong uptake within two to three weeks of sending out texts or phone calls." — **KMC**

> "We [understand] that family member's and extended families' children might need to come, because mum might not have someone to babysit the children, and while mum is in with the nurse our team are there to support the family members. Family support is really important as well, especially for Māori, so when women attend a clinic it's really encouraged that the practitioner knows to invite a support person, and that this person will be different for different groups." — **CDHB**

Financial barriers of the clinic, as well as staffing requirements, will mean that not all practices are able to provide services on week-nights and weekends or to provide smear-takers to suit all ethnic groups. However, there are other ways to reduce the barriers that many people face in attending screening, such as referring to clinics that provide free screening (see: "Free or low cost smears").

Many women are not aware that screening is important, that it is necessary from an age as young as 20 years (if they have ever been sexually active) or that it remains important for older women. The respondents indicated that increasing awareness increased screening rates. This can be done in the practice by taking the opportunity to briefly mention to women just prior to their twentieth birthday that they will now need regular screening, using alerts to mention screening to women with incomplete screening histories and reiterating the need to continue screening up until age 70 years in older women.

> "What would be ideal is if something goes out to young women [in a practice population] at the age of 19 years... to say 'when you turn 20, we encourage you, as your practice, to talk to your Practice Nurse or talk to the team about your first cervical smear test." — **CDHB**

Free or low cost smears

There is a range of ways that women can access free or low-cost cervical screening services in New Zealand. The Ministry of Health and National Screening Unit (NSU) provide funding to regional-level providers and support for doctors and nurse around the country to train to become a smear taker and to receive continuing medical education to become a smear-taker. The majority of these programmes include funding for certain groups of women to receive free smears if they contact the regional provider directly or are referred through their General Practitioner. These free smears are usually reserved for the NSU high need group, which includes Māori, Pacific and Asian women aged 20 – 70 years and all women aged over 30 years who have never had a smear or who have not had a smear in last five years. These free smears are often offered via community-based clinics, run by NSCP nurses. In addition, some DHB programmes provide funding to allied healthcare providers, such as Family Planning clinics, to give free smears. For example, NCSP Canterbury Region, via Planning & Funding (CDHB), provides 1000 free smear vouchers, where women who meet the criteria are able to arrange a free smear appointment at a Family Planning clinic.

How can General Practice use regional-level screening programmes and community groups to increase screening?

The primary focus of cervical cancer screening should be to ensure that all New Zealand women have access to preventative health care, regardless of where they choose to receive this care. As one of the respondents put it:

> "Be it that you're at a practice, you're a provider providing free clinics, you're a family planning clinic or you're a [regional level] screening programme... We want the focus to be on preventing cervical cancer." — **CDHB**

Several of the respondents expressed that regional-level cervical screening programmes were not "in competition" with General Practice. The Christchurch DHB group pointed out that many women are uncomfortable being screened by their usual General Practitioner or Nurse and that the anonymity of a regional screening provider (where available) or family planning clinic was seen as a positive for some. In addition, the cost of a General Practice consultation for a smear was too expensive for some patients. This means that General Practice must either have a lower cost screening option for certain high need women, or, alternatively, make use of their regional provider and refer some groups of women to the free screening services that are offered over much of the country.

Support for general practice is widely available, from both the NSU and local groups. Practices may be able to access resources for organising "screening days" or hosting after hours/weekend clinics, or to help train Practice Nurses to become smear takers, reducing the cost to the practice of administering a smear test. In addition to support available from regional screening groups, grants to cover the cost of nurse training are available from the NSU.

Contact your local PHO and DHB to find out what funding is available

> "General Practice Facilitators are assigned to General Practices to provide support. The Facilitators support best practice and arrange for independent nurses to work in practices that do not have nurses." — **Hawke's Bay DHB and PHO**

> "We also [provide] training, our contract is to provide two smear-taker updates a year, and clinical updates to smear-takers. As well as [training] new nurse smear-takers... we also provide education and presentations for training every quarter." — **CDHB**

Linked to this was the idea that making use of allied care providers and other public health initiatives could increase the screening rate, while still being cost effective.

