BEST PRACTICE

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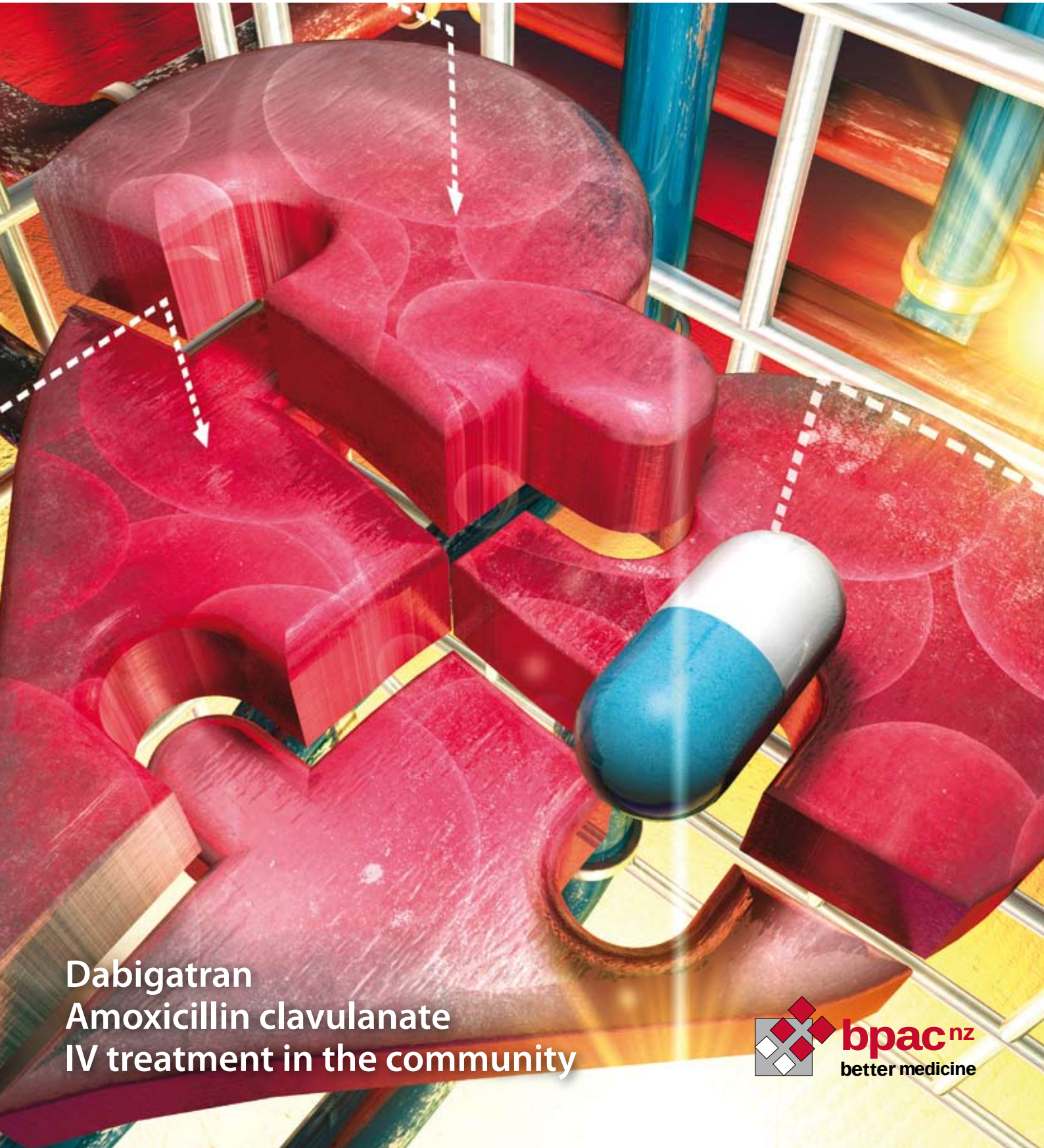

Dabigatran
Amoxicillin clavulanate
IV treatment in the community

bpac nz
better medicine

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Detecting child abuse in general practice

Contributed by David Rankin, Senior Advisor, Child, Youth and Family

Children who come to the attention of Child, Youth and Family are some of New Zealand's most vulnerable people. They have been exposed to significant trauma and are often disconnected from regular health and education services. They are likely to have high physical, behavioural and emotional needs that create a barrier to them achieving their potential.

In the Budget 2011, the Government announced funding of $30 million over four years to provide services to this group of young people. This money will enable the national implementation of the Gateway Assessment programme and will support the development of several mental health initiatives.

This second article in our series on children and young people in New Zealand who have been abused or neglected, aims to provide primary care professionals with an awareness of some of the indicators of child abuse and ways to intervene. It also outlines the initiatives that Child, Youth and Family have underway to identify and address the needs of these children.

Recognising neglect and abuse of children

Neglect is the most common form of abuse

Although the effects of neglect may not be as obvious as physical abuse, the consequences can be just as serious.

Neglect can consist of:

- **Physical neglec**t – not providing the necessities of life
- **Neglectful supervision** – leaving children without someone safe looking after them
- **Emotional neglect** – not giving children the comfort, attention and love they need
- **Medical neglect** – the failure to ensure their health needs are met
- **Educational neglect** – allowing chronic truancy, failure to enrol children in school, or inattention to their special education needs

Signs of neglect may include:

- A rough and uncared for appearance
- Persistent skin disorders or infections
- Lack of supervision (and as a consequence risk of injury, conduct problems and offending)
- Falling behind in educational achievement and attendance
- Indiscriminate attachment to adults

Emotional abuse is a component of all abuse and neglect

Emotional abuse is a pattern of behaviour where the child is rejected and put down. They may be isolated, constantly degraded and criticised or negatively compared to others. The effects of emotional abuse may only become evident as the child gets older and begins to show difficult or disturbing behaviours.

Signs of emotional abuse, in addition to those from neglect, include:

- **Sleep problems** – including bed-wetting or soiling
- **Frequent physical complaints** – real or imagined
- **Anxiety** – including poor self esteem, inability to cope in social settings and sometimes obsessive behaviour. May include self-harming and suicidal ideation.

Physical abuse is any behaviour which results in physical harm to a child

Signs of physical abuse include:

- **Unexplained bruises, welts, cuts and abrasions** – particularly in unusual places like the face, trunk, buttocks or the backs of the legs. Concern should be raised when the explanations change or do not make sense.
- **Unexplained fractures or dislocations** – especially worrying are fractures to the head or face, and hip or shoulder dislocations, particularly in young infants.
- **Burns** – anywhere on the body are concerning, and if not easily explained need to be notified. Be mindful of burns in the shape of on object like a stove ring or iron, cigarette marks or rope burn.

Sexual abuse is any act where an adult or a more powerful person uses a child or young person for a sexual purpose

Sexual abuse may be consensual or not, and can happen within or outside the family. Most sexual abuse is perpetrated by someone the child knows and trusts.

Sexual abuse may include physical sexual acts, exposure to pornographic material and internet sites, sexually oriented texting or sexual conversations. It often begins with some form of grooming – preparing the child for sexual contact by lowering their inhibitions and gaining their trust.

The following signs are an indication that a child may be being sexually abused:

- **Physical signs** – unusual or excessive itching, bruising, lacerations, redness, swelling or bleeding in the genital or anal area, urinary tract infection, blood in the urine or faeces, painful urination or other signs of being sexually active. When pregnancy or a sexually transmitted disease is identified, abuse must always be considered, especially in girls aged under 16 years
- **Age inappropriate sexual play, knowledge or interest** – and other unusual behaviour like sexually explicit drawings, descriptions and talk about sex
- **Fear of a certain person or place** – children might be trying to express their fear without saying exactly what they are frightened of, so listen carefully, and take what they say seriously. Some children may purposefully try to make themselves unattractive, or try to feel clean through obsessive washing.

Risk factors for abuse and neglect

A range of risk factors have been identified for abuse and neglect of children. These risk factors are also positively correlated with the development of severe antisocial behaviour in older children and adolescents.

Risk factors for abuse and neglect include:

- Parental history (particularly the mother) of anxiety, depression or other mental illness or a history of sexual abuse
- Families under financial stress
- Problem use of drugs or alcohol
- Parental lack of social support or social isolatation
- Family violence
- Children left home alone
- Parents with poorly developed parenting skills - often younger mothers and those who have been in the care of CYF as children themselves
- Abnormal parental expectations or distorted perception of the child

The following signs of family behaviour may raise concerns about the risk of abuse or neglect:

- **Unrealistic expectations** of an older child's ability to care for younger siblings may indicate neglect. It can cause stress and anxiety to children who are not capable of taking on these responsibilities.
- **Humiliation** of children or young people is a powerful form of emotional abuse. Children may be subjected to fierce and personal criticism, often in front of siblings or peers, or they may be given demeaning tasks to carry out.
- **Isolation** – when a family, or an adult and child, are isolated it is hard for them to get support, which makes them more vulnerable to harm or neglect. Signs of isolation may include: failing to keep appointments, lack of engagement with regular health providers, refusing to let an agency visit or moving frequently.
- **Medical neglect** – where parents do not assume a "health advocacy" role for their children
- **Dependency** – professionals can unsuspectingly become involved in meeting the increasing demands from parents for practical and emotional support. This focus on the parents often overshadows the children's needs and the parents sometimes compete with their children to be the main subjects of concern.

What to do if you are concerned

If you are concerned about a child, it is not so important to be able to categorise the type of abuse you think may be going on – it is normal to feel uncertain. However, if you notice a pattern forming or several signs that make you feel worried, this could be an indication that something is going wrong.

There are often no black and white answers to how you should react to evidence or suspicion of abuse or neglect. Usually your instinct will tell you something is wrong, and you may have clues, but you won't know for sure.

The main thing is that you take notice and take action. If there are problems, they are likely to go on until someone speaks up. Children cannot speak up for themselves and the people involved may be too ashamed, distressed or caught up in the situation to ask for help.

Do not hope that someone else will notice and do something about it. As professionals, we are the ones who work with children, know them and their families, and play an important role in keeping them safe. Each professional involved with the child often only has a part of the picture. Taking action allows the whole picture to be put together across a range of professionals and agencies.

If you are worried about a child:

- **Trust your instincts** – don't be afraid of getting it wrong
- **Spot the warning signs** – familiarise yourself with the signs of abuse and neglect
- **Listen** – take notice and listen carefully to what people say. Are the family asking for help?
- **Talk to your colleagues** – are other health and education colleagues working with this family? Are they also noticing signs that something is not right?
- **Talk to Child, Youth and Family** – our social workers are trained to work out what kinds of problems a family might be having, and find the best ways to help keep their children safe. You might want to talk your concerns through with one of our hospital based social workers, someone from your local site, or our contact centre social workers.

If you are worried that a child is not safe or being well looked after, phone 0508 FAMILY (0508 326 459).

If you think the situation may be life-threatening, phone the Police on 111.

Identifying and addressing health needs: Child, Youth and Family initiatives

Gateway Assessments for all children and young people with high needs

From 1 July, 2011, Child, Youth and Family will be rolling out the new Gateway Assessment process with the Ministries of Health and Education.

Social workers will ensure all children and young people with high needs have a comprehensive Gateway Assessment. It is expected that around 4,200 children will meet the criteria for referral each year. This will include all children who enter non-emergency care, children and young people already in care who have significant health and behavioural needs and children identified as having high needs at a Family Group Conference.

Over the last two years, Child, Youth and Family and the Ministries of Health and Education have been piloting health assessments and education profiles across four district health boards – Auckland, Counties Manukau, Lakes and Mid Central. Nelson Marlborough DHB joined the pilots in April 2011.

Central to the Gateway Assessment process is the Gateway Assessment Coordinator who is employed by the DHB and gathers together the available background information from the social worker, family, health and education contacts.

Teachers from the child or young person's school provide a profile of their education engagement and achievement.

One of richest sources of background health data has proven to be the transaction records that the New Zealand Health Information Service (NZHIS) is able to provide. These reports include birth records, prescribed medications, laboratory test requests, hospital admissions, mental health contact, PHO enrolment, immunisation records and outpatient events. ACC also provides a complete record of all reported injuries for the child. The WellChild provider also contributes to the picture, where they have been involved in the care of the child.

This information provides the leads for the Assessment Coordinator to contact various health practitioners and piece together the fragmented health record for the child or young person.

The very complex needs of these children means that the health assessment is usually undertaken by a paediatrician with the assistance of a nurse specialist. Several pilot sites engaged General Practitioners to undertake the assessment, however, the time requirement (two to three hours), interpretation of screening tools and the mental health and developmental assessments have proven challenging for primary care. Adolescent assessments are undertaken by youth health practitioners.

The output from the assessment is a comprehensive interagency report and recommendations. This report is sent to the social worker, General Practitioner (where a consistent General Practitioner can be identified), teacher and caregiver.

These children and young people often have health records that are scattered around the country between primary and secondary care. Health transactions often occur in Accident and Medical Clinics, Afterhours Centres and Emergency Departments. Child, Youth and Family are exploring opportunities to make the assessment reports and health history available to health practitioners who subsequently engage with the children. It is envisaged that the Gateway Assessment record could become the foundation for an ongoing integrated health record.

Everyone involved in ensuring the child's health and safety will be following their progress. While the social worker has overall responsibility to monitor and review the child's development plan with the family while the child is in care, the primary care provider has a key role in monitoring their growth, development and mental health.

The benefits accruing from the health and education assessment includes:

- Families gaining new insights into their child's health and behaviour that they had not previously understood - 88% of children who have been assessed had unidentified or unmet health needs.
- Connecting these children with primary care and specialist health services
- Better information for teachers to help them work with the child in the class room
- More integrated information across agencies which strengthen the relationships, leading to more informed planning and service development
- Families, teachers, social workers and health professionals working together
- Specialist child health services becoming aware of the needs of the child and advocating on their behalf to access service (particularly mental health services) to address the child's needs

The first regions to implement the Gateway Assessment programme will be the health and education pilot sites (see previous page). They began providing the revised service on 1 July 2011. This service is designed to ensure that all children with high needs who come to the attention of Child, Youth and Family have a comprehensive assessment of their health and education status as early in their development as possible. By identifying and addressing their needs it is expected that Child, Youth and Family can facilitate a material difference to the child's educational achievement and social participation. It is anticipated that this programme will reduce their involvement in the criminal justice system.

Mental health services

Child, Youth and Family was allocated funding in the Budget 2011 to increase the availability of mental health services for children and young people in care.

This funding will be used to implement a primary care based child mental health service targeted to meet the needs of children who have emotional and behavioural disorders but do not meet the criteria for specialist mental health services. It will also be used to expand, over the next four years, the number of Intensive Clinical Support Services available for young people with mental health and behavioural challenges who are in the care of Child, Youth and Family.

Child, Youth and Family are currently recruiting the team that will develop these services in consultation with the sector.

Money was also allocated in the Budget 2011, over four years, to develop a dedicated youth forensic mental health and "Alcohol and other Drugs" service across New Zealand. This will provide community youth forensic teams, increase Youth Court liaison services and provide secure inpatient beds.

