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EDITORIAL

Costs and concerns in cancer care

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cost of drugs, Pharmaceutical Benefits Scheme

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Some recently developed anticancer drugs appear to be a major advance. In metastatic malignant melanoma a number of new immune checkpoint inhibitors have created excitement and hope in a disease for which there was previously no effective treatment.[1] One magazine hailed them as 'the most revolutionary cancer treatment in decades'.[2] These targeted drugs are likely to have a major impact on the treatment outcomes for other advanced incurable cancers too, but they are very expensive.

In practice, many of the earlier targeted cancer drugs have turned out to be disappointing. They are only suitable for a limited number of patients, and only add, on average, a few months of survival.[3]

The clinical trials of new anticancer drugs use highly selected patients and the reported outcomes do not relate to the general community that we treat daily.[4] For the benefits these drugs deliver, the costs seem excessive.[5,6] How are we to determine which new drugs are cost-effective and how do we pay for the ones that are?

Among patients with incurable metastatic melanoma 40–60% have BRAF V600 mutations and can be treated indefinitely with oral dabrafenib plus trametinib. The cost to the Pharmaceutical Benefits Scheme (PBS) is $8759 per drug per month ($17 518 per month total). Patients can then be started on an immune checkpoint inhibitor, such as pembrolizumab indefinitely at 2 mg/kg every three weeks, at a cost to the PBS of $8000 or more every three weeks, or $136 000 per year. These treatments may continue for years. Then patients can be given the cytotoxic immune modulator ipilimumab for a cost of $130 000 per course of four injections, which can be repeated if appropriate. These drugs can cost more than $500 000 per patient. None of these treatments are curative and on average they only prolong progression-free survival or overall survival by months, although some patients who would otherwise have died can have enduring benefit for years. There is no predictive biomarker for benefit from pembrolizumab or ipilimumab.

Looking at cancer therapies approved by the US Food and Drug Administration (FDA) for solid tumours between 2002 and 2012, the prolongation in median overall survival was only 2.16 months.[7] Of the 12 anticancer drugs approved by the FDA in 2012 alone, only three prolonged survival, two of them by less than two months. Yet nine were priced at more than $US10 000 per month.[8]

In metastatic colon cancer, the vascular endothelial growth factor (VEGF) inhibitor bevacizumab is used in many protocols. In Australia it costs up to $8000 per month and can be used indefinitely, but only increases average survival by 0.9 months.

In 2015 a group of experts from the European Society for Medical Oncology said that many modern cancer drugs were of very little benefit to patients. They published a scoring system, unconnected with cost, that showed many drugs did not extend or improve people's lives for very long.[9]

To address the cost of anticancer drugs there is a role for individual patients, organisations and physicians to advocate for greater access to, and fairer prices for, effective new therapies. The doctrine of *justum pretium*, or just price, refers to the 'fair value' of commodities. In deciding the relationship between price and worth (or value), the doctrine advocates that, by moral necessity, price must reflect worth. This differs from the function of free-market economies where prices reflect 'what the market bears', or what buyers are willing to pay.

Some European countries are achieving comparable or superior outcomes with less outlay by considering best practice and assessing cost-effectiveness.[10-12] Many governments like Australia's are already using health-technology measurements for resource allocation. These often use cost-effectiveness thresholds like the National Institute for Health and Care Excellence in the UK which uses £20 000–30 000 per quality-adjusted year of life saved. Treatments exceeding this threshold are unlikely to be funded.

In the UK, setting thresholds has led to challenges from cancer groups. The subsequent publicity, threatened legal action and political pressure meant that major decisions not to fund two new targeted cancer drugs, trastuzumab and imatinib, were reversed. Consequently, the UK Government set up the Cancer Drugs Fund in 2010 and extended it to March 2016.[10,13] Despite a lifetime budget of £1.27 billion, it overspent its budget for 2014–15 alone by 35%. It was announced in 2016 that funding will continue but will be capped at £340 million annually. The Canadian province of Ontario developed the publicly funded Ontario Public Drug Programs in 1995.[14,15] However, a growing number of high profile cases of media and political pressure have also influenced drug approvals in the province.[10]

If we are going to consider similar government programs to maintain equitable access to expensive new cancer drugs in Australia, all physicians and scientists should insist on greater transparency of the data concerning these new drugs. As the immediate past Chair of the Pharmaceutical Benefits Advisory Committee Dr Suzanne Hill says, it no longer seems appropriate for all the data supporting government funding of these very expensive drugs to remain commercial-in-confidence. She also says it is not appropriate to not collect publicly accessible de-identified data on outcomes for all patients who receive these drugs.[16]

Finally, we will need public debate about such targeted funding, about reducing unnecessary health expenditure elsewhere and about possibly increasing taxation. <

Conflict of interest: none declared

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LETTERS

Letters to the Editor

Prescribing and borderline personality disorder

Aust Prescr 2016;39:148
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In a challenging therapeutic area, where evidence to guide practice is scarce, Andrew Chanen and Katherine Thompson provide an insightful, pragmatic review on prescribing for patients with borderline personality disorder.[1]

The authors' reference to the high rate of comorbid conditions complicating accurate diagnosis and potentially overwhelming the clinical picture was of particular interest to us. Our interdisciplinary team of care coordinators assists complex patients to navigate the healthcare system, promoting self-management and facilitating communication between healthcare providers. These patients are typically high users of hospital or emergency services and at the higher end of functional decline with multiple comorbidities. Patients with borderline personality disorder – both diagnosed and undiagnosed – are highly represented in our patient cohort.

Comorbid mood disorders, chronic pain, anxiety or substance use disorders present significant challenges for treating clinicians. Fragmented care and delayed communication regarding medication management from hospital admissions or specialist outpatient clinics only serve to magnify problems. Embedding a clinical pharmacist within our care coordination team has enhanced timely, collaborative medication management across the care continuum particularly for this patient group. Having an agreed prescribing framework between specialists (knowing who is responsible for prescribing certain drugs), a dedicated GP and dispensing community pharmacist provides reassurance and role certainty among all members of the team. The combination of care coordination with medication management is a useful adjunct in caring for patients with borderline personality disorder.

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Andrew Chanen and Katherine Thompson, the authors of the article, comment:

We thank Deirdre Criddle and Carolyne Wood for their comments. People with borderline personality disorder are highly represented among those with severe mental illness, and miscommunication and polarised opinions about management are especially common in relation to this patient group.