> "In the future, we will be looking very closely at a cervical smear outreach service to work in conjunction with our already established immunisation outreach service. This would ensure we reached women who, for many reasons, do not want to come into the medical centre directly." — **KMC**

> "We are aiming to have Māori health providers affiliated with general practices" — **Hawke's Bay DHB and PHO**

The National Screening Unit provides support and resources to General Practice, as well as helping to organise CME and training for smear takers. They can be reached on 0800 729 729 or by visiting: **www.nsu.govt.nz**

> "We all want to ensure a family is not robbed of a woman because she's dying of cervical cancer, which we can prevent. We want women to have their choices…We want women to have their health."

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Screening women aged under twenty years is not recommended

Between 2008 and 2010, 16 263 women aged under 20 years in New Zealand had a cervical smear sample taken.[6] This is not recommended practice.

Screening should begin at age 20 years (in women who have been sexually active) and continue, usually every three years, through to age 70 years.[2] The recommendation to start screening at age 20 years and the appropriate frequency of screening is based on a cost/benefit and risk/benefit analysis. The recommendations use the age-related risk of cervical cancer in the population, and take into account the cost of screening plus the risk of harm from screening and consequential (potentially unnecessary) treatment, versus the potential benefits.[2]

An important factor in setting the minimum age for screening is the epidemiology of the Human Papillomavirus (HPV). More than 99% of the abnormalities that lead to cervical cancer are caused by HPV, and HPV is generally acquired in adolescence, at the time of commencement of sexual activity.[7] Most HPV infections are asymptomatic and transient, lasting less than six months.[8] In females, approximately 10% of infections become persistent, leading to atypical cell growth and eventually pre-malignant lesions in the genital tract, particularly on the cervix. The likelihood of an infection becoming persistent increases with age, due to increased exposure time, reduced level of cells returning to normal and reduced immune response to HPV.[9]

Screening must be initiated at a point that avoids the majority of transient HPV infections, as these infections may appear as abnormalities on a smear. Because of these transient infections, screening in younger women is strongly associated with false positive results and inappropriate further investigation and treatment.[2] This can lead to worry and anxiety, withdrawal from future screening programmes and unnecessary biopsy. In contrast, cervical cancer is rare in women aged under 20 years.

The benefit of screening sexually active women aged under 20 years, does not outweigh the cost and potential adverse effects of screening. The National Screening Unit's stance is: "Unnecessary screening of women under 20 years wastes precious resources, diverts attention from women who could genuinely benefit from screening, and is unlikely to be of any benefit to these young women – in fact early and unnecessary screening can potentially cause them serious harm."[2]

What can we do for this age group?

The focus of cervical cancer prevention in younger women should be appropriate and timely use of the HPV vaccine. HPV vaccination in young women is effective and safe, and fully subsidised until their 20th birthday.

There is already clear evidence that the incidence of genital warts, caused by strains of HPV also included in the vaccine, is decreasing in New Zealand and in Australia.[10, 11] It is likely that similar trends will be seen with cervical cancer over the long term, as the two strains of high-risk HPV that are included in the vaccine (types 16 and 18) cause 70% of all cervical cancer.[12]

In addition, advice on safer sexual practices and appropriate contraception (including barrier contraception) should be given to women in this age group, as this has a modest additive benefit (in addition to the other benefits of contraception) in preventing the incidence of HPV and ultimately cervical cancer.

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OPINION

Health literacy plays an important role in boosting cervical screening uptake

Susan Reid and Carla White from health literacy and communication specialists, Workbase, explain how understanding and reducing the health literacy demands upon patients can make a difference.

A surprisingly high number of New Zealanders have significant health literacy gaps.

The Ministry of Health defines health literacy as: "a person's ability to obtain, process and understand basic health information and services in order to make informed and appropriate health decisions".

OECD statistics show that more than 56% of adult New Zealanders, 75% of Māori women, 80% of Māori men and 90% of Pacific peoples have low health literacy. Although these statistics appear to reinforce health literacy as a "brown patient" issue, our population spread means that in reality Pākehā comprise the majority of New Zealanders with low health literacy.

Health literacy is not entirely a patient-specific issue. Health systems, health professionals and health care providers all play a critical role because it is they who place many of the health literacy demands upon patients and families, such as complicated referral and booking systems.

Efforts to improve cervical screening uptakes should therefore recognise that complex processes are often involved, which can challenge all women – even those with strong health literacy skills.

Health screening study provides insights

Workbase recently undertook a (non-cervical) screening study that identified many barriers relevant to a cervical screening programme. For example, screening wasn't always offered despite being recommended for all patients. Even when offered, communication about the screening minimised its importance. Furthermore, the rationale for screening did not always make sense to patients or highlight its importance.