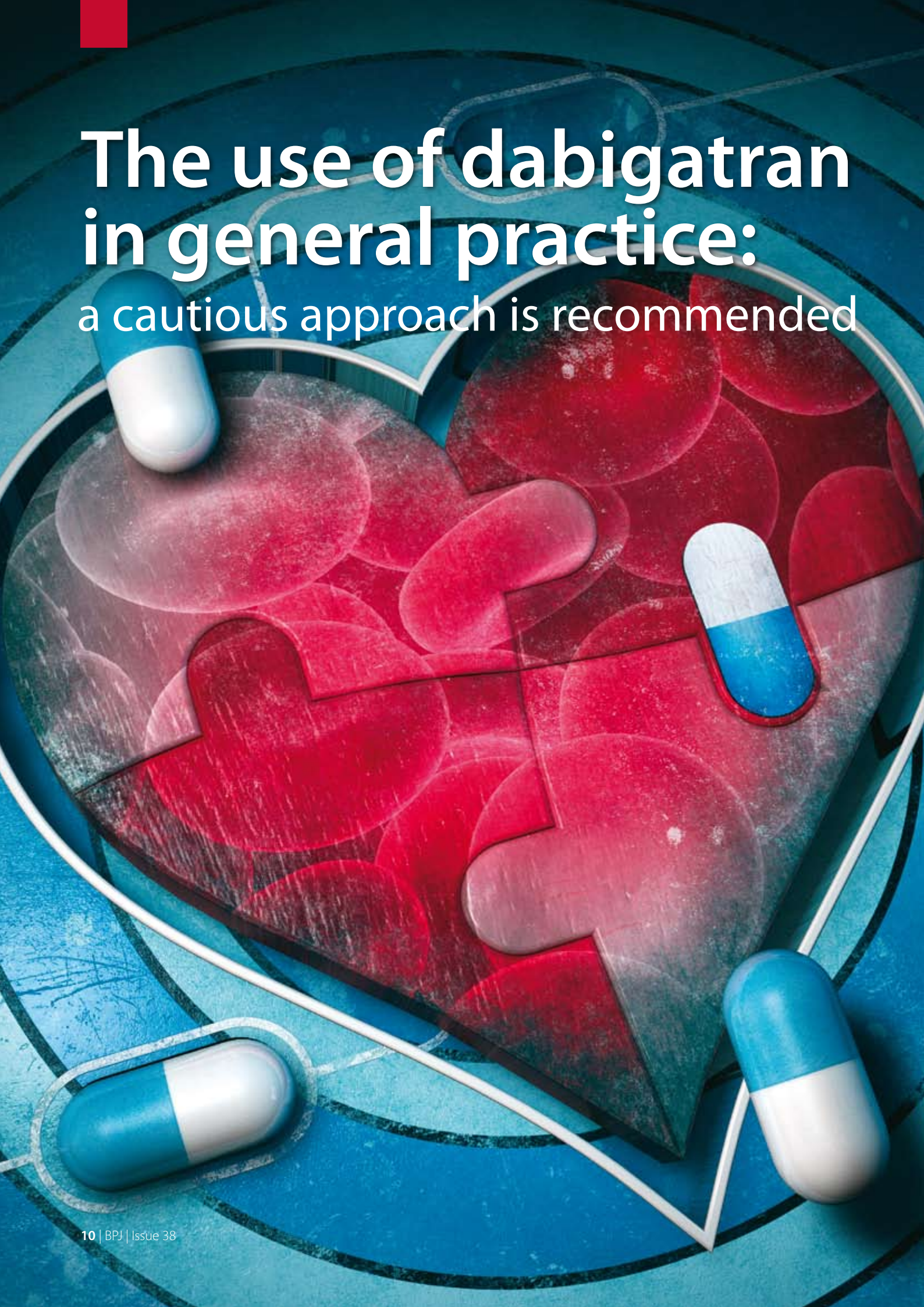
Measuring outcomes

As a condition for approving the additional funding for these services, the Government required Child, Youth and Family to develop a clear set of outcome measures. While these measures are still in development, they will explore the outcomes in terms of education, health and social welfare. Health measures will include indicators such as immunisation rates, changes in mental health screening scores, teen pregnancy rates and PHO enrolment.

These outcome measures will enable us all to understand what interventions are successful and how best to address the needs of New Zealand's most vulnerable children.

The use of dabigatran in general practice:

a cautious approach is recommended



Dabigatran – practical considerations for General Practitioners

Dabigatran (Pradaxa) is now available in New Zealand, fully funded, without Special Authority, as an alternative oral anticoagulant to warfarin, to prevent stroke in people with non-valvular atrial fibrillation (AF). Dabigatran is also registered for short-term use for the prevention of venous thromboembolism (VTE) after major orthopaedic surgery. It is available in 75 mg, 110 mg and 150 mg capsules.

Dabigatran is the first new oral anticoagulant that has been made available for clinical use for more than fifty years. It was approved for use in AF in October 2010 in the United States and Canada, and in 2011 in Japan and some European countries. Although it has been used since 2008 for short term prophylaxis of VTE, clinical experience in the "real world" setting is still limited and data on longer term safety is lacking. Recommendations for its use in AF are based largely on the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (see Page 24 for further discussion on this trial).[1]

Warfarin has a history of many years of clinical use but has two major limitations – a narrow therapeutic range of safe anticoagulation and a highly variable dose response. Variation may also occur for individual patients over time due to interactions with certain dietary components and the use of other medicines. Laboratory monitoring with INR and dose adjustment is required to achieve individually

Key concepts

- Dabigatran etexilate (Pradaxa®) 75 mg, 110 mg and 150 mg capsules were listed on the Pharmaceutical Schedule on 1 July 2011, fully funded and without restriction.
- Dabigatran is licensed for use in New Zealand for stroke prevention in patients with non-valvular atrial fibrillation and for prevention of thromboembolism post major orthopaedic surgery
- If a patient taking warfarin has stable INR measurements and good venous access, then there is no clinical indication to switch to dabigatran.
- There is limited clinical experience with dabigatran in atrial fibrillation or with long-term use. Recommendations are based largely on a single, industry sponsored randomised controlled trial.
- Compliance with twice daily dosing is important as poor adherence may compromise the efficacy of dabigatran.
- Dabigatran is predominantly renally excreted, so patients must have creatinine clearance >30 mL/min. It should be used cautiously in patients with creatinine clearance between 30 – 50 mL/min. Older patients with normal serum creatinine may have low creatinine clearance.
- Potential adverse effects include bleeding, dyspepsia and gastrointestinal haemorrhage. The risk of myocardial infarction also appears to be increased.
- Potential interactions may occur with amiodarone, verapamil, aspirin, clopidogrel, NSAIDs, ketoconazole and St John's wort.
- No specific monitoring test is available for anticoagulant effect and routine monitoring is not required. Creatinine clearance (or eGFR) should, however, be reassessed during long term use.
- No reversal agent is available.
- Dabigatran capsules are not able to be re-packaged into blister packs.
- As with every medicine it is appropriate to discuss with the patient the potential benefits and risks of dabigatran use prior to commencing treatment.

tailored, adequate, safe anticoagulation. In contrast, dabigatran has a predictable effect on anticoagulation and therefore routine monitoring is unnecessary. For this reason, dabigatran is likely to be more convenient than warfarin, however, it requires twice daily dosing. Dabigatran appears to be at least as effective as warfarin for preventing stroke in patients with AF, and has similar rates of bleeding (see Page 24 for a discussion of the evidence).

What are the registered indications for dabigatran?

Dabigatran is indicated for people with non-valvular atrial fibrillation for:[2]

- Prevention of stroke
- Prevention of systemic embolism
- Reduction of vascular mortality

Treatment should be continued life-long unless the risk benefit ratio for the patient changes.

Dabigatran is also registered for short term use for the prevention of venous thromboembolism (VTE) after major orthopaedic surgery.[2] It therefore provides an oral alternative to low molecular weight heparin, e.g. enoxaparin.

What should dabigatran not be used for?

There has, as yet, been no research on the use of dabigatran in people with AF who have haemodynamically significant valvular heart disease or in people with artificial valves.[1, 3]

Dabigatran should not be used for patients who require long-term prophylaxis for deep venous thrombosis or pulmonary embolism. Trials are underway to determine the effectiveness of dabigatran for long-term prophylaxis. It is not known whether dabigatran is clinically effective for VTE prophylaxis for long haul flights.

There have also been no studies investigating the use of dabigatran in people aged under 18 years or in pregnant women.[2] Clinical data on the excretion of dabigatran into breast milk is not available.[2]

How does dabigatran work?

Dabigatran etexilate, a direct thrombin inhibitor, is a prodrug (a medicine administered in an inactive form) which is converted to the active medicine dabigatran after oral administration.[2] Conversion to the active form takes place rapidly in the plasma and liver and an effective anticoagulant effect can be attained within two to three hours of oral ingestion.[2, 4] It takes two to three days to reach steady state.[5]

The active form, dabigatran, is a potent, competitive and reversible (in vitro) direct inhibitor of the active site of thrombin (factor IIa).[2, 6] It has high affinity and specificity for thrombin. Warfarin, in contrast, produces its anticoagulant effect via activity on a number of different coagulation factors (see "How do warfarin and dabigatran affect coagulation?" – Page 14). The anticoagulant effect of dabigatran therefore, has been shown to be predictable and consistent with a wide therapeutic window which allows for a fixed dose regimen.[2, 4]

What are the recommended doses of dabigatran?

For the prevention of stroke in people with non-valvular atrial fibrillation the recommended dose of dabigatran is:[2]

- 150 mg, twice daily, for patients with a creatinine clearance >30 mL/min*
- 110 mg, twice daily, for patients aged ≥ 80 years (because of the likelihood of an age-related decline in renal function)

* See "Dabigatran dosing in renal impairment"

For VTE prophylaxis following major orthopaedic surgery the recommended dose of dabigatran is:[2]

- 220 mg (2 × 110 mg tablets), once daily, for patients with creatinine clearance > 50 mL/min
- 150 mg (2 × 75 mg tablets), once daily, for patients with creatinine clearance 30 – 50 mL/min

N.B. The length of the course varies with the type of surgery – knee replacement surgery ten days, hip replacement surgery 35 days.

Dabigatran is predominately renally excreted

Renal excretion is the dominant elimination pathway for dabigatran. Up to 80% of circulating unchanged dabigatran and small amounts of dabigatran glucuronides are excreted via the kidneys.[2] Consequently, a reduction in renal function results in elevated plasma concentrations of dabigatran. Excretion via the kidneys also decreases with increasing age.[2, 4]

Creatinine clearance should be checked in all patients before treatment with dabigatran (see Page 15). Patients with severe renal impairment (creatinine clearance < 30 mL/min) should not be prescribed dabigatran.[2] Patients with this level of renal impairment were excluded from clinical trials and dabigatran datasheets list this as a contraindication.[2, 3, 4]

Any patient taking dabigatran, who has renal impairment or is at risk of developing renal impairment, should have their eGFR checked or creatinine clearance calculated every six to 12 months during long-term treatment.[6] In some patients, more frequent checks may be appropriate. If a patient develops acute renal failure while taking dabigatran it should be stopped.[2]

The remaining 20% of the medicine is eliminated via the liver.[4] Although hepatotoxicity has not been demonstrated with dabigatran, caution is advised when it is used in patients with severe liver disease. Patients with active liver disease or persistently raised liver enzymes (> two times upper limit of normal) were excluded from clinical trials.[2, 3] Earlier types of direct thrombin inhibitors failed to reach clinical use due to hepatotoxicity, e.g. ximelagatran.[8]

Twice daily dosing is required

Dabigatran has a short half life of approximately 12–14 hours in adults with normal renal function.[2] In people with impaired renal function, the half life is prolonged.[2] Regular twice daily dosing with an interval of approximately twelve hours is required. Efficacy is likely to be compromised with poor adherence.[6] Patients should be made aware that good compliance is important to sustain clinically effective anticoagulation.

Dabigatran dosing in renal impairment for patients with atrial fibrillation

Creatinine clearance < 30 mL/min – there is no clinical experience of the use of dabigatran in this group of patients. Dabigatran is currently contraindicated in the New Zealand medicine data sheet, for this group of patients.

Creatinine clearance 30 – 50 mL/min – use dabigatran with caution in this group of patients.

For patients with non-valvular AF, with creatinine clearance 30 – 50 mL/min, there are no specific recommendations to reduce the dose of dabigatran from 150 mg, twice daily. However, patients with renal function in this range may be at increased bleeding risk due to reduced dabigatran excretion, especially if other risk factors are present. Some practitioners recommend using a lower dose of 110 mg dabigatran, twice daily. However, it is not known if this dose is safer and evidence shows that it is likely to be less effective than the 150 mg dose.

The decision whether to prescribe dabigatran for patients in this group, and at what dose, should be individualised, with consideration given to factors such as the patient's overall bleeding risk and their specific creatinine clearance level. Discussion with a cardiologist may be helpful. Recommendations are likely to become clearer as more clinical experience becomes available with this medicine.

How do warfarin and dabigatran affect coagulation?

All anticoagulant agents work by inhibiting the activity of thrombin. Thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, therefore its inhibition prevents the development of thrombus.

The anticoagulatory effect of warfarin is due to inhibition of several components of the coagulation pathway including vitamin K-dependent factors II, VII, IX and X, and proteins C and S, therefore indirectly inhibiting thrombin. Dabigatran, in contrast, selectively and directly inhibits thrombin (Figure 1).[7]

By inhibiting thrombin, dabigatran prevents a number of processes in the coagulation pathway including:[6]

- The conversion of fibrinogen into fibrin
- Positive feedback amplification of coagulation activation
- Cross-linking of fibrin monomers
- Thrombin-induced platelet activation
- The inhibition of fibrinolysis

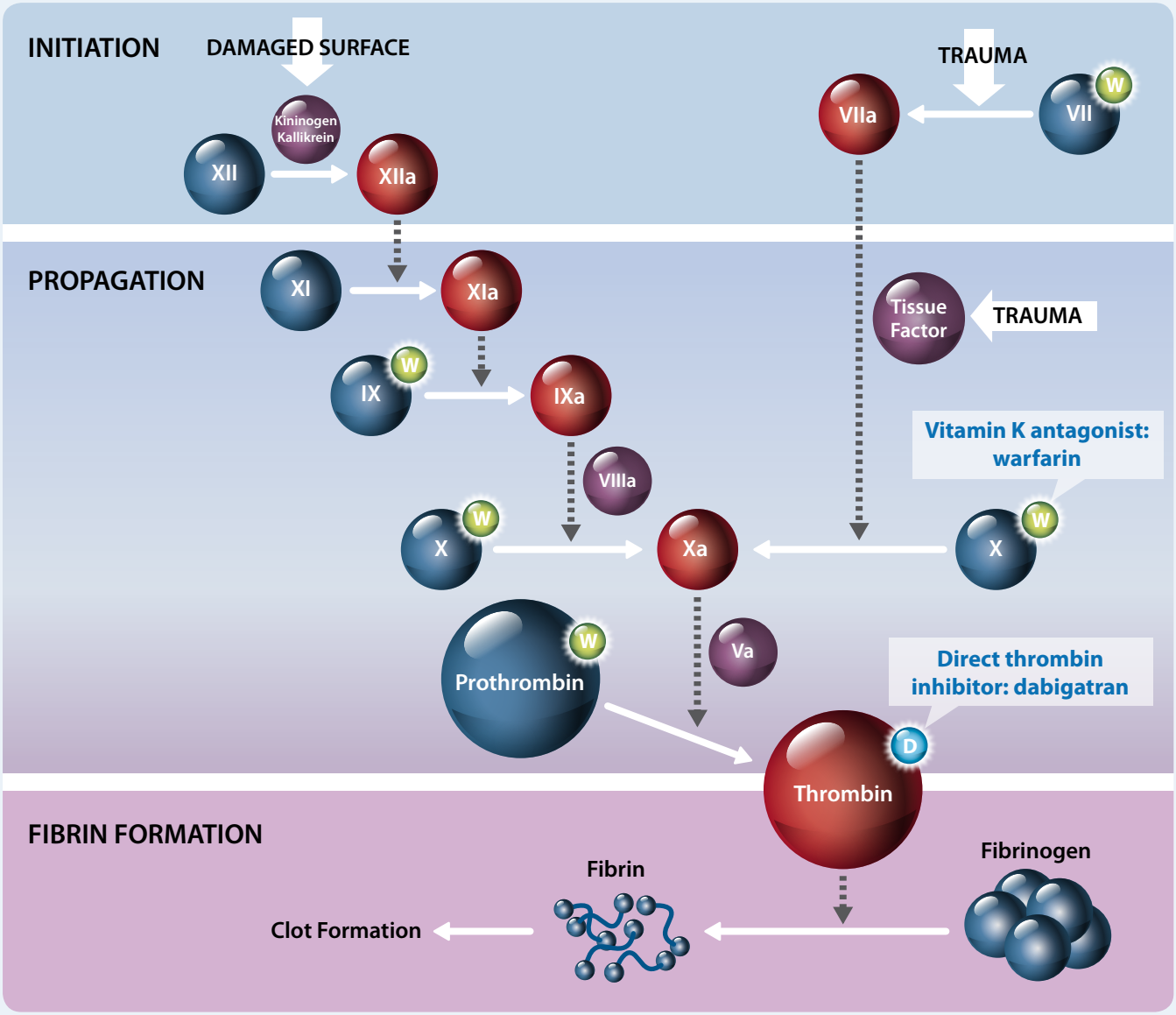


Figure 1. Coagulation cascade showing site of action of anticoagulants warfarin and dabigatran

There is limited evidence on the clinical effect of a missed dose. It is advised that:[2, 4]

- If a dose is missed, the dose can be taken when the patient remembers, provided it is more than six hours until the next scheduled dose
- If it is within six hours of the next scheduled dose, the patient should be advised not to take the missed dose
- A double dose should not be taken to make up for a missed dose

Dabigatran is not affected when taken with food

Although there is evidence that meals high in fat may delay the time taken to reach peak concentration in the plasma by approximately two hours, this does not appear to affect the bioavailability and clinical effectiveness of dabigatran.[2, 8] The capsules can therefore be taken with water, with or without food. Advising patients to take the capsules with breakfast and the evening meal may help with compliance.