Comorbidity can be a misleading term in this context. Many patients report co-occurring symptoms or syndromes (such as mood or anxiety disorders) that are not truly separate diseases (that is, not true comorbidities) and which require care to be integrated with the treatment of borderline personality disorder. However, truly comorbid conditions (such as cardiovascular disease) are also more common among this patient group[1] and the interaction of borderline personality disorder with the management of these conditions often leads to poor outcomes, including premature mortality.[2]

Of the possible mechanisms that might underlie these poor outcomes, the relational difficulties that lie at the heart of borderline personality disorder are commonly enacted with health professionals. This often leads to suboptimal clinical decision making by the health professionals or poor self-care by the patients.

Interdisciplinary care coordination is a promising innovation in the care of these patients and warrants support to develop an evidence base in borderline personality disorder.

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The challenge of costly drugs

Aust Prescr 2016;39:149
http://dx.doi.org/10.18773/austprescr.2016.072

The authors of the editorial on 'The challenge of costly drugs' provided a comprehensive summary of the issues surrounding the funding of high-cost medicines entering the Australian market.[1] The proposed idea of an electronic national formulary for all Australian hospitals has merit. However, such a proposal must first address the issues of cost-shifting between the federal and state governments and the delivery of health care.

As the authors mentioned, many high-cost medicines only have a role in the hospital setting, and medicines for public hospital patients are funded by state governments. In contrast, medicines listed on the Pharmaceutical Benefits Scheme (PBS) are federally funded. With different funding sources for medicines in different settings, formulary decisions can be influenced by cost-shifting.[2]

Pharmacoeconomic evaluation of a new medicine is directly impacted by the funding source.[3] If the cost-effectiveness of a new medicine is assessed from the perspective of the state government (for consideration of inclusion on a hospital or state-wide formulary), and the comparator is a PBS-funded medicine, there is bias towards the medicine that is federally funded. If both medicines have comparable efficacy and safety and a comparable price, from the perspective of the state government the PBS-funded medicine will be more cost-effective.

The authors mentioned that 'state governments do not fund comprehensive pharmacoeconomic assessment'. Even if funding was available to conduct economic analyses, the high prices and the paucity of evidence for many high-cost medicines in the hospital setting would mean their cost-effectiveness is likely to be high and uncertain. Funding resources to investigate clinical outcomes of high-cost medicines used in public hospitals would be the first step towards clarifying some of the uncertainty with regards to efficacy, and consequently cost-effectiveness.

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Charles Denaro and Jennifer Martin, authors of the article, comment:

We thank Nadine Hillock for her letter. At the moment the Australian Government pays states for the use of high-cost medicines in outpatients and day therapy units using a myriad of complex programs. It also pays for medicines listed on the PBS for hospital discharge and outpatient prescriptions in the majority of states that have an agreement with the Commonwealth. So a national formulary for hospitals funded by the Commonwealth cannot be seen as a bridge too far. At the moment numerous state- and Commonwealth-based bureaucrats and pharmacists are consumed with ensuring each side is compliant with these needlessly complex programs. This does nothing to improve the nation's productivity and wastes precious resources. So while a national formulary will not completely solve cost-shifting, it should substantially reduce the current madness.

We wholeheartedly agree that, when there is limited evidence for the efficacy of high-cost medicines used anywhere, then robust pharmacovigilance is essential. Tying the marketing approval of high-cost medicines with pharmacovigilance programs funded by pharmaceutical companys must be considered whenever there is significant uncertainty over cost-effectiveness. Often high-cost medicines are used off label in hospitals and in this case hard clinical outcomes are not routinely captured or published. Why would we allow a hospital in one part of the country to use a high-cost medicine for a particular off-label indication, when another hospital elsewhere has previously tried it and found it not to be effective? We would advocate for government funding of a national database for high-cost medicines and off-label use.

LETTERS

Treating osteoporosis: concerns about calcium

Aust Prescr 2016;39:150
http://dx.doi.org/10.18773/austprescr.2016.073

I enjoyed reading the recent article by Akhil Gupta and Lyn March on the treatment of osteoporosis.[1] I especially appreciated the inclusion of the numbers needed to treat (NNTs) with antiresorptive drugs to prevent a fracture. Such measures of absolute benefit are helpful for shared decision-making with our patients. However, I was disappointed that the same care was not taken in the discussion of calcium supplementation. Here, the authors simply stated that 'combined calcium and vitamin D supplements seem safe and effective for most people who require them'.

I agree with the authors' concerns that the cardiovascular safety of calcium supplementation are unresolved.[2,3] In this context of possible harm, I believe we need to carefully consider the purported benefits of calcium. A systematic review found that calcium supplementation has little if any effect in reducing fracture.[4] There was an overall 11% (95% CI* 4–19%) relative risk reduction in total fracture, which became smaller and statistically insignificant when the authors restricted their analysis to trials at low risk of bias (4%, 95% CI –1 to 9%). For the typical person with osteoporosis, these figures will equate to large NNTs for fracture prevention – much larger than those for antiresorptive drugs – if indeed there is any real benefit at all. I struggle to see then how calcium supplementation can be deemed 'effective for most people' as claimed.

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* confidence interval

Lyn March and Akhil Gupta, the authors of the article, comment:

Thank you for your comments on our recent article. You make some important points about the weak effect of calcium alone for fracture prevention. We did not include calcium and vitamin D in the tables of numbers needed to treat as we did not feel they were sufficiently effective on their own or in combination, but rather as part of the whole treatment package when antiresorptives are being prescribed.

The benefits and harms of calcium supplements for osteoporosis remain controversial. We state in the article that 'it is recommended that people get this through their diet' but also suggest that 'most Australians do not reach the recommended dietary intake so daily supplements of 500–600 mg of calcium are sometimes needed'. There are insufficient data from randomised trials to offer the same level of certainty about numbers needed to harm for calcium. In the context of 'safe and effective' we were referring to it as a mode for achieving the recommended daily calcium requirement, not as it being an effective drug for reducing fractures. It would have been better if we had omitted 'and effective' as it could be misleading.

Dealing with drug-seeking behaviour

Aust Prescr 2016;39:151
http://dx.doi.org/10.18773/austprescr.2016.074

In the article dealing with drug-seeking behaviour,[1] I was surprised to see no mention of Drugs and Poisons Information System Online Remote Access (DORA). It is a Tasmanian state-wide register that allows doctors to notify concerns about a patient's medicine use and ensures all subsequent prescriptions for drugs of concern are listed. Pharmacists can also access this information. I believe that at least one other state runs a similar system.

In the first instance, checking to see if an individual is registered on DORA will allow the prescriber or dispenser to establish if there are conditions already in place. This is very useful out of hours when contacting GPs is often not possible.