Significantly, health professionals felt patients' non-completion of screening procedures arose from a lack of patient compliance rather than from the health professionals' failure to properly engage the patients and provide an adequate and relevant rationale for screening.

In other cases, patients actively decided to decline the screening offer. Some were influenced by family members who had not been screened when in the same situation; others felt the risks did not apply to them.

Patients who completed the screening did so because their health professional had made a compelling case that was inextricably linked to the patient's (and wider family's) wellbeing.

How to take a health literacy approach to cervical screening

Identify the barriers: It is important to understand why women are not participating in cervical screening. For example:

- Is an offer actually being made?
- Is it conveyed in a casual or desultory manner that makes the woman think screening is unimportant?
- Does communication about the offer offend women because it makes them feel like they are being told off?
- Is cervical screening a priority for the woman (and, if not, what would help make it so)?
- Are women aware that screening is important?
- Are personal resourcing issues a problem (e.g. transport, childcare)?
- Are there cultural barriers?

This research can be conducted in several ways, including talking to women when they come into the clinic. Some people may feel more comfortable talking over the phone in the first instance rather than face to face, so also consider phone surveys.

Ask the women who get screened regularly what motivates them and, for those that don't have regular screening, frame the question in a non-judgemental way: "We have realised we could do a better job of explaining cervical screening to people - tell me what would you like to know".

Remove the barriers: Once the barriers are identified, then work can begin on removing or reducing them. For example, cultural barriers can be addressed by engaging local community leaders or community health workers to assist with talking to specific groups of women about their perceptions of cervical screening, and cultural or other barriers to participating.

Use the right resources: The National Screening Unit's website has a wealth of resources so take time to select ones that work for your communities. For example, print out some of the personal stories and make them available for people to read. Some people respond better to real life examples so consider asking a patient who has had cervical cancer treatment to tell her story and advocate for screening.

Bear in mind that more information is not necessarily better. Communicate information in small chunks, which are relevant to a woman's specific needs (e.g. what to expect when having a cervical screening test, what cervical cancer treatment involves) rather than overwhelming her by providing all of the information at once.

Use the right words: Find out which key words are typically used in your target community. For example, "cervical" is not always commonly used and is difficult to pronounce. Maybe "smear test" is more widely understood?

It is important to be sensitive about how requests are framed. For example, telling a woman who is overdue for a smear: "I notice your smear is overdue..." could immediately make her feel she has done something wrong and make her less inclined to engage in further discussion.

Improve your communication tools: Ask women how they would prefer to receive screening reminders: by text, email, letter or phone? Analyse written communication to ensure that the tone is welcoming and non-judgemental. Consider changing the standard reminder letters to a card that congratulates the woman for undergoing regular screening and reminds her that it is time to look after herself again and come back for another screening.

Think outside the square: Improve screening rates by providing better incentives to participate. For example: how can you further improve access – by providing mobile services? What can you do to better acknowledge or reward someone for undertaking screening – by providing vouchers for free manicures to women attending?

Be strategic: Health providers and professionals play a crucial role in building patients' health literacy. Integrating health literacy practices requires health organisations to incorporate it into strategic and operational planning, service delivery, leadership and management. Efforts should also be made to: involve patients in planning and evaluating programmes, develop the health workforce's skills, improve patients' access to and navigation of services and the system, and improve oral and written communication.

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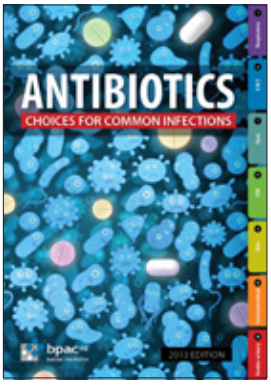

Amoxicillin clavulanate vs. amoxicillin for treatment of UTI

Dear Editor,

I note in the "Antibiotics: Choices for Common Infections" booklet provided with the August 2013 edition of Best Practice Journal, that amoxicillin with clavulanic acid is recommended as an alternative agent for treating UTI in children. I would be interested in understanding the rationale for this recommendation, given the poor oral absorption and urinary excretion of clavulanic acid compared with amoxicillin.