The capsules should be swallowed whole and not chewed, or opened to sprinkle the contents on food or in fluids, as this significantly increases (75%) the oral bioavailability and may therefore increase the risk of bleeding.[2]

Dabigatran cannot be re-packaged into blister packs

Dabigatran capsules must be used within 30 days once the bottle is opened. If exposed to moisture the capsules have the potential to break down and there is a risk of loss of potency.[2, 10] It is recommended that the capsules are stored in their original bottle, with the lid tightly closed, to protect from moisture. The lid of the bottle contains a desiccant to help prevent moisture affecting the capsules. The manufacturer has recommended to pharmacies that dabigatran should not be re-packaged into weekly blister packs. New packaging to overcome this issue is likely to be supplied in the future.

What are the interactions with other medicines?

The knowledge on medicine and dietary interactions involving dabigatran is still in its infancy and few clinically significant interactions have been reported.[2, 11] Table 1 lists the major medicine interactions that are currently known. Unexpected or even potentially life-threatening medicine interactions may be identified with more widespread and prolonged use.[5] Vigilance is therefore required when initiating dabigatran or when any changes in the patient's medicine profile are made.

Metabolism of dabigatran etexilate to its active form does not use cytochrome P-450 pathways, which reduces the likelihood of drug-drug and drug-diet interactions.[2, 6] Dabigatran etexilate (the prodrug) is a substrate for the efflux transporter P-glycoprotein (P-gp) although the active medicine dabigatran is not.[2] Therefore there is the potential for interactions with medicines that are substrates, inhibitors or inducers of P-gp (Table 1, over page).[2, 8, 11]

Dabigatran is contraindicated in patients taking oral ketoconazole, a P-gp inhibitor.[2] Although no dose adjustment is recommended in the New Zealand datasheet, dabigatran should be used with caution in patients taking amiodarone or verapamil (also P-gp

Calculating creatinine clearance

Most laboratories report eGFR automatically with serum creatinine results, and eGFR can be used as an estimate of renal function. However, eGFR may not be a good estimate of renal function in people at extremes of body size (BMI < 18.5 or > 30 kg/m^2) or in older people. In this case, an estimate of creatinine clearance is preferable, determined using a hand held or electronic calculating tool or by using the Cockcroft-Gault equation:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times \text{constant}}{\text{serum creatinine (µmol/L)}}$$

The constant = 1.23 for men, 1.04 for women.

Table 1. Summary of known dabigatran interactions[2, 4, 9, 11]

Interaction	Medicine	Clinical considerations
Agents that increase gastric pH, decrease absorption: ↓ dabigatran concentration	Antacids	No clinically significant reduction in plasma concentration has been shown with concomitant use of antacids. Two hour separation of dabigatran and antacids is advised by some, or use an alternative medicine.
	Proton-pump inhibitors*	Pantoprazole has been shown to reduce the plasma concentration of dabigatran by up to 30% and similar effects would be expected with other PPIs such as omeprazole. A subgroup analysis of the RE-LY trial indicated that the interaction is not clinically significant and that the combination of a PPI and dabigatran need not be avoided. Further studies are required.
P-gp inhibitors: ↑ dabigatran concentration	Amiodarone Verapamil	Amiodarone and verapamil have been shown to increase the plasma concentration of dabigatran and although no dose adjustment is generally recommended, this combination of medicines should be used with caution. Two hour separation of dabigatran is advised by some but switching to an alternative medicine may be preferable, particularly for patients on verapamil
	Digoxin	Concomitant use of digoxin with dabigatran has been shown to result in a small, non-clinically significant, increase in plasma concentration. However, in practice this combination appears safe and well tolerated
CYP3A4 and P-gp inhibitors: ↑ dabigatran concentration	Ketoconazole	Concurrent use of dabigatran with oral ketoconazole is **contraindicated** due to a marked increase in plasma concentration
	Clarithromycin	No dose adjustment is recommended for clarithromycin although it is known to cause a non-clinically significant increase in plasma concentration
CYP3A4 and P-gp inducers: ↓ dabigatran concentration	Rifampicin	Avoid concurrent use of dabigatran with rifampicin if possible as this strong P-gp inducer significantly reduces the plasma concentration of dabigatran
	Carbamazepine	This P-gp inducer is expected to also reduce the plasma concentration of dabigatran and should be avoided or used with caution
Antiplatelet agents: ↑ anticoagulant effect	Aspirin Clopidogrel	No dose adjustment is recommended, however, a cautious approach is necessary. Clopidogrel has been shown to increase plasma concentration and in the RE-LY trial the use of antiplatelet agents doubled the risk of major bleeding (although this also applied to warfarin). Current expert opinion is that these medicines should not be used with dabigatran, although in secondary care their use may be considered on a case by case basis.
NSAIDs: ↑ bleeding risk ↑ antiplatelet effect	All NSAIDs**	No dose adjustment is recommended Concurrent administration of NSAIDs may increase the risk or severity of a bleed. Monitor for any abnormal bleeding
St John's wort: ↓ dabigatran concentration	St. John's wort preparations	This P-gp inducer is expected to reduce the plasma concentration of dabigatran. Avoid or use with caution.

P-gp = P-glycoprotein, CYP3A4 = cytochrome P450 3A4, NSAIDs = non-steroidal anti-inflammatory drugs

* Patients taking PPIs may be at increased risk of gastrointestinal bleeding due to the indication for which the PPI was prescribed. Pantoprazole may reduce the bioavailability of dabigatran by up to 30%, however, this decrease does not appear to affect the anticoagulant efficacy of dabigatran.[8, 12]

** A study including dabigatran and diclofenac found no pharmacokinetic interaction appears to occur, although there have been limited studies on the use of NSAIDs and dabigatran. The concurrent use of NSAIDs may theoretically increase the risk of bleeding with dabigatran.[12] Evidence regarding interactions with Cox-2 inhibitors is lacking, however, it is expected that the risk of bleeding will be increased as with conventional NSAIDs.

inhibitors).[2, 9] Some experts advise that patients take dabigatran two hours before taking verapamil and antacids.[4, 9] However, this may be impractical and using an alternative medicine may be a safer course of action until there has been more clinical experience with dabigatran.

Key clinically relevant features from Table 1:

- Antiplatelet agents and NSAIDs (both conventional and Cox-2) should be used with caution in people taking dabigatran because the risk of bleeding may be increased.[2] Evidence shows that people taking dabigatran concomitantly with aspirin or clopidogrel have approximately double the risk of major bleeding, irrespective of the dose.[1, 2] (N.B. a similar risk applies to patients taking warfarin). Patients taking these medicines or NSAIDs should be monitored clinically for signs of bleeding, e.g. ask about bleeding noses, wounds that keep bleeding, gums that are bleeding more than usual. Some patients may require an intermittent check for anaemia.
- The use of dabigatran with oral ketoconazole is contraindicated because clinical trials have shown that ketoconazole increases the maximum plasma concentration by approximately 150%.[2]
- Amiodarone and verapamil are medicines that are used in a similar population of people to those that require anticoagulation. A cautious approach should be taken as there is evidence that if amiodarone and verapamil are taken within two hours of dabigatran, the plasma concentration of dabigatran increases.[2, 9] Clinical use over time may help determine whether this increase produces clinically significant adverse effects with combinations of these medicines.
- Proton pump inhibitors do not appear to affect the anticoagulant efficacy of dabigatran.[2, 12]

There are no known food interactions with dabigatran and there has been no direct interaction between alcohol and dabigatran in animal models.[4]

Is there any need for routine coagulation monitoring?

Routine coagulation monitoring is not required for patients taking dabigatran because of the rapid onset of action, a wide therapeutic window and predictable pharmacokinetics and pharmacodynamics.[13, 14] There is currently no test available to routinely guide dabigatran dosage. In particular, dabigatran has variable and unpredictable effects on INR, which is not useful for monitoring.[14]

If a patient taking dabigatran experiences bleeding symptoms, the following should be considered:

- Is the patient taking any other medicines that affect coagulation, e.g. aspirin?
- Is the patient taking any medicines known to interact with dabigatran?
- Does the patient have impaired renal function, or has renal function deteriorated?

Management of bleeding complications in patients taking dabigatran should be individualised according to the site and severity. Dabigatran should be stopped and the source of bleeding investigated. Unless the bleeding is mild and able to be managed within the community, patients with bleeding should be referred urgently to secondary care (see Figure 2, Page 20).

If bleeding is a problem for a patient on dabigatran, what laboratory tests can be used to assess coagulation?

The activated partial thromboplastin time (aPTT) and thrombin time (TT) can be used to guide management of patients with acute bleeding, but these tests are not suitable for fine tuning dabigatran dosage.[13, 14] These tests can indicate whether dabigatran is “on board”, i.e. whether there is anticoagulant activity, e.g. if compliance is an issue or to determine if the medicine has been excreted. The time of the last dose of dabigatran should be included on the blood request form as this is critical for interpreting results.

Activated Partial Thromboplastin Time (aPTT) – this test does not have a linear relationship with drug levels. The test is moderately sensitive to the effect of dabigatran but the response is blunted at higher doses.

Thrombin Time (TT) – at recommended doses, dabigatran increases TT. This test is very sensitive and although there is a linear dose-response relationship, the time is very prolonged at therapeutic doses and the effect is also method specific making results potentially difficult to interpret.

The Ecarin clotting time (ECT) – this test is sensitive and has a linear dose-response relationship but is not widely available in New Zealand.

The primary role of these tests is to give a general guide as to whether a patient taking dabigatran, who is bleeding, still has a significant anticoagulant effect from the medicine. If neither the aPTT nor TT is prolonged there is no significant residual anticoagulant activity.[14] If the TT only is prolonged, there is some residual anticoagulant effect, but at a low level only. If both tests are prolonged there is likely to be a significant effect from dabigatran present (or another haemostatic defect).[13, 14]

Other tests to monitor coagulation status in patients taking dabigatran are being developed, however, they are not widely available and require standardisation for use.

Dabigatran may also have an effect on a number of other coagulation tests and its use should be recorded on the request form if a patient taking dabigatran requires any coagulation test such as thrombophilia markers and lupus anticoagulant testing.

Adverse effects of dabigatran – bleeding is the most relevant

All anticoagulant medicines inherently increase the risk of bleeding and patients should be informed of the risks and advised to let their General Practitioner know if they have any concerns.

The most common adverse effect with dabigatran is bleeding and the risk of major bleeding is comparable to that of warfarin.[1] In the RE-LY trial, dabigatran (150 mg or 110 mg), caused fewer intracranial haemorrhages and life-threatening bleeds when compared to warfarin, however, rates of major gastrointestinal bleeding were higher for patients on dabigatran than those on warfarin.[1] Overall the bleeding risk for patients taking dabigatran is greater at the higher dose of 150 mg, twice daily, and decreases when lower doses are used.

Major or severe bleeding, regardless of location, may lead to disabling, life-threatening or even fatal outcomes. Dabigatran should not be used in patients with clinically significant bleeding or who are at high risk for bleeding.

There is no antidote for bleeding from dabigatran, unlike vitamin K for warfarin. If haemorrhagic complications occur treatment should be stopped.

For advice about tools to estimate stroke and bleeding risk, see: “The warfarin dilemma”, BPJ 31 (Oct, 2010).

Dyspepsia is a commonly reported adverse effect with dabigatran. In the RE-LY trial, 11.8% of people taking 110 mg, twice daily, and 11.3% of patients taking 150 mg, twice daily, experienced dyspepsia compared with 5.8% in patients taking warfarin.[1] Each capsule contains a tartaric acid core, because absorption of dabigatran elexilate requires an acid environment.[6, 11] It is thought that the acid core may contribute to the development of dyspepsia. Dabigatran, therefore, may not be well tolerated particularly in patients with a history of gastrointestinal problems.[5, 11]

Rates of myocardial infarction may be higher

The incidence of myocardial infarction (MI) in the RE-LY trial was significantly lower in patients in the warfarin group compared to the dabigatran group.[1] Some evidence suggests that dabigatran may not actually increase the risk of MI but rather that warfarin provides a protective

effect.[2, 15] Whether dabigatran poses a genuinely increased risk of MI is still unclear.[5]

What adjustments in dabigatran dose are required for operative procedures?

At present there is limited evidence and clinical experience with the use of dabigatran prior to surgery. It is anticipated that the risk of bleeding with dabigatran is likely to be similar to the risk for a patient taking warfarin. However, it should be considered that prolonged bleeding times with dabigatran cannot be reversed, unlike warfarin (with vitamin K able to be used).

Planning has always been required for patients taking warfarin and the situation will be no different for patients taking dabigatran. Good communication should be maintained between primary and secondary care so clear consistent instructions for patients can be given and followed. The bleeding risk, the type of surgery planned and the renal function of the patient should be considered.

For people with a standard risk of bleeding, dabigatran should be temporarily discontinued for 24 to 48 hours before elective surgical procedures.[2, 6] For people at increased risk (e.g. older people, concomitant use of antiplatelet medicines, cardiac, respiratory or liver disease) or those having procedures with a high bleeding risk (e.g. any major surgery, spinal anaesthesia), dabigatran should be discontinued two to four days prior to the surgery.[2] If the risk of bleeding is high, a normal aPTT result will indicate a lack of residual anticoagulant effect.[13, 14]

Warfarin does not need to be stopped for some procedures such as dental extractions and minor surgery if the patient's INR value is at the lower end of the therapeutic range and their individual risk of bleeding is low. There is limited information about

Reporting patient bleeds with dabigatran

The Haematological Society, in association with Medsafe, PHARMAC and the Centre for Adverse Reactions Monitoring (CARM) is collecting data about adverse bleeding events experienced by patients using dabigatran.

Dr Paul Harper, consultant haematologist at Palmerston North Hospital is co-ordinating this review. **He asks that all patient bleeds, adverse events or discontinuation of therapy with dabigatran (Pradaxa) be reported to CARM**. Events should be reported regardless of whether the patient required hospitalisation. If in doubt, report – it is not necessary to be certain that an adverse reaction is caused by a medicine in order to make reporting worthwhile.