Secondly, DORA allows 'no fault' registration. Once an individual is registered on the system as 'of concern', it does not affect them in any way, and prescribing and dispensing continues as normal. However, their primary doctor or local emergency department can simply keep an eye on what is happening, and have the data to move to the next stage if necessary. It can also be useful for noting past issues and adjusting prescribing accordingly, opening the way for frank discussion, and reducing the risk of unwise prescribing in those with a history of addiction.

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Jenny James, the author of the article, comments:

The author rightly draws attention to DORA and its potential benefits. Currently Tasmania is the only state to have a real-time electronic system for reporting and recording of controlled drugs.

The Australian Government has committed funding to set up a national system. If this system is well designed, it will have the potential to improve the quality use of opioids and other drugs of dependency prescribed in general and specialist practices. Potential benefits include a reduction of inappropriate prescribing and subsequent adverse events, promotion of a more patient-centred approach to the quality use of opioids, and encouragement for prescribers to move towards a more holistic approach in pain management.

There are some potential unintended consequences including doctors avoiding the use of Schedule 8 drugs in appropriate situations such as palliative care, greater stigmatisation of an already marginalised group of patients, and people changing their pattern of drug misuse towards illicit drugs or other prescribed psychotropic medications. An evaluation of a national system will be an important part of this process.

LETTERS

Where to find information about drugs

Aust Prescr 2016;39:152
http://dx.doi.org/10.18773/austprescr.2016.075

As the article by Richard Day and Leone Snowden[1] states, 'good medicines information is critical to medical practice'. It provides an excellent and comprehensive listing and discussion of available resources of drug information.

Beyond the scope of their article are telephone drug information services to which many healthcare providers may unknowingly have access. These services provide medicines advice and therapeutic information for free to healthcare professionals. They are mostly located within hospitals and are staffed by pharmacists specially trained and experienced in the retrieval and analysis of medicines information.

Formal provision of medicines information by trained staff has been associated with positive impact on patient care, outcomes and medicines safety.[2] While it is important for individuals to know where and how to locate information, many may not possess the skills and knowledge to do so or have the time required to analyse, synthesise and construct a clinically relevant solution to a complex medical dilemma.[2] When the authors note that 'further detail may need to be sought' or 'references from these sources require critical appraisal', trained medicines information pharmacists may be extremely helpful. They are the people to turn to when health professionals are unable to find the information they need.[2]

Telephone drug information services contribute to high-quality patient care and public health by promoting the quality use of medicines. They can be relied upon to provide accurate, current, unbiased, evidence-based therapeutic advice to healthcare professionals who may not have access to certain resources, or the necessary time or skills to use them to their best advantage.

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ARTICLE

Choosing non-oral, long-acting reversible contraception

SUMMARY

Long-acting reversible contraception methods include the copper and hormonal intrauterine devices, the contraceptive implant and the contraceptive injection. These should be discussed with women considering their options for contraception.

These methods are more effective at reducing unintended pregnancy than oral contraceptives and have a good safety profile with few contraindications.

The progestogen-only intrauterine device can be used to manage heavy menstrual bleeding.

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Keywords
contraceptive implant, depot contraception, intrauterine contraception device, medroxyprogesterone acetate

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Introduction

Long-acting reversible contraception methods have been underused in Australia but their uptake is now increasing.[1] Methods include the copper and hormonal intrauterine devices (IUDs), the contraceptive implant and the contraceptive injection. However, the injection is often considered a 'second-tier' method due to its requirement for more frequent administration and therefore lower effectiveness.

There is compelling evidence that women using a shorter acting method such as the oral contraceptive pill are significantly more likely to experience an unintended pregnancy than those using long-acting reversible contraception.[2-5] An Australian web survey[6] found that approximately 60% of women who experienced an unintended pregnancy had been using either condoms or the oral contraceptive pill at the time they conceived.

All long-acting reversible contraception methods can be combined with condoms for women at risk of sexually transmitted infections.

Medical eligibility for long-acting contraception

Some medical conditions are associated with increased risks when certain contraceptives are used because the contraceptive method adversely affects the condition or because the condition (or its treatment) affects the contraceptive. The World Health Organization developed guidelines for the safe prescribing of contraception. These have been adapted into Medical Eligibility Criteria[7] which relate to the safety of contraception methods in women with pre-existing medical conditions. This system has four categories (see Box). Table 1 gives the Medical Eligibility Criteria categories for IUDs, and Table 2 gives the categories for the contraceptive implant and contraceptive injection.[7]

Intrauterine devices

The devices available in Australia are the copper IUDs and the levonorgestrel IUD. Both types are extremely effective and provide immediately reversible contraception. See Table 3 for a comparison of these devices.[8] IUDs are suitable for women of all ages and parity, and can be used for extended durations in older women (see Table 4).[9] They can be used by breastfeeding women, those who cannot use oestrogen-containing contraception methods and those on drugs that induce liver enzymes.

Contraindications include current or recent pelvic infections, undiagnosed abnormal vaginal bleeding and significant distortion of the uterine cavity. For the levonorgestrel IUD, a current or past history of breast cancer is also a contraindication.[8]

Box Medical Eligibility Criteria categories for use of contraceptive methods [7]

Category 1 – a condition for which there is no restriction for the use of the contraceptive method

Category 2 – a condition for which the advantages of using the method generally outweigh the theoretical or proven risks

Category 3 – a condition for which the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since the method is not usually recommended unless other more appropriate methods are not available or acceptable

Category 4 – a condition that represents an unacceptable risk if the contraceptive method is used

Table 1 **Medical Eligibility Criteria categories for intrauterine devices in significant medical conditions** [7]

Condition		Category	
		Copper IUD	LNG IUD
Personal characteristics and reproductive history			
Postpartum: breastfeeding or non-breastfeeding, including post-caesarean section	48 hours to 4 weeks	3	3
	Puerperal sepsis	4	4
Immediate post-septic abortion		4	4
Cardiovascular disease			
Ischaemic heart disease or stroke that develops during use (use of LNG IUD is category 2 and copper IUD is category 1 in women with pre-existing disease)		1	3
Breast and reproductive tract conditions			
Current breast cancer		1	4
Previous breast cancer with no evidence of disease for at least 5 years		1	3
Unexplained vaginal bleeding (suspicious for serious condition) before evaluation – initiation (use of either method is category 2 if develops during use)		4	4
Gestational trophoblastic disease (includes hydatidiform mole, invasive mole and placental tumour) – persistently elevated beta human chorionic gonadotropin or malignant disease		4	4
Cervical cancer awaiting treatment – initiation (use of either method is category 2 if develops during use)		4	4
Endometrial cancer awaiting treatment – initiation (use of either method is category 2 if develops during use)		4	4
Ovarian cancer awaiting treatment – initiation (use of either method is category 2 if develops during use)		3	3
Uterine fibroids, with distortion of the uterine cavity		3	3
Distorted uterine cavity (any congenital or acquired uterine abnormality distorting the uterine cavity in a manner that is incompatible with IUD insertion)		3	3
Current pelvic inflammatory disease – initiation (use of either method is category 2 if develops during use)		4	4
Chlamydial or gonorrhoeal infection or purulent cervicitis – initiation (use of either method is category 2 if develops during use)		4	4
HIV			
HIV infected and using antiretroviral therapy		2/3	2/3
Gastrointestinal conditions			
Severe (decompensated) cirrhosis		1	3
Hepatocellular adenoma and malignant liver tumour		1	3