In 1986, Horber, et al reported that the systemic bioavailability of oral amoxicillin was about 70% compared with that of clavulanic acid, which was about 50%. This team also demonstrated that: "In subjects exhibiting normal renal function the urinary excretion of unchanged amoxicillin and clavulanic acid following p.o. administration was 56 and 22%, respectively."[1]

Thus, rather than the proportion of clavulanic acid to amoxicillin present in urine being approximately 25%, as is present in oral formulations of amoxicillin/clavulanic acid combinations and as could be expected of serum concentrations, the proportion in urine is probably reduced to less than 10%.

This pharmacokinetic difference between the two beta-lactams won't be evident in the in vitro laboratory sensitivity testing where adequate concentrations of both agents are tested against bacterial strains. So it is understandable that sensitivity testing will indicate pathogen susceptibility to amoxicillin/clavulanic acid combinations. However, the significant reduction in clavulanic acid present in urine may be clinically significant in vivo and could increase the risk of treatment failure.

To consider this another way, given that the amount of clavulanic acid present in urine is likely to be significantly reduced, and as a consequence its therapeutic effect is likely to be significantly reduced, why isn't amoxicillin alone (rather than in combination with clavulanic acid) recommended as an alternative agent for treating UTI in children? Is clavulanic acid adding any value to amoxicillin in the treatment of UTI?

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The information in the "Antibiotics: Choices for Common Infections" booklet (Jul, 2013) was derived from expert consensus. In the booklet, it is recommended that the first choice antibiotic treatment for uncomplicated UTI in children is co-trimoxazole (due to the trimethoprim component). Cefaclor and amoxicillin clavulanate were listed as alternative treatment options. It is common practice for amoxicillin clavulanate to be used in the treatment of UTIs in children. In fact, current Starship Children's Health clinical guidelines list amoxicillin clavulanate as the most preferred oral treatment option (followed by co-trimoxazole then cefaclor).[1]

However, the question asked by the correspondent is whether amoxicillin clavulanate is superior to amoxicillin alone for the treatment of UTI. Amoxicillin has fallen out of favour as a treatment option for UTI due to increasing resistance to *Escherichia coli*, which accounts for the majority of uncomplicated urinary tract infections in children.[2] Clavulanic acid is a beta-lactamase inhibitor which works synergistically with amoxicillin to extend the spectrum of antibiotic susceptibility. In theory, this means that UTIs are less likely to be resistant to treatment with amoxicillin clavulanate than amoxicillin alone.

The objective of the Horber et al study, referred to by the correspondent, was to assess changes in the way amoxicillin and clavulanic acid are excreted with declining renal function.[3] Because of this, there were only six participants with normal renal function in the study. After oral administration of the drugs, lower urinary concentrations of clavulanic acid compared to amoxicillin were found in these six subjects. This suggests that the amount of bioavailable clavulanic acid

may be too low to make it clinically superior to amoxicillin alone.[3] However, the surrogate values in the study may not be representative of a large population.

Perhaps a more clinically relevant measure of antibiotic efficacy is resolution of infection. A 1986 study involving 52 elderly patients with urinary tract infection found that 87.5% of those treated with amoxicillin clavulanate had resolution of infection, compared to 43% of those treated with amoxicillin alone.[4] Five out of eight patients who did not initially respond to amoxicillin, responded to amoxicillin clavulanate. Although this study involved elderly subjects rather than children, and again, the number of included subjects was low, some interesting observations were made. The authors commented that:

> "It has been suggested that, because of the high concentrations attainable in urine, amoxycillin [amoxicillin] is often effective in treating UTIs caused by organisms which are resistant to the drug in vitro. The results of our study, however, indicate that amoxycillin-resistant organisms do not respond to amoxycillin alone. Augmentin [amoxicillin clavulanate], on the other hand, is likely to cure urinary tract infection irrespective of the amoxycillin susceptibilty of the organism in vitro. Of the patients infected with amoxycillin-resistant organisms, 80% were cured by augmentin. By contrast, only 10% of the patients with amoxycillin-resistant organisms were cured by amoxycillin."

A small randomised controlled study in 1981 found that 11 out of 13 (85%) adult patients with penicillin-resistant UTI had an absence of bacteriuria after treatment with amoxicillin clavulanate, compared to 2 out of 8 (25%) patients receiving amoxicillin alone.[5]

Although both of these studies have limitations, and cannot necessarily be extrapolated to the treatment of UTI in children, they serve the purpose of demonstrating that medicines can have a clinically important treatment effect, despite their underlying pharmacokinetic profiles being less than ideal.