Adverse reaction reports should include as much information as possible, and can be made via:

- *bestpractice* Decision Support – click "Adverse drug reaction reporting" under the module list
- Or reporting cards – found inside the back cover of Prescriber Update and with the MIMS Catalogue
- Or directly with CARM, online at: https://nzphvc-01.otago.ac.nz/carm phone: 03 479-7247, fax: 03 479-7150 or email: carmnz@otago.ac.nz

The Safe and Quality Use of Medicines Group (SQM) has published an urgent alert following hospital admissions for the treatment of bleeding after dabigatran initiation. This report can be found on the SQM website at: www.safeuseofmedicines.co.nz

Dabigatran associated bleeding

Identify the site and cause of bleeding if possible

Assess the severity of the bleeding using clinical signs and CBC if indicated

Check aPPT and TT, fibrinogen assay, creatinine and electrolytes, calcium
– Note the time of the last dabigatran dose on the request form

Consult with a haematologist for advice about ongoing management

Stop dabigatran – either delay the next dose if bleeding is mild or discontinue if bleeding is more severe

Mild bleeding	For moderate, severe or life-threatening bleeding*
If applicable elevate affected body part and apply compression Consider use of oral tranexamic acid (15 mg/kg, four times per day) Ensure good fluid intake to maximise renal excretion	**Refer urgently to hospital** Measures as for mild bleeding Initiate standard resuscitation measures if required (e.g. establish IV access, give IV fluids, oxygen)

* **Moderate to severe bleeding** – a reduction in Hb≥20g/L, symptomatic bleeding in an organ or critical area, e.g. intraocular, intracranial, intramuscular, retroperitoneal, intraarticular or pericardial bleeding.[2]

Life-threatening bleeding – a reduction in Hb≥50g/L, symptomatic intracranial bleed, hypotension requiring inotropic agents, e.g. dopamine, bleeding requiring surgery[2]

Figure 2: Treatment of dabigatran associated bleeding in primary care (adapted from van Ryn[14])

the use of dabigatran in this situation, but it can be assumed that a similar assessment of risk can take place, although bearing in mind that a bleeding event with dabigatran cannot be reversed.

Evidence shows that dabigatran can be used safely in patients undergoing cardioversion.[2, 16]

How can bleeding be managed for people taking dabigatran?

Unlike warfarin and heparin, no specific antidote is available to reverse the anticoagulant effects of dabigatran. Administration of vitamin K or an infusion of plasma will not reverse the anticoagulant effect.

Unless the bleeding is mild, it is anticipated that most patients will require referral to secondary care for urgent treatment, although this will depend on individual patients and the location and severity of the haemorrhage. Treatment in secondary care may involve the use of oral charcoal (if ingestion of dabigatran was less than two hours previous), transfusion of blood products or clotting factors, use of anti-fibrinolytic agents intravenously and consideration of haemodialysis, particularly if there is moderate to severe renal impairment (Figure 2).[14]

Severe or life-threatening bleeding may be immediately obvious due to the clinical state of the patient, e.g. tachycardia, pallor, hypotension, bleeding with injury. However, some patients, particularly younger patients, may have normal vital signs, even with a significant blood loss. In addition, there may be bleeding within a body cavity, e.g. stomach, bowel or chest, that is not clinically detectable until a large volume of blood has been lost. Although an urgent complete blood count to assess the haemoglobin level may be useful, in a general practice setting, unless the bleeding is mild, referral to secondary care is recommended for patients taking dabigatran who are bleeding. As a guide, the categories used in the RE-LY trial to define the severity of bleeding were; a decrease of 20g/L Hb signifying moderate to severe bleeding and a decrease of 50g/L Hb, life-threatening bleeding.[1]

Details of the management of moderate, severe or life-threatening bleeding is available from: www.pharmac.govt.nz/2011/06/13/Dabigatran%20bleeding%20management.pdf.

Which patients with non-valvular atrial fibrillation should use dabigatran?

Careful patient selection is important when considering dabigatran use[1, 2, 6, 17]

Patients with non-valvular atrial fibrillation **who may benefit** from dabigatran include those who:

- Require anticoagulation but are currently on no treatment, e.g. patients who have declined treatment with warfarin or aspirin or those taking medicines that are contraindicated with warfarin
- Are already on warfarin but where there are difficulties with monitoring, e.g. difficult venous access, problems with accessing lab facilities due to mobility issues, cost or lack of time, those who are non-compliant with monitoring
- Are already on warfarin but have INR values that are often sub-therapeutic or difficult to control
- Wish to change for convenience

Patients **who may not benefit** from dabigatran include those who:

- Are on warfarin with a stable (or easy to control) INR and who are comfortable with the need for INR monitoring. Patients on warfarin who have INR values that are consistently within the therapeutic range are less likely to benefit from a switch to dabigatran.
- Are unlikely to be compliant with the twice daily dosing required for dabigatran
- Prefer to continue with warfarin (some patients may like the reassurance of periodic monitoring)
- Require blister packed medicines

Comparison of dabigatran and warfarin

When treating patients with atrial fibrillation it must first be decided whether anticoagulation is indicated. This can be determined using a risk assessment tool such as $CHADS_2$ or CHA_2DS_2VASc. The next step is to choose the most suitable anticoagulant for that individual patient.

See "The warfarin dilemma" BPJ 31 (Oct, 2010) for further discussion on risk assessment tools.

Summary of properties of dabigatran and warfarin[2, 4, 6, 13]

Property	Dabigatran	Warfarin
Indication for AF	Non-valvular atrial fibrillation	Valvular or non-valvular atrial fibrillation
Mechanism of action	Direct inhibition of thrombin	Reduced synthesis of prothrombin and other clotting factors
Administration	Oral Twice daily (for AF)	Oral Once daily
Dosing	Fixed dose, dependent on creatinine clearance and age	Individualised to each patient and target INR
Onset of action	0.5–2 hours	36–72 hours
Elimination half-life	12–14 hours	20–60 hours
Duration of action	24 hours	48–96 hours
Stable, predictable pharmacokinetics	Yes	No
Interactions with diet and alcohol	No	Yes
Interactions with medicines	Interactions largely unknown, clinical experience over time likely to reveal more. Known interaction with p-glycoprotein inhibitors e.g. oral ketoconazole, verapamil, amiodarone	Multiple
Monitoring	No routine monitoring required. If tests are used, timing of blood sample is important for correct interpretation.	INR every one to eight weeks depending on clinical situation
Risk of major haemorrhage	Similar for both medicines Major GI bleeding rates may be higher than with warfarin, however, rates of intracranial haemorrhage and life-threatening bleeding may be lower with dabigatran.	Similar for both medicines.
Other adverse effects	Dyspepsia Possibly increased risk of MI	Multiple reported, however, in clinical practice these are relatively rare
Antidote	None available but can be removed by dialysis	Vitamin K Fresh-frozen plasma
Cost	Fully funded	Fully funded

AF = atrial fibrillation, INR = international normalised ratio, GI = gastrointestinal

Dabigatran is **contraindicated** in patients who:

- Have chronic kidney disease with a creatinine clearance less than 30 mL/min
- Have had a recent haemorrhagic stroke (within six months)
- Are taking oral ketoconazole
- Have any active bleeding or any impairment of haemostasis

Dabigatran **should not be used** (primarily due to lack of evidence) in patients who:

- Have haemodynamically significant valvular heart disease or mechanical heart valves (there is currently no evidence on the suitability of dabigatran in these conditions)
- Have severe liver disease

Dabigatran **should be used with caution** in patients who:

- Are aged ≥ 80 years (although this group may have an increased need for anticoagulation, they may also have impairment of renal function)
- Have moderate kidney disease, i.e. creatinine clearance of 30 – 50 mL/min
- Have existing or a history of gastrointestinal problems such as GI ulceration or poorly controlled gastro-oesophageal reflux
- Are taking amiodarone, verapamil, rifampacin, clarithromycin
- Are taking other medicines that affect haemostatis, e.g. aspirin, clopidogrel
- Have had recent trauma, major surgery or gastrointestinal bleeding

Initiating dabigatran or switching between oral anticoagulants

Initiation in patients not previously anticoagulated with warfarin

No loading dose is required when initiating dabigatran, the medicine is started and continued at the same dose.[2]

How do you change from warfarin to dabigatran?

Stop warfarin and start dabigatran when the INR is less than 2.0.[2]

How do you change a patient from dabigatran to warfarin?

Check the creatinine clearance. Warfarin should be started three days prior to stopping dabigatran if the creatinine clearance is > 50 mL/min. If the creatinine clearance is 30 – 50 mL/min, start warfarin two days before stopping dabigatran.[2]

Best Practice tip: If switching a patient from warfarin to dabigatran, notify the local laboratory by phone or email so that they can update their records and avoid unnecessary INR testing. Patients taking warfarin are often registered with a laboratory for regular, long-term repeat INR's.

The evidence for dabigatran – can we RE-LY on this?

The Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial was a "non-inferiority" trial.[1] In this type of trial, a new medicine is compared with a current standard treatment in an attempt to determine whether the new medicine is no worse than the usual medicine.[18] The new medicine does not have to be superior to the older medicine. In contrast, randomised trials usually assess if a new medicine is better than a current medicine or placebo and are called superiority trials.

The RE-LY trial therefore had to show that outcomes for the people who took dabigatran were at least as good as the outcomes for the people who took warfarin.

Summary of findings from the RE-LY trial

This large, randomised, non-inferiority clinical trial compared two doses of dabigatran (110 mg and 150 mg administered twice daily) to warfarin treatment (aiming for INR values of 2–3) in over 18,000 patients with atrial fibrillation.[1] The study was of hybrid design with medicine administration blinded for patients on dabigatran but not for warfarin.

Compared to warfarin, the 150 mg, twice daily dose of dabigatran significantly reduced the rate of stroke or systemic embolism.[1] The 150 mg dose was therefore found to be superior to warfarin for the prevention of stroke or systemic embolism. There was no significant difference in the rate of stroke or systemic embolism with the 110 mg, twice daily dose of dabigatran when compared to warfarin. Twice daily dabigatran 110 mg was therefore found to be non-inferior to warfarin.[1]

Both doses of dabigatran were associated with fewer intracranial haemorrhages and other life-threatening bleeds

Comparison of adverse events in the RE-LY trial[1]

Event	% of incidents per year			Significance (P ≥ 0.05)
	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	
Stroke or systemic embolism	1.53	1.11	1.69	D150 **superior** to W D110 **not inferior** to W D150 **superior** to D110
Myocardial infarction	0.72	0.74	0.53	W **superior** to D150
Intracranial haemorrhage	0.23	0.30	0.74	D110 **superior** to W D150 **superior** to W
Life-threatening bleeding	1.22	1.45	1.80	D110 **superior** to W D150 **superior** to W
Gastrointestinal bleeding	1.12	1.51	1.02	W **superior** to D150 D110 **superior** to D150
Death from vascular causes	2.43	2.28	2.69	D150 **superior** to W
Death from any causes	3.75	3.64	4.13	No difference

when compared to warfarin, however, gastrointestinal bleeding events were significantly increased with the higher dose of dabigatran.[1] The rate of myocardial infarction was significantly higher (p = 0.048) in patients in the dabigatran group.[1]

There were no significant differences in the mortality rates from any cause between either of the dabigatran treatment groups and the warfarin group.[1]

What were the strengths of the RE-LY trial?

The trial was large, including over 18,000 patients from multiple countries. Follow up of participants was excellent with 99.9% of patients completing follow up assessments over a median time frame of two years.[1] Patients were allocated randomly into the three treatment groups (dabigatran 110 mg twice daily, dabigatran 150 mg twice daily or warfarin). Administration of dabigatran was blinded, however, warfarin was not because of the need for INR monitoring. The investigators were aware of this potential for bias and therefore implemented strategies to minimise bias such as arranging for assessment of the outcomes to be carried out by two independent parties who had no knowledge of the treatments received.

What were the limitations of the RE-LY trial?

This was an industry funded trial, however, the coordination of the study, data management and analysis of the results were carried out on an independent basis at McMaster University in Canada.[1, 19]

The study participants represented a select group of people and the outcomes of treatment with dabigatran may be different in a "real world" setting.[20] Participants had AF and a minimum of one other risk factor for stroke, e.g. previous stroke, hypertension, coronary artery disease.[3] People excluded from the study included those with:[3]

- Haemodynamically significant valvular heart disease or a prosthetic valve
- Any stroke in the previous two weeks or a severe disabling stroke in the last six months
- An increased risk of bleeding, e.g. GI bleeding within the previous year, documented GI ulcer within the last month, major surgery within the last month, uncontrolled hypertension, a history of bleeding, any haemorrhagic disorder
- Severe renal impairment (creatinine clearance ≤ 30 mL/min)
- Active liver disease
- Anaemia or thrombocytopaenia

Although the administration of dabigatran was blinded, participants receiving warfarin could not be administered this medicine in a blinded manner due to the need for INR measurement and subsequent adjustment of doses. There have been comments in the literature stating that this may have altered the way patients in the warfarin arm of the trial were managed, i.e. performance bias.[21, 22]

The standard of anticoagulation in patients on warfarin, with INR values in the therapeutic range for 64% of the time, has been said to be poorer than that achieved in many centres, although the level is similar to that achieved in most randomised controlled trials.[22, 23] In addition, the INR values at which adverse events occurred were not reported. Some researchers believe that the benefits reported for dabigatran would be minimised if they were compared with patients taking warfarin who had INR values consistently within the therapeutic range.[22] To address some of the questions regarding INR control raised by the United States Food and Drug Administration and other researchers, a subsequent analysis of RE-LY data has reported that the primary outcomes remained consistent irrespective of the quality of INR control.[21, 24]

Other concerns that have been raised include the higher rates of withdrawal due to adverse effects in the dabigatran arms of the study and the concomitant use of antiplatelet agents in all three arms of the trial.[21]

At this stage the longer term effects (post two years) of dabigatran are not known although there is an ongoing multi-centre follow up study in place (RELY-ABLE).

There is still a lot to learn about dabigatran

Dabigatran may well provide a solution to some of the problems associated with the use of warfarin such as its unpredictable and significant inter-individual variability in response and narrow therapeutic window which necessitates frequent INR monitoring as well as numerous food and medicine interactions.[5] However, the importance of the frequent patient contact that accompanies INR monitoring should not be forgotten as this often goes beyond "a simple blood test".

The consequences of long-term use of dabigatran are unknown and this may be important in the setting of stroke prevention in patients with atrial fibrillation as these patients usually require life-long treatment.[5, 6] Thrombin plays an important role not only in coagulation but also in immune response, infection, angiogenesis, endothelial function, and tumour growth.[6]

The main clinical trial (RE-LY), which has prompted the review of recommendations in atrial fibrillation guidelines, included just over 18,000 people who took dabigatran for two years.[1] There is still a lot to learn about dabigatran – its effectiveness, adverse effects, longer term safety and interactions with other medicines. This information will only be gathered once it has been used extensively over the next few years.

Like all medicines the promise that dabigatran brings must be balanced against its potential risks and uncertainty, therefore a cautious approach to its use is recommended.