IUD intrauterine device LNG levonorgestrel
Adapted under licence from FSRH. © Faculty of Sexual and Reproductive Healthcare 2006 to 2016.[7]

Apart from a small risk of infection in the first three weeks after insertion, modern devices are not associated with an increased risk of future infertility or pelvic infection. Women may experience a vasovagal episode at the time of insertion and there is a small chance of uterine perforation. Expulsion can occur and is more likely within the first year. The management of women presenting with 'missing' IUD threads is outlined in the Figure.[10]

IUDs can be inserted in primary care or in a specialist setting. GPs, and an increasing number of nurses, are being trained to insert these devices. Pregnancy must be excluded before insertion of any IUD.

The levonorgestrel intrauterine device

The levonorgestrel IUD (Mirena) is a T-shaped plastic intrauterine device with a reservoir of 52 mg of the progestogen levonorgestrel in its stem. The hormone is released slowly into the uterus at a rate of 20 microgram per day over a period of five years. It is subsidised on the Pharmaceutical Benefits Scheme (PBS) for contraception and heavy menstrual bleeding.[8]

The device causes endometrial atrophy, thickens cervical mucus (preventing sperm penetration) and, in some users, prevents or delays ovulation. It may also prevent implantation,[11,12] and has contraceptive efficacy of 99.8% in typical and perfect use.[13]

Table 2 **Medical Eligibility Criteria categories for depot medroxyprogesterone acetate injection and etonorgestrel implants in significant medical conditions** [7]

Condition		Category	
		DMPA injection	ENG implant
Personal characteristics and reproductive history			
Postpartum: breastfeeding	Less than 6 weeks	2	1
	6 weeks to 6 months, fully or mostly breastfeeding	1	1
Postpartum: non-breastfeeding		1	1
Arterial disease and risk factors			
Multiple risk factors for cardiovascular disease (e.g. older age, smoking, diabetes, hypertension and obesity)		3	2
Hypertension, with vascular disease		3	2
Past history of ischaemic heart disease, stroke or transient ischaemic attack		3	2
Develops ischaemic heart disease, stroke or transient ischaemic attack during use		3	3
Breast and reproductive tract conditions			
Unexplained vaginal bleeding (suspicious for a serious condition) before evaluation		3	3
Current breast cancer		4	4
Previous breast cancer with no evidence of disease for at least 5 years		3	3
Gastrointestinal conditions			
Severe (decompensated) cirrhosis		3	3
Hepatocellular adenoma or malignant liver tumour		3	3

DMPA depot medroxyprogesterone acetate ENG etonorgestrel
Adapted under licence from FSRH. © Faculty of Sexual and Reproductive Healthcare 2006 to 2016.[7]

Table 3 **Comparison of intrauterine devices** [8]

	Hormonal intrauterine device	Copper intrauterine device
PBS subsidy	Yes	No (costs $100)
Mechanism of action	May thicken cervical mucus Affects sperm/oocyte motility Thins endometrium May inhibit ovulation	Toxic to sperm Endometrial effect
Duration	5 years	5 or 10 years
Efficacy	99.8%	99.2%
Effect on bleeding	Significantly reduces menstrual bleeding	Can increase menstrual bleeding and pelvic pain
Hormonal adverse effects	Can occur	None
Other benefits	Protects the endometrium in women requiring hormone replacement therapy	Provides highly effective emergency contraception