In summary, amoxicillin clavulanate is used as a second-line treatment for UTI in preference to amoxicillin alone, because most consensus-derived guidelines recommend this, and in practice, it works. A recent Cochrane review concluded that although antibiotic treatment for children with UTI is effective, there is not enough evidence to answer the question of which antibiotic is superior.[6]

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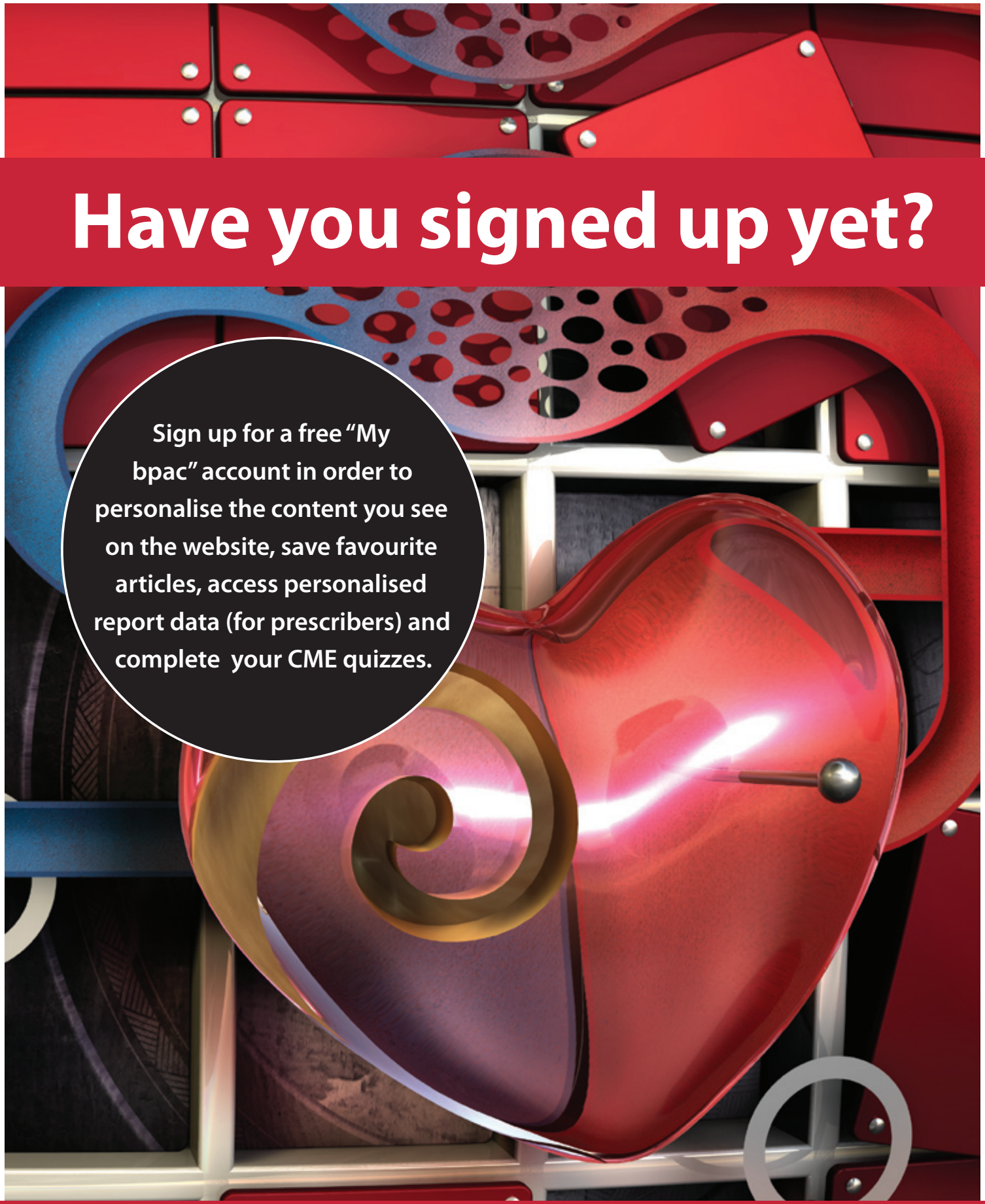

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