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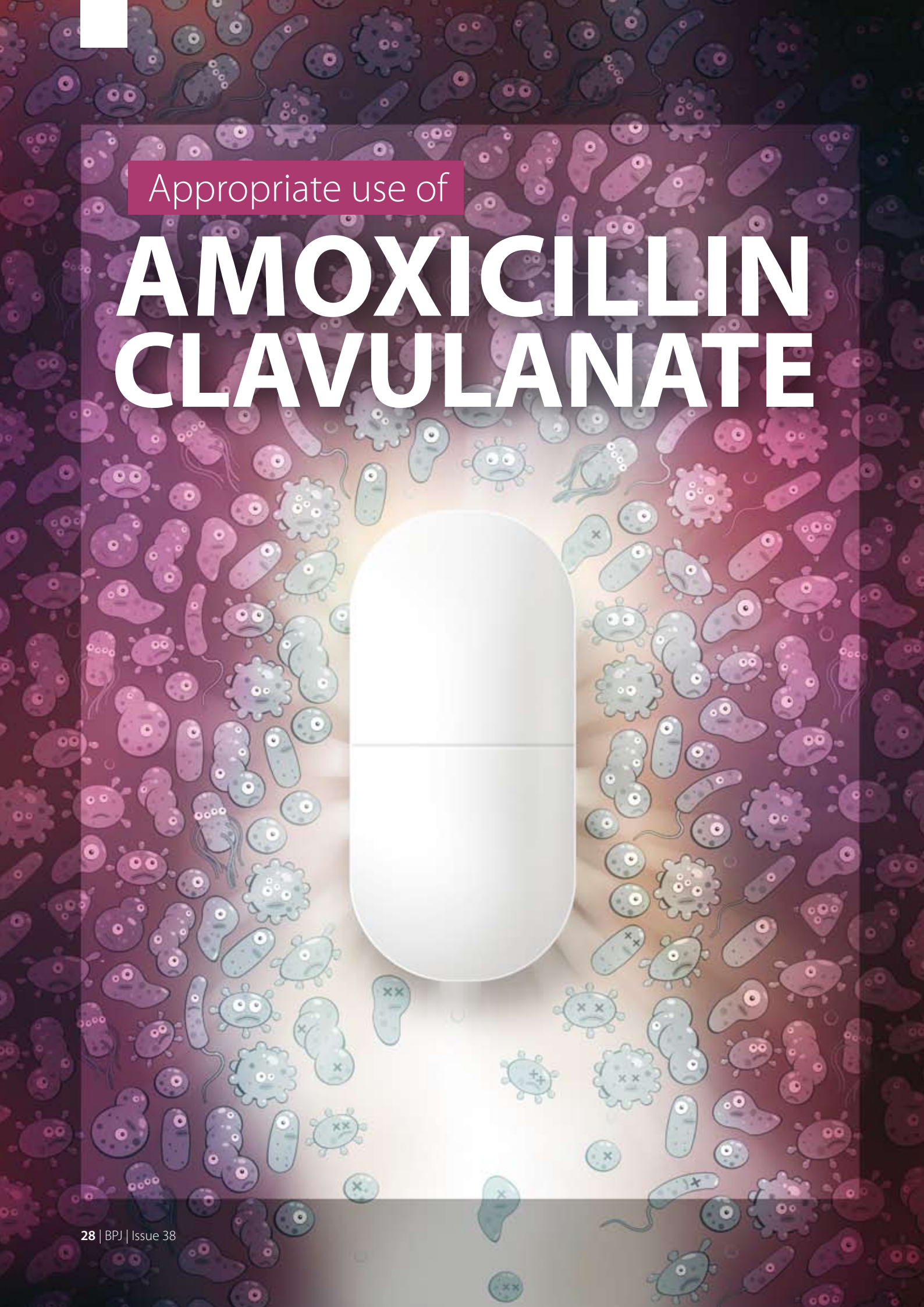
Appropriate use of

AMOXICILLIN CLAVULANATE



Why should amoxicillin clavulanate be reserved for only certain conditions?

Amoxicillin clavulanate is a broad spectrum antibiotic which is used frequently in New Zealand general practice. While amoxicillin clavulanate and other broad spectrum antibiotics (quinolones and cephalosporins) are effective, they are best avoided when other more narrow-spectrum antibiotics could be used because they increase the risk of *Clostridium difficile*, MRSA and other resistant infections.[1] Amoxicillin clavulanate has been associated with cholestatic jaundice (see opposite).[2] It is also commonly associated with antibiotic related diarrhoea and vaginal and oral thrush.

The use of amoxicillin clavulanate is declining in New Zealand, however, the volume of prescriptions for this medicine is still high. Between April 2008 and March 2009, the average number of amoxicillin clavulanate dispensings per General Practitioner in New Zealand was 170. In the same period in 2009/2010, this average decreased to 153.

Cholestatic jaundice with amoxicillin clavulanate

Hepatitis and cholestatic jaundice have been reported with the use of amoxicillin clavulanate. It appears that this adverse effect can occur during treatment or up to six weeks after treatment cessation. Increasing age, prolonged treatment and male gender are risk factors. Cholestatic jaundice occurs in approximately 1 in 6000 patients. Acute liver toxicity occurs in people taking amoxicillin clavulanate at six times the rate of people taking amoxicillin. As a result of this adverse effect, the United Kingdom Committee on Safety of Medicines (CSM) recommended that amoxicillin clavulanate only be used for bacterial infections that are thought to be caused by amoxicillin-resistant strains and treatment length should be suitable for the indication and not usually exceed 14 days.[2, 3]

Table 1: First and second line indications for amoxicillin clavulanate

	First-line	Second-line
Bites (mammalian – including human)	✓	
Diabetic foot infections	✓	
Periorbital/facial cellulitis	✓	
Acute pyelonephritis	*Ciprofloxacin*	✓
Sinusitis	*Amoxicillin*	✓
Pneumonia	*Amoxicillin*	✓

Preliminary data from 2010/2011 suggest that the rate of decrease is slowing, with an average of 147 dispensings for amoxicillin clavulanate per General Practitioner (data calculated from NZHIS Pharmaceutical Warehouse).

Amoxicillin clavulanate is best reserved for the few indications where it is necessary so that it remains an effective antibiotic when needed and the adverse effects associated with the use of broad spectrum antibiotics are avoided.

When is use of amoxicillin clavulanate appropriate?

First-line indications for amoxicillin clavulanate

Amoxicillin clavulanate has only a few indications where it is recommended as a first line antibiotic, e.g. mammalian bites (including human), diabetic foot infection and periorbital cellulitis. These infections require this broad spectrum antibiotic to cover the large range of potential causative organisms.

Mammalian bite treatment or prophylaxis

Amoxicillin clavulanate is appropriate for mammalian bites because it is active against the organisms most commonly isolated: e.g. alpha- and beta haemolytic streptococci, *Staphylococcus aureus*, *Staphylococcus epidermis*, *Corynebacterium species* and *Eikenella corrodens* in human bites and *Pasteurella*, streptococci, staphylococci, *Moraxella*, *Neisseria* and anaerobes in other mammalian bites.[1]

All infected bites should be treated with antibiotics. Prophylactic treatment with antibiotics is appropriate for human and cat bites (even if they do not appear to be infected) and any bites that occur to the hand, foot, face, tendon or ligament, or in immunocompromised people. Consider referral to secondary care for any bites that involve the bones or joints.[1]

N.B.: Injuries that occur to the fist as a result of contact with teeth are essentially treated the same as for bites.

Diabetic foot infections

Diabetic foot infections may involve staphylococci, streptococci or facultative anaerobes such as *Bacteroides species*. Early infection is usually due to *S. aureus* and/or streptococci. Later infection may be polymicrobial with a mixture of gram-positive cocci, gram-negative bacilli and anaerobes. To cover these organisms, a broad spectrum antibiotic such as amoxicillin clavulanate is appropriate as a first-line option.[1]

Radiological assessment may be required to determine whether the infection involves the bones of the feet (i.e. whether there is osteomyelitis). Intravenous antibiotics will be required if this is the case.

Facial and periorbital cellulitis

Amoxicillin clavulanate is appropriate for facial and periorbital cellulitis because it covers a broader range of organisms than flucloxacillin. In the past, facial cellulitis, arising from infection in the buccal mucosa, was often a result of *H. influenzae* infection, however, this is less common now because of the *H. influenzae* type B (Hib) immunisation programme.[1]

In all but very mild cases of facial cellulitis and especially perioribital cellulitis, referral to secondary care is advised.[5]

Second-line indications

There are a few indications where amoxicillin clavulanate is a suitable second-line alternative to cover persistent infection, when anaerobes are suspected (e.g. in some cases of sinusitis or when treating post viral/influenza pneumonia) or as an alternative to ciprofloxacin for acute pyelonephritis.

Acute pyelonephritis – second-line alternative to ciprofloxacin

Amoxicillin clavulanate is appropriate for second-line use in acute pyelonephritis because it has good kidney penetration and covers the broad range of pathogens that may cause acute pyelonephritis.[1] Using a broad spectrum antibiotic such as amoxicillin clavulanate reduces the

risk of treatment failure and the potential for serious complications.

It is only appropriate to manage a patient with pyelonephritis as an outpatient if they have mild symptoms, e.g. low fever and no nausea or vomiting. Patients should be referred to secondary care for intravenous antibiotics if they are systemically unwell or vomiting.

Sinusitis – after failure of first-line antibiotics

Most cases of sinusitis are viral or resolve spontaneously (80% resolve spontaneously without antibiotics in 14 days).[1] Patients can be advised that it is common for symptoms of sinusitis to continue for approximately two weeks.[6] Antibiotics should only be considered if symptoms have been present for five to seven days in conjunction with fever or unilateral maxillary sinus tenderness, severe headache or worsening symptoms after initial improvement.

While acute sinusitis rarely involves anaerobes, they are more likely to be the cause of chronic infections.[1] If first-line antibiotics have been tried and were ineffective, check compliance and then consider second-line options such as amoxicillin clavulanate.[7] Amoxicillin clavulanate is appropriate as a second-line choice for persistent sinusitis because it has good activity against anaerobes and also *H. influenza*, *Streptococcus pneumoniae* and *M. catarrhalis*, which are commonly associated with sinusitis.[8]

Pneumonia – when anaerobes are suspected

Amoxicillin clavulanate is appropriate for post viral/influenza pneumonia where *S. aureus* is often implicated. It is also appropriate in aspiration pneumonia to cover anaerobes.

Patients with mild pneumonia are able to be managed at home, however, hospital admission should be considered for patients with two or more of the following features; age > 65 years, confusion, respiratory rate > 30/min, diastolic blood pressure < 60 mm Hg. Patients with these features have an increased risk of mortality.[9]

Mastitis in non-lactating women

S. aureus is usually the cause of mastitis in lactating women, and therefore flucloxacillin is the first-line antibiotic treatment. However, anaerobes are the most common pathogen implicated in non-puerperal mastitis, particularly in sub-areolar infections.[5] Therefore it is appropriate to use amoxicillin clavulanate to treat mastitis in non-lactating women.

How does amoxicillin clavulanate work?

Amoxicillin clavulanate is a combination of the antibacterial agent amoxicillin and clavulanic acid. Clavulanic acid has minimal antibacterial action but is a potent inhibitor of beta-lactamase produced by some bacteria, including, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and some Enterobacteriaceae.[3] It is also effective against a wide variety of anaerobes. In particular, clavulanic acid has good activity against plasmid mediated beta-lactamases which are often associated with transferred drug resistance.[4] The combination of amoxicillin and clavulanic acid prevents amoxicillin from being degraded by beta-lactamases therefore extending its spectrum of activity to include organisms which would normally be resistant to amoxicillin alone.

Clavulanic acid is generally less active against chromosomally-mediated beta-lactamases therefore organisms with these beta-lactamases such as *Enterobacter spp*. and *Pseudomonas aeruginosa* are resistant.[3]

Antibiotics for upper respiratory tract infections

(adapted from NICE, 2008)[6]

Antibiotics, including amoxicillin clavulanate, are often prescribed unnecessarily for self-limiting viral respiratory tract infections. Clinicians should avoid prescribing, or provide a delayed prescription, for patients with conditions such as acute otitis media, acute sore throat (unless high risk for rheumatic fever), common cold, acute rhinosinusitis and acute cough/acute bronchitis. The following groups of patients may be suitable for an immediate antibiotic prescription, depending on the severity of the condition and patient/carer preference:

- Children aged under two years with bilateral acute otitis media
- Children with acute otitis media with otorrhoea (discharge)
- Anyone with acute sore throat/acute tonsillitis when three or four red flags (see box) are present.

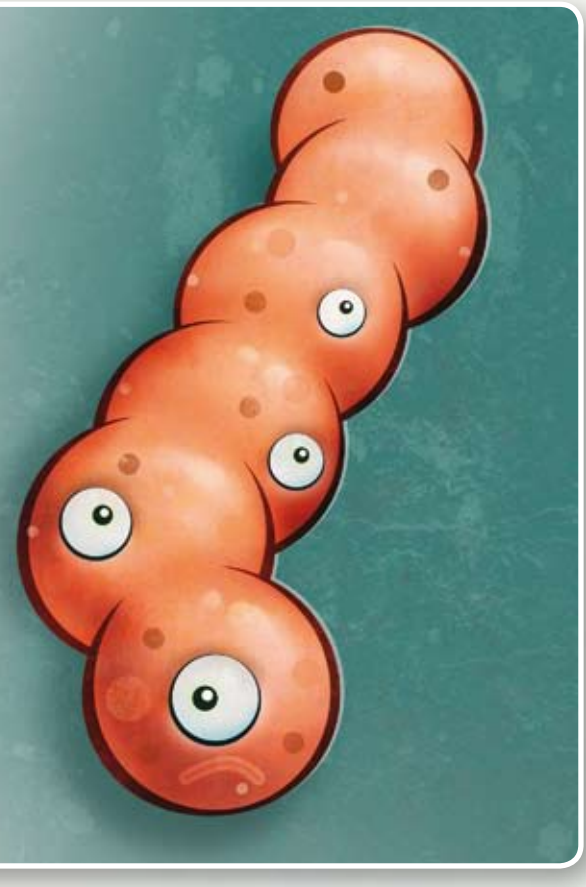
When patients are not given a prescription or are offered a delayed prescription, they should be reassured that antibiotics are not indicated and that they have little effect on the condition (i.e. length of illness and symptoms) and may cause adverse effects such as diarrhoea, vomiting and rash. Patients should be advised to come back if the condition worsens or becomes prolonged. Patients provided with a delayed prescription should be advised about when to use it, such as if symptoms do not settle in the expected time course of the illness or if a significant worsening of the illness occurs.

Red flags for sore throat:

- Temperature > 38 degrees celsius
- No cough or coryza (which may suggest a viral cause)
- Swollen anterior cervical lymph nodes
- Tonsillar swelling or exudate

All children presenting with sore throat who are of Pacific or Maori ethnicity, aged three years and over and who live in areas with high incidence of rheumatic fever (i.e. low socioeconomic areas of the North Island), should have a throat swab taken and should be prescribed empirical antibiotics (penicillin V [phenoxymethylpenicillin] or amoxicillin) if they have ANY of the red flags.

See “Rheumatic Fever in Maori: What can we do better?” BPJ 37 (Aug, 2011).



All patients, whether they are provided a prescription or not, can be advised of the likely natural history of the illness, especially the average total length of time of an illness:[6]

- Acute otitis media: four days
- Acute sore throat/acute pharyngitis/acute tonsillitis: one week
- Common cold: seven to ten days
- Acute sinusitis: two weeks
- Acute cough/acute bronchitis: three weeks

It is appropriate for some patients to be provided with a prescription initially because they may be at greater risk of complications. These patients include:

- Those systemically very unwell
- Those with symptoms or signs of serious illness and/or complications
- Those with comorbidity that puts them at increased risk of serious complications, e.g. patients with significant heart, lung, liver or renal disease or those who are immunosuppressed
- Patients older than 65 years with acute cough and **two** or more of the following criteria, or patients older than 80 years with acute cough and **one** or more of the following criteria:
  - Hospitalisation in the previous year
  - Type 1 or type 2 diabetes
  - History of congestive heart failure
  - Current use of oral glucocorticoids

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Community-based IV administration:

Primary care reducing hospital admissions

GENERAL PRACTICES AROUND NEW ZEALAND are increasingly providing intravenous (IV) administration of medicines in the community, in order to offer treatment to patients who would otherwise need to be admitted to hospital. Different funding and support structures exist around the country to enable practices to offer these services and as yet there is no national model for providing community IV treatment. The purpose of this article is to highlight the conditions for which IV treatment in the community would be appropriate, and the reasons that practices may wish to offer these services, alone or as part of a treatment network.

The advantages of community-based treatment

In general, given the option, people prefer to receive community-based treatment than be admitted to hospital.[1–3] Treating people in their own communities allows them to remain with family and continue work, education or fulfil other commitments. In comparison, hospital stays are disruptive and require patients, and their families, to adapt to hospital routines while experiencing a reduction in privacy and comfort.

The benefits of a community-centric approach extend beyond patient satisfaction. Patients treated at home are not at risk of acquiring nosocomial (hospital acquired) infections.[4] A study of patients with cellulitis, conducted in Christchurch, showed that community-based treatment resulted in patients receiving a comparable standard of care, with no significant difference in condition advancement, length of treatment or adverse events, when compared to hospital admission.[2] Community-based treatments also, generally, result in significant cost savings when compared to hospital admission. In one New Zealand study it was found that 31% of all hospital admissions could have been avoidable.[5] Reducing avoidable hospital admissions can increase the quality of care for patients admitted into secondary care.[6] Some patients could also be discharged from hospital earlier if strategies exist for effective delivery of community-based treatments. As DHBs attempt to improve service and reduce cost through innovation, it is likely that community-based treatment will become increasingly common in New Zealand.