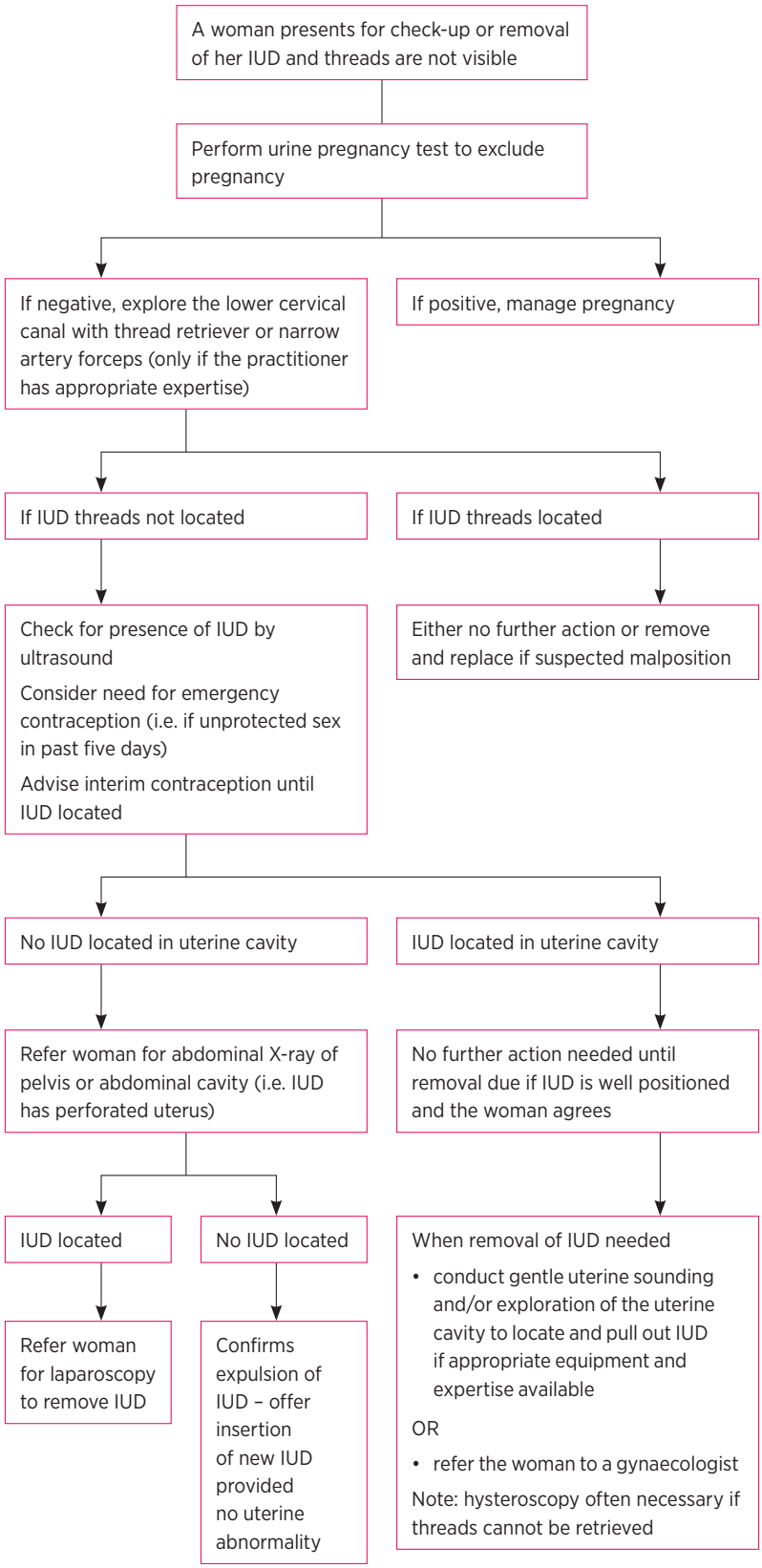
PBS Pharmaceutical Benefits Scheme

Table 4 **Duration of use of intrauterine devices in older women** [9]

Age and circumstances	Action
Age at least 40 years at time of insertion of a copper IUD	Can be retained until 1 year after the last menstrual period if this occurs when the woman is over the age of 50 years (2 years if under 50 years) (off-label use)
Age at least 45 years at time of insertion of a levonorgestrel IUD	Can use the device for 7 years* or if amenorrhoeic until menopause (off-label use). After this the IUD should be removed
Age at least 50 years, levonorgestrel IUD, amenorrhoeic (determining menopause)	If serum follicle-stimulating hormone is at least 30 IU/L on two occasions 6 weeks apart then remove IUD 1 year later

IUD intrauterine device
* unless being used as part of hormone replacement therapy, in which case the levonorgestrel IUD should be replaced at 5 years

Fig. **Management of a woman with missing intrauterine device threads** [10]



IUD intrauterine device
Adapted with permission from Medicine Today[10]

The levonorgestrel IUD reduces heavy menstrual bleeding significantly and, although frequent spotting or bleeding are common in the first three to five months, most women will establish a pattern of either very light bleeds or amenorrhoea after six months.[14,15]

Due to the very low dose of levonorgestrel absorbed systemically, most women do not experience progestogen-related adverse effects such as headache, breast tenderness or acne.

When inserted within the first seven days of the natural cycle, the levonorgestrel IUD will be effective immediately. However, if put in later in the cycle, another form of contraception or abstinence is recommended for seven days.

The copper intrauterine devices

There are several types of copper IUDs in Australia. They can be used for different durations:

- TT380 (T-shaped) – can be used for up to 10 years
- TT380 short (T-shaped) – can be used for up to 5 years
- Load 375 – can be used for up to 5 years.

The copper IUDs are not on the PBS and cost approximately $100. They are the most effective form of non-hormonal reversible contraception and may be preferred by women who wish to, or need to, avoid hormones. Copper IUDs have a typical use efficacy of 99.2%.[13] They can increase menstrual bleeding and dysmenorrhoea. A trial of a non-steroidal anti-inflammatory drug (NSAID) may be a useful management strategy.

Once inserted the copper IUD is immediately effective. It is the most effective form of emergency contraception if inserted within five days of unprotected sex and also has the advantage of providing ongoing, long-term effective contraception.

The contraceptive implant

The contraceptive implant available in Australia is a single, ethylene vinyl acetate 4 cm rod containing 68 mg of the progestogen etonorgestrel (Implanon NXT). It is easily implanted directly under the skin of the upper, inner, non-dominant arm using local anaesthetic, by a trained doctor or nurse. The hormone is slowly released over three years. This product is listed on the PBS.[8]

The etonorgestrel implant provides reversible contraception by preventing ovulation, thickening cervical mucus, preventing sperm penetration and possibly preventing implantation by thinning the endometrium.[16] It is 99.9% effective in typical and perfect use.[13]

When inserted within the first five days of the natural cycle, the implant will be effective immediately.

If inserted later in the cycle, another form of contraception is recommended for seven days after insertion.

The implant can be used by most women including those who cannot use oestrogen-containing methods and those with malabsorption. It can be used during breastfeeding but is contraindicated in women with a personal history of, or current, breast cancer (see Table 2).

Concomitant use of drugs that induce liver enzymes, including phenytoin, carbamazepine, St John's wort and rifampicin, increase etonorgestrel metabolism. This potentially decreases the implant's effectiveness and has been associated with implant failure and unintended pregnancies.

The bleeding pattern experienced with the implant is varied and unpredictable. Approximately 3 in 5 women have infrequent, irregular bleeding, 1 in 5 have amenorrhoea, and 1 in 5 have frequent or prolonged bleeding. About half of those with frequent or prolonged bleeding will improve after three months.[17]

Registered medical practitioners are generally required by their insurer to complete the online training program that is provided by the manufacturers (www.implanonnxt.com.au – password: implant). Nurses can also be trained to insert the implant providing they meet any medicolegal requirements. A standardised training program for nurses is currently under development.

The contraceptive injection

The contraceptive injection used in Australia is depot medroxyprogesterone acetate 150 mg (Depo-Provera or Depo-Ralovera) given intramuscularly every 12 weeks. It is listed on the PBS.

The injection works in the same way as the etonorgestrel implant.[18] Its efficacy is 99.8% with perfect use and 94% with typical use (reduced due to the need to return every three months for a repeat injection).[13]

The injection can be used by most women although it is not recommended as first line for women who are under 18 or over 45, as there is some evidence of a small decrease in bone density. However, this decrease appears to be regained on cessation and has not been shown to increase fracture risk.[18]

The contraceptive injection may be associated with weight gain.[18] Return to fertility can take 12–18 months so a woman's pregnancy plans need to be considered.[19]

The initial bleeding pattern can include irregular, prolonged or frequent bleeding but up to 70% of women develop amenorrhoea by 12 months.[20-22] When the injection is given within the first five days of the natural cycle it will be effective immediately. If given later in the cycle, another form of contraception is recommended for seven days. Pregnancy should be excluded if it is to be given after day five or the injection delayed, if possible, until pregnancy can be excluded. There is no evidence of teratogenesis if the injection is inadvertently given during pregnancy.[8]

Bleeding problems with progestogen-only implant and IUD

Provide accurate information about expected bleeding patterns when long-acting contraception is initiated. Encouraging review and offering management advice for troublesome bleeding is an important part of contraceptive counselling.