IV administration of medicines

Each year many patients are admitted to secondary care for the treatment of acute conditions such as dehydration or infection, requiring IV administration of fluids or medicines. Primary healthcare professionals are well placed to offer services for administering IV treatment, given the necessary resources, appropriate patient selection and the provision of refresher training, if required. In countries such as Australia, Canada, the United States and the United Kingdom, home based delivery of IV antibiotics has been shown to be safe and cost effective.[7–9] Several localised studies, conducted in the Christchurch and Auckland regions, have also found primary care to be an effective means of delivering IV treatments to suitable patients.[9, 10]

Deciding who to treat

The decision to treat a patient in the practice, or at their home, is based on clinical judgement. An algorithm can be used to assist this decision (Figure 1 over page).

Issues that need to be considered when deciding to administer IV treatment include:

- Does your practice have the equipment, space, time and skills?
- Is the patient old enough? Patients aged under 15 years may present added complications, such as specialised dosing requirements, and in most circumstances should be referred to secondary care for IV treatment

- Will the infusion(s) be delivered at home or in the clinic?
- Is the medicine stable and suitable to be delivered in a primary care setting?
- Can the required medicines be easily obtained?
- What volume of infusion is required and how long will each treatment last?
- How frequently will the treatment be required?
- Will consultation with a community or hospital pharmacist be of assistance?

What conditions can be treated?

There are no national guidelines on which conditions are most suitable for community-based IV treatment. Primary Options for Acute Care (POAC) is an organisation that funds practices in the Auckland, Waitemata and Counties Manukau DHBs to deliver community-based IV services. The most common conditions, for which IV treatments were delivered by these practices, between June 2010 and June 2011 were:

- Cellulitis – 5388 cases
- Respiratory infection – 2379 cases
- Dehydration – 1036 cases
- Kidney infection – 424 cases

Individual reports for Auckland, Waitemata and Counties Manukau DHBs are available from: www.primaryoptions.co.nz/page/News_and_Reports

Cellulitis

Patients presenting with cellulitis represent the largest group suitable for community-based treatment. A United

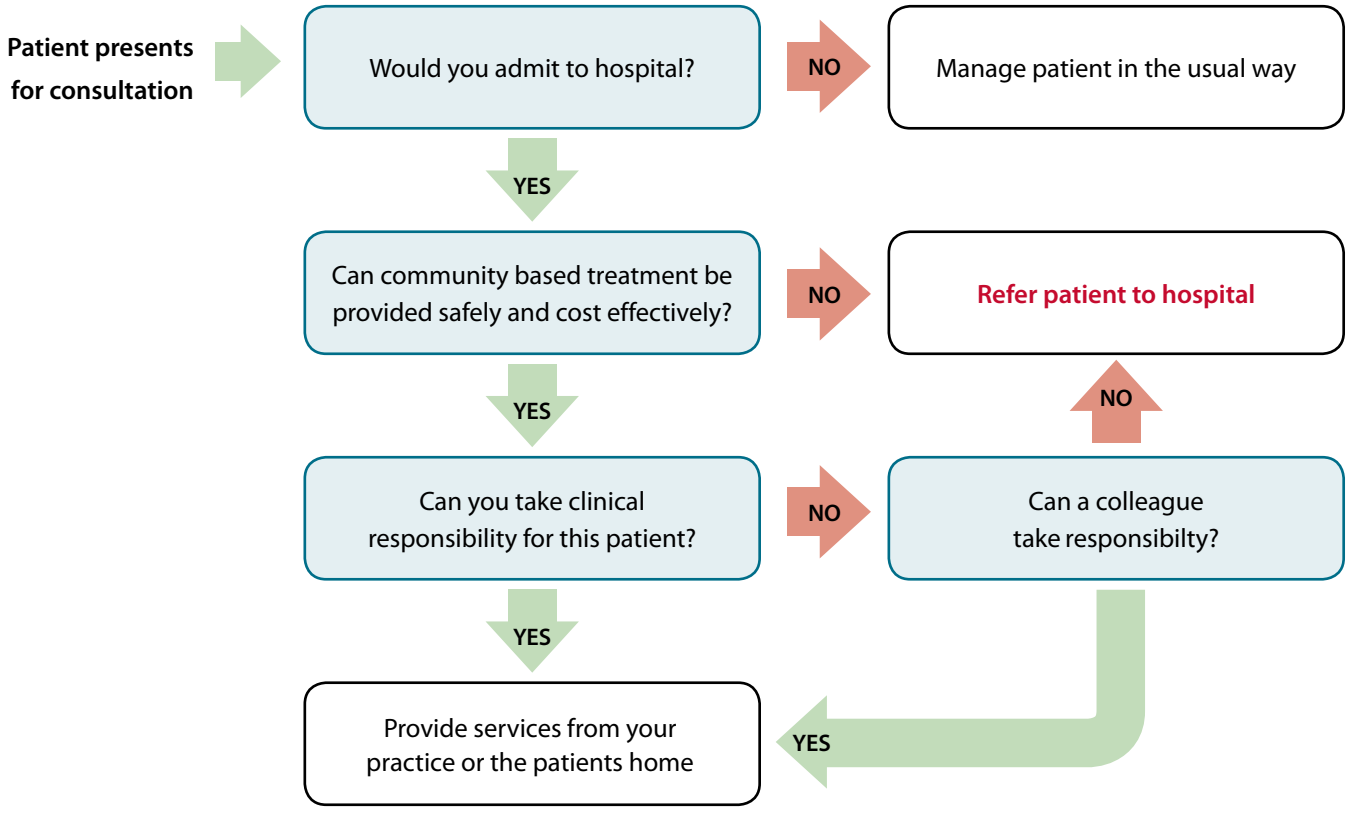

Figure 1: Referral process algorithm – adapted from POAC information manual[11]

Kingdom based study found that one-third of patients presenting to hospital with cellulitis could have been treated at home.[2] An analysis of the POAC service in the Auckland region, found that the average cost of treating a patient with cellulitis in the community was $246.36, compared to nearly $3000 for a hospital admission, which lasted on average 4.4 days.[10]

The first-line treatment for cellulitis is oral antibiotics.[12] Patients presenting with severe cellulitis, or those that do not respond to oral antibiotics, can be considered for community based IV antibiotic treatment. Recommended medicines for community based IV treatment of cellulitis may differ from those used in a hospital setting. For example, POAC recommends treatment with cephazolin (2 g daily) plus oral probenecid (500 mg twice daily),[13] as this is more practical than six hourly administration of flucloxacillin.

N.B. POAC supplies its practices with a "cellulitis kit". Cephazolin is not funded on the Pharmaceutical Schedule for this indication.

Admission to hospital is recommended for patients with cellulitis who present with:

- Haemodynamic instability – tachycardia, relative hypotension, severe dehydration or compromised circulation
- Severe pain or swelling
- Unstable risk factors such as heart failure or diabetes
- Severe or worsening symptoms following an animal or human bite
- Periorbital or facial cellulitis (unless very mild)
- Veins that are difficult to cannulate due to age or previous IV drug use

Once the decision to give community based IV antibiotics is made, patients should be reviewed daily and switched to oral delivery of antibiotics as soon as it is clinically reasonable (usually within 48 hours). The patient should be admitted to hospital if any of the following are observed:

- No improvement in condition after 24 hours
- Worsening infection and skin necrosis
- Worsening fever and/or pain
- Rising white blood cell count
- Diarrhoea suggestive of *Clostridium difficile*

Dehydration management

Vomiting and diarrhoea are the most common causes of dehydration, due to excessive fluid loss or reduced fluid intake. Patients, who present with moderate to severe signs and symptoms of dehydration, may be suitable for community-based IV treatment, depending on clinical assessment and individual patient factors.

Mild – The patient may have no symptoms other than a mild thirst and concentrated urine. An oral electrolyte solution can be used for rehydration. In most cases patients will be able to safely manage oral rehydration in their own home. Depending on the circumstance, it may be advisable to discuss the situation with the patient's family, as dehydration can be an indication that a patient is having difficulty coping at home.

Moderate – The patient will have a significant thirst, low urine production, sunken eyes, dry mucous membranes and may be weak, light-headed and experiencing postural hypotension. Depending on the circumstances, consider testing glucose and electrolyte levels or taking urine or faecal samples. Rehydration with a specialised oral electrolyte solution is recommended (e.g. pedialyte or enerlyte).[14] The high osmolality and low sodium content of fruit juices and carbonated drinks may increase gastrointestinal fluid loss.

Alternatively, IV fluid (normal saline – 0.9% NaCl) can be administered. An adult may be given 1000 mL of fluid initially, and then reviewed. Another 500 – 1000 mL can be given every two to four hours as required. However, no more than 2 L should be given. The patient should be encouraged to take oral fluids and their status reviewed

daily. Patients requiring more than 2 L of IV saline, due to ongoing losses, should be considered too unstable for treatment in a community setting.[13]

Severe – This is a serious condition in which patients will often display significant thirst, tachycardia, low pulse volume, cool extremities, reduced skin turgor, significant hypotension and confusion. Immediate referral to hospital is recommended.

N.B. Patients, who are experiencing vomiting, may benefit from the administration of an antiemetic such as metoclopramide at the same time as hydration treatment.[14] Metoclopramide is generally not recommended for use in children and adolescents.

Refer the following patients to secondary care:

Patients requiring IV fluids for dehydration who meet any of the following criteria should be referred to hospital:[13]

- Children
- People with diabetes
- Renal failure
- Heart failure
- Septicaemia
- Undiagnosed abdominal pain
- Intracranial symptoms

Caution is also advised for elderly people or people with; pre-existing heart failure, difficulty managing at home, prolonged symptoms, an evolving illness or recently returned from overseas.

Other situations where community-based IV infusion might be considered include:

- Antibiotic treatment of pyelonephritis
- Antibiotic treatment of respiratory infections
- Chemotherapy in rural settings

Infection control

IV treatment procedures can sometimes result in serious infections. It is important that standard infection control procedures are followed at each stage of the process.

Hand washing

Hands should be washed with soap and water immediately before and after patient contact. Paper hand towels, and not hot air dryers, should be used to dry hands. Wrist and hand jewellery should be removed and any cuts or abrasions covered with a waterproof dressing. Finger nails should be short and clean.

Personal protective equipment

Powder-free gloves should be worn when performing infusion procedures and disposed of in medical waste bags.

Reconstitution

Whenever possible, infusions in a ready-to-use form should be purchased. Health professionals performing reconstitution need to be aware of the compatibility and stability of solutions and record all calculations and ensure all containers are well labelled. Aseptic technique should be followed, including disinfecting the tops of all vials, ampoules and bags with a chlorhexidine and alcohol based solution. Manufactures guidelines should be followed at all times and careful attention paid to the expiration date of any products used.

Notes on injectable drugs (6th edition), published by the New Zealand Hospital Pharmacists' Association, provides reconstitution instructions for all commonly used medicines in New Zealand. This resource can be ordered in hard copy or electronic form, from: www.nzhpa.org.nz/media/3240/noidsflyer6.pdf

Community pharmacists can also assist with information on reconstitution of medicines.

Sterilising reusable equipment

Protocols for cleaning and sterilising should be developed for each practice. All equipment, dressings and solutions that come into contact with the patient must be sterile. Equipment such as drip stands need to be cleaned regularly. Medicines and solutions should be stored and used according to the manufacturer's instructions.

Site selection and placement of the cannula for IV treatment

Before insertion, it is important to confirm the vein will accommodate the gauge and length of the cannula required. When selecting a cannula, the smallest gauge and shortest length practical should be chosen. The insertion site should be decontaminated with an antimicrobial solution (such as 2% chlorhexidine and alcohol solution) applied with a sterile applicator and then allowed to dry.[15]

In most cases in a primary care setting, the cannula will be removed after each treatment and the patient will be re-cannulated the next day. However exceptions to this may include patients for whom cannulation was difficult and patients who are "needle phobic".

Considerations for site selection and placement of the cannula are detailed in Table 1.

Stablising cannulae left in place

In cases where the cannula is left *in situ*, it is important that any efforts to stabilise it do not restrict access to it, or impede its function. Sterile dressings should be applied to the area following insertion. Dressings must be inspected at regular intervals and changed if they are lifting or blood stained. The insertion site should be clinically inspected daily for; tenderness, fever without an obvious source, symptoms of local or systemic infection or the presence of discharge from the cannula insertion site.[15] The condition of the insertion site and the integrity of the device should be briefly documented in the patient notes at each inspection.

Maintenance

Daily flushing of the device with 3 – 5 mL of 0.9% NaCl ensures that it does not become blocked. Further flushing should occur between the introduction of medicines which do not mix. If any resistance is felt then the cannula should be removed and reinserted elsewhere. Cannulae should not be left in place for longer than 96 hours.[15, 16]

Removal

If the cannula is being removed due to infection, the tip should be sent for microbiological testing and blood cultures taken. The tip of the needle should also be examined to ensure it is intact. Any faulty devices should be reported to the manufacturer.

Table 1: Considerations for site selection and placement of the cannula

Do consider a patient's[19]	Take care[19]	If possible[19]
▪ Age ▪ Condition ▪ Diagnosis ▪ Vascular function ▪ Infusion history ▪ Treatment frequency, duration and type	▪ Not to use veins in the lower limbs of adults – due to the risk of embolism and thrombophlebitis ▪ Not to cannulate the feet of people who have diabetes ▪ To avoid areas of flexion if possible	▪ Select distal portions of upper limbs ▪ Subsequent insertions should occur in a distal fashion ▪ Remove hair with clippers or scissors as razors can cause micro-abrasions which may become infected

The Royal College of Nursing has published standards for infusion therapy, available from: www.rcn.org.uk (key words: infusion therapy).

Training

IV administration can be associated with a number of adverse events. It is important that clinicians who perform this technique have adequate training and are familiar and competent with the:

- Anatomy and physiology of the circulatory system
- Reconstitution and mixing of IV medicines
- Various access devices that are available
- Potential problems of vein selection caused by age, inflammation, thrombosis, disease and infection
- Practice of risk management to reduce needle stick injuries and blood spills
- Monitoring and care of the infusion site
- Practice of infection control
- Recognition and management of anaphylaxis

Further information relating to training for IV skills can be found on the intravenous nursing website, available from: www.ivnnz.co.nz

Oesteoporosis and Paget's disease

Since September 2010, the bisphosphonate zoledronic acid (Aclasta) has been funded under Special Authority for the treatment of oesteoporosis and Paget's disease. The medicine may be prescribed and administered in a General Practice.

Zoledronic acid is given once a year, as a slow IV infusion delivered over a period greater than 15 minutes. Patients must sit, or stand, upright for 30 minutes after taking bisphosphonates orally, therefore zoledronic acid is a useful alternative for people unable, or unwillingly, to do this. IV infusion can be delivered by a trained Practice Nurse in any clinic with space available for 30 minutes. IV infusion can also be considered for people likely to be non-compliant with oral treatment or people who are intolerant to oral bisphosphonates due to gastrointestinal problems.

As there have been reports of renal impairment associated with zoledronic acid, it is important that it is not given to patients with a creatinine clearance below 35 mL/min. Patients should also be sufficiently hydrated before, and after the infusion, particularly if they are taking diuretics, or any other medicines that impact on renal function.[17]

Zoledronic acid is contraindicated in patients with hypocalcaemia and it is recommended that serum calcium levels be assessed if the patient has; vitamin D deficiency, recently undergone thyroid or parathyroid surgery or has calcium malabsorption.[18] Patients with Paget's disease of the bone need adequate calcium and vitamin D and may benefit from calcium supplementation for two weeks following infusion.

In the first few days following treatment, some patients may complain of flu-like symptoms. These symptoms usually resolve within a day or two and may be alleviated by taking paracetamol with 500 mL of water following the infusion. This has the added benefit of promoting hydration.

For further information see: "Zoledronic acid funded with Special Authority from September 1 2010", BPJ 30 (Aug, 2010).

Will this work in your practice?

The implementation of a programme for IV administration of medicines in a general practice can present some challenges. Issues to consider include; training, equipment supply, timely access to medicines, funding for services and patient selection criteria. Support services can provide guidance and practical answers to these problems. In some cases, practices may create their own solutions such as; requesting local community pharmacies stock antibiotics or cellulitis kits, collaborating and/or diversifying to provide coverage over larger areas, or collective purchasing of equipment to be shared between practices as required.

Initiatives for primary care IV administration will vary depending on local DHB protocols. Therefore, it is not possible to outline a "one size fits all" mechanism for their operation or to detail how cost recovery will work. However, through prior consideration of the concept, primary care is better placed to influence its implementation.

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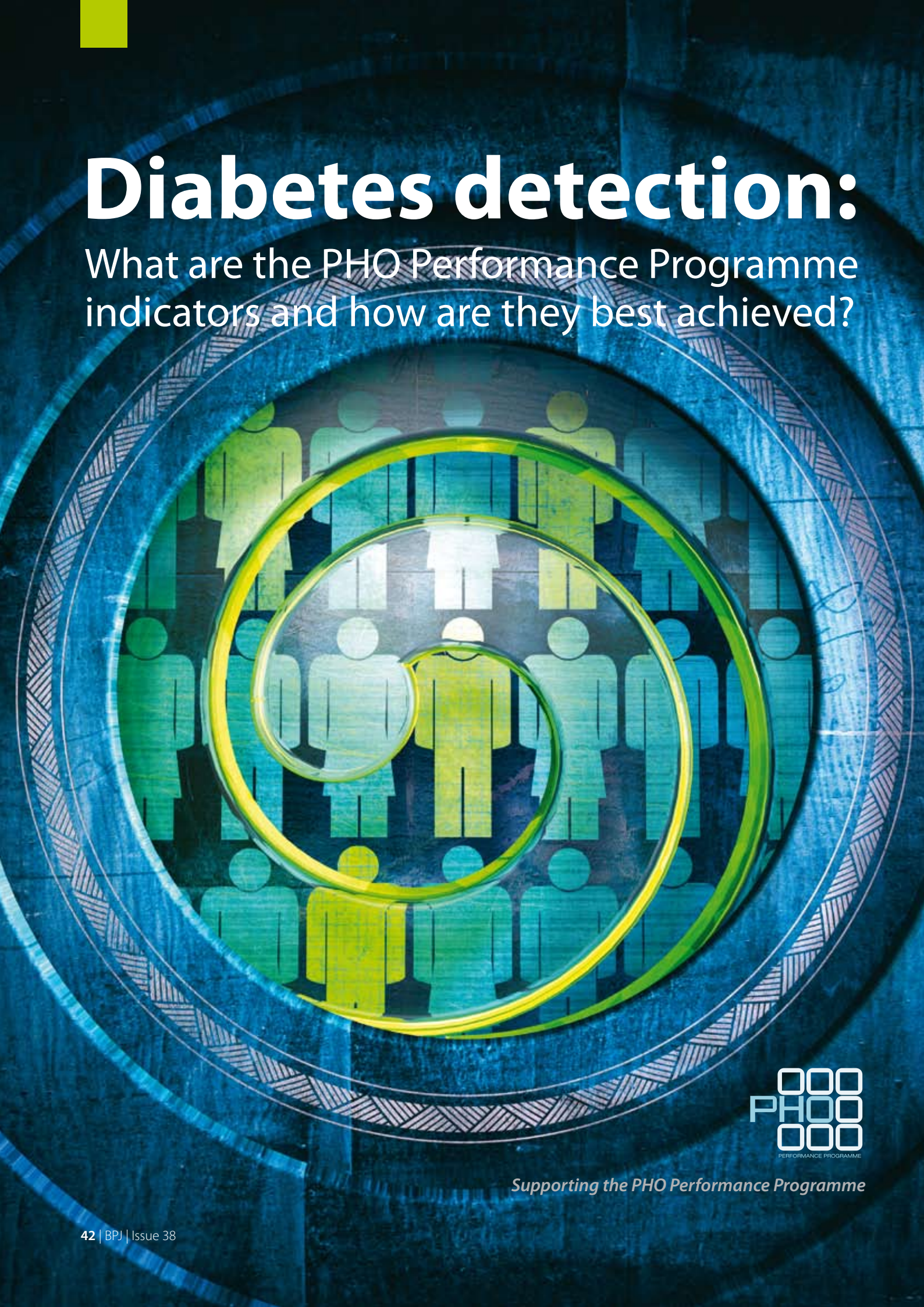
Diabetes detection:

What are the PHO Performance Programme indicators and how are they best achieved?



Supporting the PHO Performance Programme

What is the PHO Performance Programme?

The purpose of the PHO Performance Programme is to improve equality and health outcomes for everyone accessing primary healthcare in New Zealand. Performance based payments are made to PHOs to improve key indicators, which are reviewed annually.[1] Not all indicators attract funding, however, as some are provided for information only. Those indicators that are currently funded are shown in Table 1. Performances are measured against ideal practice, adjusted to take into account factors such as ethnicity and age that may differ between regions. In order to be eligible to enter the programme a PHO must meet and then continue to fulfil the following prerequisites:[1]

- Minimum 85% ethnicity recording
- Minimum 70% valid NHI numbers on patient registers
- Compliance with the fees agreement
- Signed PHO agreement
- Complete practitioner information
- Complete PHO reporting
- Approved PHO performance plan

See "BPJ 36 (Jun, 2011) and BPJ 37 (Aug, 2011) for previous articles in this series.

PHO performance indicator for diabetes detection

Diabetes detection indicator definition

The PHO performance indicator and target for diabetes detection is: **For 90% of enrolled patients with diabetes, to have been identified and coded within their patient notes.**

The purpose of the diabetes detection indicator is to determine what proportion of a PHO's population estimated to have diabetes has been diagnosed. The number of patients coded with diabetes is divided by the estimated prevalence of diabetes (the denominator) within that PHO.

The estimated prevalence of diabetes within any PHO is derived from a national calculation of diabetes prevalence, which is then adjusted to take into account individual PHO differences in age, gender and ethnicity. The national prevalence data estimate is the number of people within New Zealand who have had diabetes related health service contact, divided by the number of people in New Zealand, either enrolled with a PHO or having had contact with the New Zealand health service, from 1 July 2009 to 30 June 2010.[1]

Table 1: Funded PHO Performance Indicators for the period commencing 1 January, 2011

Chronic conditions	Cervical cancer screening Breast cancer screening Ischaemic cardiovascular disease detection Cardiovascular disease risk assessment **Diabetes detection** Diabetes follow-up after detection Smoking status
Infectious disease	Influenza vaccine in people aged over 65 years Age appropriate vaccinations for children aged two years
Financial	GP referred laboratory expenditure GP referred pharmaceutical expenditure

This may mean that in some cases, individual practices with excellent detection methods, may not appear to be meeting the target if the actual prevalence of diabetes in their patient population is significantly less than that estimated for their PHO. Conversely, some practices may have estimated detection rates of over 100%.

Diabetes detection comprises 9% of a PHO's performance payment (3% for achieving the target in the total population and 6% for achieving the target in the high needs* population).

Conditions defined as diabetes

For the purpose of the PHO Performance Programme indicator, the term "diabetes" includes:

- Type 1 diabetes
- Type 2 diabetes
- Diabetes that could be either type 1 or type 2, but is clinically indeterminate

N.B. Gestational diabetes is excluded.

How should a diagnosis of diabetes be recorded?

To allow retrieval of information, electronic Read codes should be entered into the Patient Management System (PMS).

Consultations coded with a "diabetes mellitus" root Read code of C10. count towards achieving the PHO Performance Programme target. The Read codes which are most commonly used, in practice, are outlined in Table 2.

N.B. Read codes C10A. (malnutrition-related diabetes) and C10B. (steroid-induced diabetes) are not eligible for counting towards the target.

* High needs is defined as Maori and Pacific peoples and people living in New Zealand Deprivation Decile 9 or 10 socioeconomic areas (most deprived)

Table 2: Commonly used Read codes for diabetes for the PHO Performance Programme[2]

Description	Root Read Codew
Type I Diabetes mellitus	C108.
Type II Diabetes mellitus insulin dependent	C1089
Type II Diabetes Mellitus non-insulin dependent	C109.

For a list of all Read codes that are identified for the PHO Performance Programme see "Code Mappings for data transfer specification and clinical performance indicator data format standard document." Available from: www.dhbnz.org.nz/Site/SIG/pho/Technical-Documents.aspx

Who should be tested for diabetes?

Testing to detect pre-diabetes, or type 2 diabetes, should be considered in:

- People with symptoms of diabetes
- People at high risk of diabetes (see below)
- People having a cardiovascular risk assessment

Factors associated with an increased risk of diabetes include:

- Maori, Pacific, Asian or Indian ethnicity
- Age over 40 years
- Family history of type 2 diabetes (parent or sibling)
- Increased BMI and/or central obesity
- Impaired glucose tolerance or impaired fasting glycaemia
- Adverse lipid profile (especially low HDL and high triglycerides)
- High blood pressure
- History of gestational diabetes or have given birth to an infant weighing over 4 kg
- Polycystic ovary syndrome
- Taking medicines such as steroids or some antipsychotics

Fasting plasma glucose is the recommended initial test for detecting diabetes. Opportunistic (non-fasting) measurement of HbA_{1c} is appropriate if compliance with a fasting test is a barrier (Table 3).[3]

Table 3: Detecting diabetes[3]

Fasting plasma glucose result	Action
≥ 7.0 mmol/L	Repeat fasting plasma glucose, two results at this level constitute a diagnosis of diabetes
6.1 – 6.9 mmol/L	Request an oral glucose tolerance test (OGTT), indicates impaired fasting glucose
5.5 – 6.0 mmol/L	Request an OGTT if at high risk of diabetes
≤ 5.4 mmol/L	Retest in five years or earlier if risk factors, normal result

HbA_{1c} result	Action
≥ 6% (42 mmol/mol)	Measure fasting plasma glucose

See "Detecting diabetes", bpac^{nz} (Jul, 2008) for further information about testing.

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Medicine safety: a report from the Health Quality & Safety Commission

SEVENTEEN SERIOUS MEDICINE ERRORS were reported in our hospitals during 2009/10, and this is likely to only be the tip of the iceberg.

Dr Janice Wilson, Health Quality & Safety Commission's Chief Executive, says medicine errors are an ongoing and potentially serious cause of patient harm, and improving medicine safety is one of the Commission's top priorities in 2011/12.

"We know that the medicine errors are not just happening in hospitals – they are also occurring in primary care settings, although we know relatively little about these errors."

Most medicines are prescribed, dispensed and used in primary care settings. For example, in the United Kingdom, one-fifth of the annual prescriptions for medicines (0.5 million) are written in hospitals and four-fifths are written in the community (two million).

Medicine errors feature prominently in reports of iatrogenic harm, from various countries.[1] In Australia, for example, medicine errors in primary care settings have been shown to be a leading cause of hospital admissions, particularly in the elderly population.[2]

Several studies have estimated the rates of errors on prescriptions. Estimates range from between less than 1% to 11% of all prescriptions, depending on the definitions used.[3]

Error rates seem to be lower for dispensing medicines than for prescribing, administering or monitoring medicines. For example, one study found an average of 26 dispensing incidents for every 10,000 items dispensed in community pharmacies (an error rate of 0.1%). Of these incidents, 22 were classified as near misses, where the error was discovered before the medicine was given to the patient, and four were classified as dispensing errors, where the wrong medicine was given to the patient.[4]

New Zealand studies have indicated that each transition point in care can generate errors of about 25%, e.g. on admission to, or discharge from, hospital.[5] Not all errors result in adverse events, and some will be picked up before medicines are dispensed or administered. Adverse medicine events in hospital settings add an average of 7.5 days to a patient's stay in hospital and impose additional financial costs on the health system.

Dr Wilson says the Health Quality & Safety Commission will lead and coordinate the health sector's implementation of the Medication Safety programme. This programme aims to reduce harm from medicine errors and improve medicine management systems in hospitals, general practice, pharmacy, residential aged care facilities and the wider health and disability sector.

In 2011/12 the Commission will focus on:

- Completing the roll-out of a national adult medication chart

- Completing the roll-out of a medicine reconciliation process for the times when care settings change (e.g. between primary care and hospitals)
- Working with the National Health IT Board to accelerate the e-medication programme, which will make information about patient medicines available electronically to all health professionals working with that patient
- Reporting on adverse drug events.

Dr Wilson says the national medication chart and the medicine reconciliation process being rolled out by District Health Boards have the potential to greatly reduce medicine errors.

"The national medication chart is a relatively simple but effective way to reduce medicine errors and is expected to be in place in most public hospitals by January 2012," she says.

Dr Wilson says that once use of the national medication chart is widespread within DHB hospitals, the Commission will review the chart features needed for paediatric and long stay (hospital) patients and then turn its attention to primary care, with a focus on aged care.

Likewise, the use of a formal medicine reconciliation process will make sure that patient medicines are checked at critical handover points, also helping to reducing errors.

"The Commission is focusing on medicine errors in hospitals at the moment but is also looking to expand that work to include medicines reconciliation at discharge," Dr Wilson says.

"The aim is to provide better and more accurate discharge information about patient's medication to primary care. We want to work across the health sector, including primary care, to make improvements in this area."

Work is on-going, in conjunction with the electronic medicine reconciliation pilots, to format the electronic discharge summary to include medicines on admission, medicines on discharge and the reason for any change.

An electronic prescribing service is also being trialled in the community, with the aim of improving patient safety by making prescriptions more accurate; by reducing manual data entry and therefore transcription errors; and by the ability to send status updates to the prescriber if requested, e.g. to notify a doctor that a prescription has been collected.

"The New Zealand Prescription Service enables General Practitioner prescriptions and hospital discharge prescriptions to be sent to community pharmacists electronically," Dr Wilson says.

"A key project is the New Zealand Prescription Service trial, which is the first phase of a national roll out. The trial will

run for about 12 months and will involve multiple phases, vendors and geographic locations."

The Commission welcomes bpac^{nz}'s establishment of an incident-reporting database for primary care. In addition, the New Zealand Pharmacovigilance Centre is in the pilot phase of trialling a medication incident reporting system targeting primary care and linked to the Centre for Adverse Reactions Monitoring (CARM).

Dr Wilson says New Zealand has an excellent health system by international standards and most people are treated safely and effectively. A small number, however, experience preventable events either in hospitals or in primary care settings.