After excluding other causes of irregular bleeding and offering reassurance, medical management can include:

- combined hormonal contraceptive taken continuously or cyclically for three months (if not contraindicated)
- five-day course of an NSAID (e.g. mefenamic acid 500 mg) 2–3 times a day
- five-day course of tranexamic acid 500 mg twice a day, particularly if bleeding is heavy.

Advise that the implant or IUD can be removed any time and that the contraceptive injection can be discontinued or given at a slightly reduced interval of 10 rather than 12 weeks.[23]

Conclusion

When it comes to contraception 'one size does not fit all' and women need evidence-based information about the risks and benefits of all methods in order to make the best choice for themselves. Choice is based on a number of factors including medical eligibility, desire for non-contraceptive benefits, experience of adverse effects as well as personal preference. Long-acting reversible contraception methods offer highly effective and cost-effective options for women of all ages. A discussion on the pros and cons of the different options should be a part of consultations about contraception. ◀

Mary Stewart has attended advisory meetings and presented at educational meetings for Bayer Healthcare and MSD as part of her role but has not received personal remuneration for this work.

Family Planning NSW has received sponsorship from Bayer Healthcare and MSD for its educational courses.

Deborah Bateson has attended advisory meetings and presented at educational meetings for Bayer Healthcare and MSD as part of her role but has not received personal remuneration for this work. She has been supported to attend conferences by Bayer Healthcare and MSD.

Q:

SELF-TEST QUESTIONS

True or false?

1. St John's wort could potentially decrease the effectiveness of the contraceptive implant.
2. The levonorgestrel intrauterine device can be used to reduce heavy bleeding.

Answers on page 185

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ARTICLE

Bacterial skin and soft tissue infections

SUMMARY

Bacterial skin infections are common presentations to both general practice and the emergency department.

The optimal treatment for purulent infections such as boils and carbuncles is incision and drainage. Antibiotic therapy is not usually required.

Most uncomplicated bacterial skin infections that require antibiotics need 5–10 days of treatment.

There is a high prevalence of purulent skin infections caused by community-acquired (non-multiresistant) methicillin-resistant *Staphylococcus aureus*. It is therefore important to provide adequate antimicrobial coverage for these infections in empiric antibiotic regimens.

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antibiotics, cellulitis, impetigo, soft tissue infection

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Introduction

It is important to have a good understanding of the common clinical manifestations and pathogens involved in bacterial skin infections to be able to manage them appropriately. The type of skin infection depends on the depth and the skin compartment involved. The classification and management of these infections are outlined in Table 1.

Impetigo

Impetigo is a superficial bacterial infection that can develop either through direct invasion of normal skin (primary) or infection at sites of damaged skin (secondary) (Fig. 1). It is common in children and is highly contagious. There are two forms:

- non-bullous or crusted impetigo – distinct yellow, crusting lesions that may be itchy. Typically involves face or extremities
- bullous impetigo – usually caused by *Staphylococcus aureus*. Presents as bullae that rupture to form a brown crust.

Boils and carbuncles

Boils and carbuncles are associated with infection of a hair follicle and extend into subcutaneous tissue. They are tender and painful but the patient is usually systemically well. In most cases, lesions can be treated with incision and drainage alone. Antibiotic therapy is only required if there is spreading cellulitis or systemic infection.

Folliculitis

This usually presents as a crop of pustules affecting areas of moist skin with hair. It is most commonly caused by *S. aureus* but can also be linked to other organisms like *Pseudomonas aeruginosa* when associated with specific exposures like hot tubs and spas.

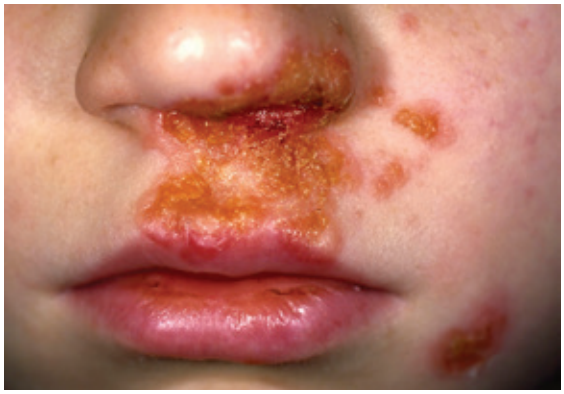
Cellulitis and erysipelas

Both cellulitis and erysipelas manifest as spreading areas of skin erythema and warmth. Localised infections are often accompanied by lymphangitis and lymphadenopathy. Not infrequently, groin pain and tenderness due to inguinal lymphadenitis will precede the cellulitis. Some patients can be quite unwell with fevers and features of systemic toxicity. Bacteraemia, although uncommon (less than 5%), still occurs.

Erysipelas involves the upper dermis and superficial lymphatics. Skin lesions are usually raised with a clear demarcation of infected skin. Classically, erysipelas affects the face (Fig. 2), but it can also involve other areas such as the lower limb. It is most commonly caused by *Streptococcus pyogenes* (group A streptococcus).

Cellulitis extends further into the deep dermis and subcutaneous tissue. It commonly involves the lower