"The challenge for us all is to improve our systems and processes so that fewer errors occur, and to learn from the mistakes that do happen. It's about improving the way we do things so that people experience safe, good quality health care whether it's at their General Practice, the local pharmacy, in a rest home, or at hospital."

www.hqsc.govt.nz

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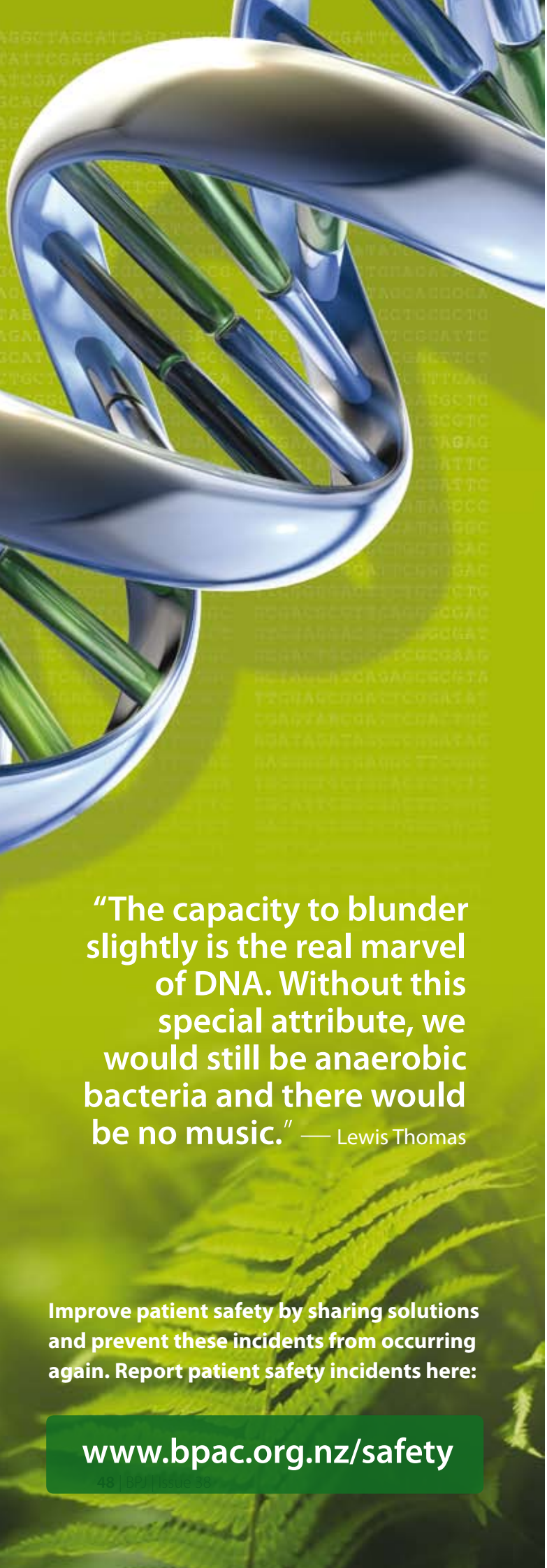

New maternity referral guidelines released

In July 2011, the Ministry of Health updated its Referral Guidelines for Lead Maternity Carers (LMC). This updates and replaces the referral process as outlined in "The role of General Practice in the care of pregnant women", BPJ 35 (Apr, 2011). These guidelines have been designed to enhance communication, collaboration and documentation between all providers of clinical care for a pregnant woman.

For the full article, please visit www.bpac.org.nz keywords: maternity referral

Simvastatin: risk associated with high doses

The United States Food and Drug Administration (FDA) has issued a recommendation that the use of high-dose simvastatin (80 mg) is restricted, due to increased risk of myopathy. The recommendation states that simvastatin 80 mg should only be prescribed if a patient has previously been taking the medicine for longer than 12 months with no signs of myopathy. Furthermore, prescriptions for 80 mg simvastatin should not be issued to new patients and those already taking simvastatin should not have their dose increased to 80 mg per day.[1]

The FDA advice comes following the analysis of the SEARCH trial, which found that patients taking 80 mg per day of simvastatin had an increased risk of myopathy compared to patients taking lower doses of the same medicine, or other medicines of the same class.[1, 2] The study, which included over 12 000 people, found that 52 patients in the 80 mg group, and one in the 20 mg group, developed myopathy. Approximately 60% of reported cases of myopathy were due to a genetic variation affecting the uptake of simvastatin into the liver, resulting in increased plasma levels of simvastatin which in turn increases the risk of myopathy.[1] Most cases were likely to occur in the first year of treatment. Increased age and female gender were also found to increase the risk of myopathy.[1]

Symptoms of myopathy, which in severe cases can develop into rhabdomyolysis, include; muscle pain and tenderness, weakness and dark or red urine. Confirmation of diagnosis can be achieved by testing for elevated serum creatine kinase levels.[3]

Medsafe response

Medsafe is currently in the process of updating the data sheets for all medicines available in New Zealand that contain simvastatin.

For example, the changes to the Lipex data sheet include:

- In the **Dosing and Administration** section: The 80 mg dose of LIPEX should be used only for those patients who have not achieved their LDL-C goal utilising the 40 mg dose.
- The following **Contraindications** have been added:
  - Myopathy secondary to other lipid lowering agents
  - Concomitant administration of potent CYP3A4 inhibitors, e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone)
  - Concomitant administration of gemfibrozil, cyclosporin or danazol
- The inclusion of additional information in the **Warnings and Precautions** section, including: The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C lowering efficacy. Therefore the 80 mg dose of LIPEX should only be used in patients at high risk for cardiovascular

complications who have not achieve their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking LIPEX 80 mg for whom an interacting agent is needed, a lower dose of LIPEX or an alternative statin regimen with less potential for drug-drug interactions should be used.

- The addition of information (including dose caps) in the drug interactions section of the **Warnings and Precautions** section
- Additional information in the **Interactions** section

A Prescriber Update will also be released shortly advising of restrictions to the 80 mg dose of simvastatin in New Zealand.

Use of high dose simvastatin

In New Zealand, simvastatin, combined with diet and exercise, remains the first-line cholesterol lowering treatment for patients with an estimated five year CVD risk of 15–20%. The usual dose is simvastatin 20–40 mg per day, which may be increased to 80 mg in patients who require intensive treatment. It is important to remember that the statin dose response is not linear, i.e. the 80 mg dose reduces LDL cholesterol by an additional 6% over the 40 mg dose.

In patients taking 80 mg simvastatin, consider switching to atorvastatin 40 mg daily, which is an equivalent dose. In addition, consider that the benefits of statin treatment for elderly people are less clear than in younger populations,[4] therefore older patients may benefit more from a reduction in dose.

For further information about prescribing statins see: "An update on statins", BPJ 30 (Aug, 2010).

To view previous Medsafe guidance on statin-induced myopathy see: "Statin interactions: reports of serious myopathy" Prescriber Update 2011;32(2), available from: www.medsafe.govt.nz.

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Use of vitamin D during pregnancy

Dear Editor,

In "Vitamin D supplementation: navigating the debate" (BPJ 36, June 2011) you mention the Australian and New Zealand College of Obstetricians guidelines recommending vitamin D supplementation for pregnant women considered to be at risk of deficiency. This advice is alluded to again in "Routine laboratory testing during pregnancy" (Best Tests, July 2011).

I have recently seen a patient who was prescribed vitamin D in pregnancy but the patient leaflet she was given with the prescription advised against the taking of cholecalciferol in pregnancy and the datasheet (dated 26/8/10) includes the following advice:

> *"**Use in Pregnancy**: Problems in humans have not been documented with intake of normal daily requirements. Maternal hypercalcaemia during pregnancy in humans may be associated with increased sensitivity to effects of vitamin D, suppression of parathyroid function, or a syndrome of peculiar (elfin) facies, mental retardation and congenital aortic stenosis in infants.*
>
> *Overdosage of vitamin D has been associated with foetal abnormalities in animals. Animal studies have shown calcitriol to be teratogenic when given in doses 4 and 15 times the dose recommended for human use. Excessive doses of dihydrotachysterol are also teratogenic in animals. Animal studies have also shown calcifediol to be teratogenic when given in doses of 6 to 12 times the human dose.*
>
> *FDA Pregnancy Category C"*

I would be grateful to know how we should be advising patients regarding the safety of vitamin D supplements in pregnancy given the contradictory nature of the advice given in the Guidelines and the medicine information sheets. Also is the FDA category C equivalent to the Australian category C?

***Dr Phil White, General Practitioner,** Dunedin*

The Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommends that women with known vitamin D deficiency or who are at risk of deficiency (e.g. dark skinned, women who are veiled), should receive vitamin D supplementation during pregnancy.[1, 2] The recommended treatment is with cholecalciferol. Calcitriol is not routinely used during pregnancy and would only be considered in the case of hypocalcaemia or chronic renal failure.[2] Calcium supplementation is recommended in women whose dietary intake is inadequate.

Cholecalciferol is considered safe to use during pregnancy when used at therapeutic levels.[3] The United States Food and Drug Administration (FDA) pregnancy Category C is different from the Australian Drug Evaluation Committee pregnancy Category C. The FDA Category C is: "Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks."

There appears to be a lack of consensus as to the exact dose and regimen of cholecalciferol recommended for pregnant women. A normal regimen for an adult with vitamin D deficiency would be a loading dose of 2 x 1.25 mg cholecalciferol followed by 1 x 1.25 mg cholecalciferol

per month. Ideally women, at risk of vitamin D deficiency, should be treated pre-conceptually with this dose.

National Health and Medical Research Council guidelines for nutrient reference values for Australia and New Zealand recommend that a daily amount of 80 µg (3200 I.U) cholecalciferol should not be exceeded during pregnancy. The guidelines recommend a supplement of 10 µg (400 I.U) cholecalciferol per day for pregnant women at risk of vitamin D deficiency.[4] Guidance from the Royal College of Obstetricians and Gynaecologists (United Kingdom) and the National Institute for Health and Clinical Excellence (United Kingdom), is in accord with this recommendation.[5, 6]

However, a recent study found that higher doses of cholecalciferol (100 µg / 4000 I.U) given daily are safe during pregnancy (i.e. no evidence of hypercalcaemia and hypercalcuria), and resulted in higher vitamin D status in women and neonates than the currently recommended 10 µg per day.[7]

Some practitioners are recommending that the usual adult dose of cholecalciferol (a loading dose of 2 x 1.25 mg cholecalciferol followed by 1 x 1.25 mg cholecalciferol per month) is used for pregnant women with vitamin D deficiency. However, there is no evidence of the safety of this dose in pregnancy.

Although guidelines may change in the future, at this time it would be reasonable to recommend that pregnant women at risk of vitamin D deficiency obtain their vitamin D requirements through a daily pre-natal multivitamin supplement that contains approximately 10 µg (400 I.U) cholecalciferol. Pregnant women are often already taking a multivitamin in order to meet requirements for folic acid and iodine, therefore this recommendation avoids the addition of an extra medicine.

There are currently no subsidised pre-natal multivitamins available, therefore this may be a barrier for some women. Pregnant women, especially those at risk of deficiency, are recommended to eat foods rich in vitamin D and to receive adequate sunlight.

Elevit with Iodine contains 12.5 µg (500 IU) cholecalciferol per tablet. Several other pre-natal vitamins contain cholecalciferol, but at lower than recommended doses.

ACKNOWLEDGEMENT: Thank you to **Dr Helen Patterson**, Consultant in Obstetrics and Gynaecology, Senior Lecturer, Dunedin School of Medicine and **Dr Lisa Houghton**, Lecturer, Department of Human Nutrition, University of Otago for expert guidance in formulating the answer to this question.

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Vitamin D in patients with impaired renal function

Dear Editor,
I enjoyed reading "Vitamin D supplementation: navigating the debate" (BPJ 36, June 2011), however, I am hoping that you might further clarify when I might prescribe calcitriol for my patients.

In the article it refers to calcitriol being used for patients with chronic kidney disease, however, most of my elderly patients with some degree of chronic kidney disease are currently being prescribed cholecalciferol. Do I need to switch them over to calcitriol? At what level of renal impairment should I do so?

***General Practitioner**, Dunedin*

In "Vitamin D supplementation: navigating the debate" (BPJ 36, June 2011), it was stated that:

> "Patients with severe renal impairment, who require vitamin D supplementation, should be prescribed hydroxylated derivatives of vitamin D such as alfacalcidol and calcitriol. Doses of these medicines vary from patient to patient and require careful monitoring of serum calcium levels to prevent hypercalcaemia. These patients are most likely to be treated in secondary care".

Cholecalciferol is the form of vitamin D, most frequently recommended for people who require supplementation. However, cholecalciferol is not recommended in people with severe renal impairment as they are unable to convert it to its active metabolite – calcitriol. For this reason, some people with severe renal impairment who require vitamin D supplementation, are recommended to use calcitriol as it does not require metabolism by the kidneys.[1, 2]

Calcitriol should not be used routinely in patients with chronic kidney disease. Calcitriol is most appropriate for patients with confirmed metabolic disturbances resulting from chronic renal failure including patients under-going dialysis (or pre-dialysis), in renal osteodystrophy and secondary hyperparathyroidism.[2, 3, 4]

If considering use of calcitriol, it is recommended to first consult with a renal physician and the patient should have appropriate assessment of their parathyroid hormone, calcium, vitamin D and phosphate status.

Cholecalciferol may be used in people with mild to moderate renal impairment, but it is recommended to monitor their plasma calcium levels more frequently.[2, 5]

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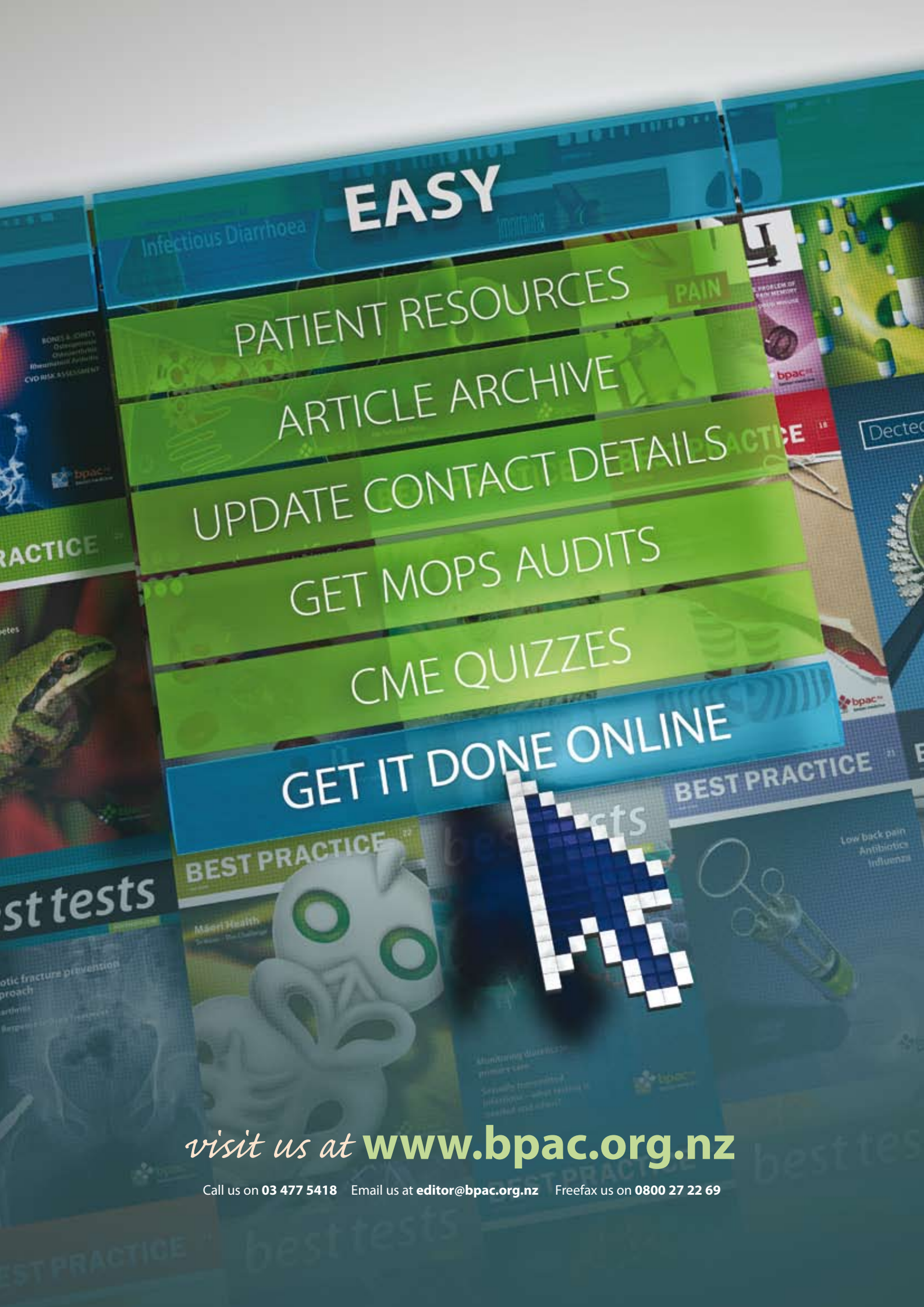
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