Fig. 1 **Impetigo**



Source: © Professor Raimo Suhonen, used with permission from DermNet NZ

Table 1 **Therapeutic approach to common bacterial skin infections**

Infection	Likely pathogens	Management
Impetigo	*Staphylococcus aureus* *Streptococcus pyogenes*	Mild or localised disease: • wash crusts • topical mupirocin Multiple lesions or recurrent disease: • cultures to guide treatment • oral antibiotics (dicloxacillin/cephalexin/trimethoprim plus sulfamethoxazole) for up to 10 days • intravenous antibiotics if no improvement • for recurrent infection due to *S. aureus* consider decolonisation Advice and education of household members to reduce transmission: • avoid contact with lesions • wash hands regularly, particularly after touching lesions
Boils and carbuncles	*S. aureus* *S. pyogenes*	Incision and drainage most important step in management: • culture and susceptibility testing for lesions • antibiotics if spreading cellulitis or systemic symptoms – oral dicloxacillin/cephalexin for 5 days – oral clindamycin, or trimethoprim plus sulfamethoxazole for community-acquired-MRSA for 5 days
Folliculitis	*S. aureus* *S. pyogenes* *Pseudomonas aeruginosa*	Treatment usually supportive Warm compresses or topical mupirocin In severe infection treat as per impetigo
Cellulitis and erysipelas	*S. aureus* Beta-haemolytic streptococci	Examine for predisposing factors Consider unusual exposures (see Table 2) – broaden antibiotic therapy if this is the case Culture and susceptibility testing for lesions, tissue or blood Elevate limb Treat underlying predisposing skin infection e.g. tinea Mild disease: • oral dicloxacillin/cephalexin/clindamycin for 5–10 days • oral phenoxymethylpenicillin if culture is positive or clinical presentation of *S. pyogenes* Severe disease or systemic features: • intravenous flucloxacillin/cephazolin/vancomycin Consider decolonisation or prophylactic antibiotics with recurrent disease
Periorbital cellulitis	*S. aureus* *Streptococcus* species *Haemophilus influenzae* type b (in unvaccinated patients)	Mild disease: • oral dicloxacillin/cephalexin/clindamycin for 7 days If suspect *H. influenzae* type b infection (unvaccinated, < 5yrs old): • oral amoxycillin plus clavulanate, or cefuroxime for 7 days Severe disease or systemic features: • treat as orbital cellulitis
Orbital cellulitis	*S. aureus* *Streptococcus* species *H. influenzae* type b (in unvaccinated patients) Anaerobic bacteria	Inpatient hospital management with urgent surgical opinion Blood cultures and CT scan of orbits Intravenous antibiotics
Necrotising fasciitis	*S. aureus* *S. pyogenes* Gram negatives, *Clostridium* species Anaerobic bacteria	Inpatient hospital management with urgent surgical debridement Culture and susceptibility testing of tissue Broad-spectrum intravenous antibiotics including clindamycin (antitoxin effect by suppressing synthesis of bacterial endotoxins)

MRSA methicillin-resistant *Staphylococcus aureus*

Fig. 2 **Erysipelas**

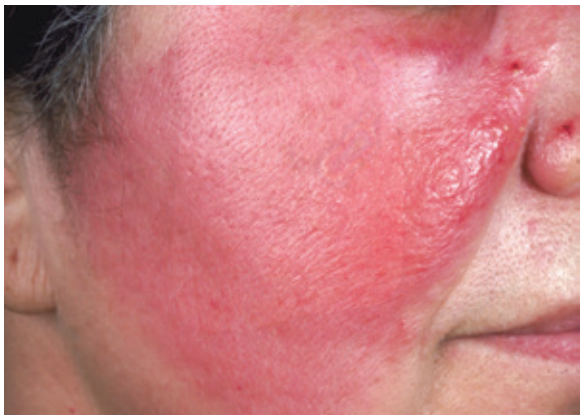


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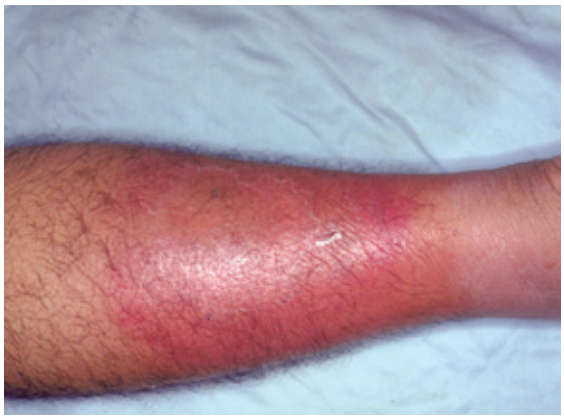
Fig. 3 **Cellulitis**



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limbs (Fig. 3) and in most cases is unilateral. Bilateral lower limb cellulitis is exceedingly rare and usually reflects stasis dermatitis and does not require antibiotic treatment. Other areas of the body such as the eye and the abdominal wall can also be affected. Periorbital cellulitis involves the eyelids and does not extend into the bony orbit. Orbital cellulitis is a much more serious infection with deeper extension and impairment of vision and extraocular eye movements, often with pain.

Cellulitis is usually caused by either *S. aureus* or beta-haemolytic streptococci (groups A, B, C or G). Differentiating between these two organisms can help guide therapy. Streptococcal infection is usually characterised by acute onset of rapidly spreading erythema, lymphangitis and lymphadenopathy. Staphylococcal cellulitis is usually associated with purulent lesions with erythema. Cultures from wounds or blood can further help delineate the causative organism. In the absence of positive cultures however, it can be difficult to discriminate between the two and antibiotic therapy to cover both organisms (for example flucloxacillin, dicloxacillin, cephalexin, clindamycin) is often used.

Diagnostic approach to cellulitis

When evaluating a patient with cellulitis, review systemic features. Potential portals of entry for infection should also be looked for. These include:

- disruption to the skin barrier, insect bites, wounds, abrasions
- pre-existing skin infection, tinea pedis, impetigo
- underlying skin disease, eczema, psoriasis
- lymphoedema or surgical disruption of the lymphatic or venous system
- peripheral vascular disease with impaired arterial supply
- chronic venous insufficiency.

It is important to consider less common causes of skin infection associated with specific clinical circumstances or exposures (Table 2). In these cases, specimens should be collected for culture and sensitivity testing and treatment regimens broadened to cover likely pathogens. In difficult-to-treat or atypical infections, specialist opinion is recommended.

Table 2 **Skin infections associated with unusual exposures and clinical scenarios**

Exposure history	Associated organisms
Freshwater exposure	*Aeromonas hydrophila*
Saltwater exposure	*Vibrio* species especially *V. vulnificus*
Other aquatic infections	*Mycobacterium marinum, Erysipelothrix rhusiopathiae*
Soil or thorn injuries	Atypical mycobacteria, nocardia, fungi, *Sporothrix schenkii*
Cat bites	*Pasteurella multocida*
Dog bites	*Capnocytophaga canimorsus, Pasteurella canis*
Human bites	*Eikenella corrodens*
Hot tub exposure	*Pseudomonas aeruginosa*
Immunosuppression or neutropenia	*Pseudomonas aeruginosa, Cryptococcus* species, nocardia, mycobacteria

Many conditions may masquerade as cellulitis (see Box 1). These conditions should always be considered in atypical cases to avoid the unnecessary use of antibiotics.

Necrotising skin infections

Necrotising skin infections, the best known of which is necrotising fasciitis, are a medical and surgical emergency that require prompt debridement and appropriate intravenous antibiotics. Infections can be caused by single or multiple pathogens (e.g. *S. pyogenes*, Gram negatives, *Clostridium*).

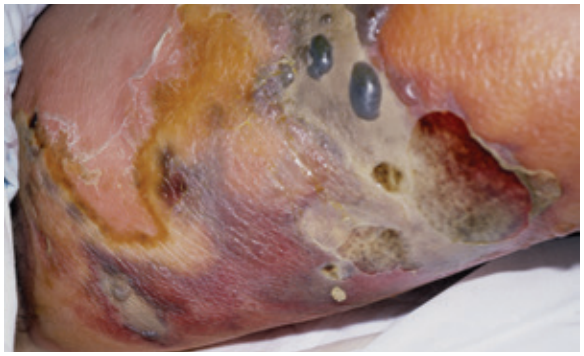
Infection usually involves the necrosis of underlying soft tissues or muscle. Typical early clinical features are induration and erythema of the affected area with pain out of proportion to overlying skin changes. As infection progresses, the skin can change colour to purple or blue and eventually breaks down to form bullae and gangrene (Fig. 4). The patient is usually quite unwell with systemic toxicity, haemodynamic instability and multi-organ failure.

Urgent hospital referral is essential in all cases. Surgical exploration is the only way to establish the diagnosis of necrotising fasciitis and is also the definitive management in all cases. Exploration also allows material to be obtained for appropriate cultures to guide antibiotic therapy.

Box 1 **Non-infectious differential diagnosis for cellulitis**

- Stasis dermatitis
- Superficial thrombophlebitis
- Deep venous thrombosis
- Congestive cardiac failure
- Drug reactions
- Insect bites
- Cutaneous vasculitis
- Acute gout

Fig. 4 **Necrotising fasciitis**



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Methicillin-resistant *Staphylococcus aureus* (MRSA)

There has been a rapid increase in the rates of community-associated multiresistant MRSA skin infections in Australia[1,2] and worldwide. It is important to consider the possibility of this pathogen if contemplating empirical antibiotic therapy for bacterial skin infections (clindamycin or trimethoprim plus sulfamethoxazole). Culture and susceptibility testing of lesions should be used to guide therapy as community-associated MRSA is resistant to beta-lactam antibiotics such as flucloxacillin, dicloxacillin and the cephalosporins.

When to use topical antibiotics

According to current recommendations, topical mupirocin is only recommended in cases of mild impetigo and folliculitis. All other infections should be managed with either incision and drainage or oral and intravenous antibiotics. Topical fusidic acid monotherapy has been associated with increased fusidic acid resistance[3,4] among strains of *S. aureus* and it is not our preference to use this on its own.

When to use oral antibiotics

Patients with no signs of systemic toxicity and uncontrolled comorbidities can usually be managed with oral antibiotics as outpatients.

When to consider hospital referral and intravenous antibiotics

Patients with severe disease who are systemically unwell will require assessment in hospital for monitoring and intravenous antibiotics. Parenteral antibiotics can either be administered as an inpatient or through an Outpatient Parenteral Antibiotic Treatment or Hospital in the Home program. Factors that would favour hospital management of cellulitis include:[5]

- comorbid conditions (renal impairment, diabetes, congestive cardiac failure, splenectomy) or immunosuppression
- rapidly progressive infection
- concern for deep space infection (presence of bullae, necrosis or muscle involvement)
- high fevers and rigors
- haemodynamic instability
- suppurative wound or bite (especially on face or hand) requiring surgical drainage
- lack of systemic or local response to oral antibiotics, or rising or unchanging C-reactive protein concentrations despite adequate therapy
- positive blood cultures
- inability to tolerate or absorb oral antibiotics.

How to manage recurrent skin infections

Recurrent cellulitis is extremely challenging. Each repeated episode of cellulitis can cause inflammation and disruption of the lymphatic system and subsequent lymphoedema. The affected limb is subsequently more prone to infection and a vicious cycle of cellulitis and limb swelling is established.

Treating the underlying cause of infection is the most important step in management. In cases of chronic lymphoedema and venous stasis, compression of the affected limb by bandaging or stockings helps to increase venous return and contractility of the lymphatic ducts, therefore decreasing swelling and cellulitis. Further supportive measures such as elevation of the limb may also confer symptomatic relief. For example in cellulitis of the leg, raising the foot higher than the hip with supportive cushions helps to reduce swelling and pain. Prophylactic long-term suppressive antibiotics offer symptomatic benefit and cost–benefit in cases of recurrent streptococcal cellulitis.[6,7] Options include twice-daily oral penicillin or cephalexin.

For recurrent staphylococcal infections, decolonisation measures should be considered (Box 2).[8] In difficult cases of recurrent infections despite prophylactic antibiotics, expert consultation with an infectious disease specialist is recommended.

Conclusion

Bacterial skin infections have a variety of presentations from localised, trivial infection to rapidly progressive infection with systemic toxicity and considerable mortality. It is important to be able to recognise and treat these infections in the community, and in cases of severe infection to refer the patient promptly for specialist care. <

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Topical mupirocin is the first-line treatment for multiple impetigo lesions.

4. Erysipelas is most commonly caused by *Streptococcus pyogenes*.

Answers on page 185

Box 2 **Suggested decolonisation regimen for recurrent boils or staphylococcal skin infections** [8]

Treat acute lesions.

Collect nasal or perineal swabs to determine antibiotic susceptibility of *Staphylococcus aureus*.

Once active skin lesions resolve, eradicate staphylococcal carriage with

- mupirocin nasal ointment for 5 days
- PLUS EITHER
- chlorhexidine 2% or triclosan 1% wash for 5 days in showers
- OR
- sodium hypochlorite solution (60 mL of 6% solution per bathtub) or triclosan 2% bath oil for 5 days in baths

Do not share towels. Wash bed linen (at least weekly) and towels (after each use) in hot water and hang out to dry in the sun.

Decolonisation of household contacts is not recommended unless the measures outlined fail to prevent recurrence in the index case or contacts have a history of recurrent skin infection.

If decolonisation measures fail, repeat topical regimen together with

- oral rifampicin for 7 days
- PLUS
- oral dicloxacillin, fusidate sodium or trimethoprim plus sulfamethoxazole depending on susceptibility of the organism.

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EXPERIMENTAL AND CLINICAL PHARMACOLOGY

PCSK9 inhibitors – mechanisms of action

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SUMMARY

PCSK9 is a proprotein convertase which is involved in the degradation of low-density lipoprotein (LDL) receptors in the liver.

Mutations in the PCSK9 gene cause familial hypercholesterolaemia in a subset of patients by reducing the number of LDL receptors on the surface of hepatocytes. This decreases their ability to clear LDL cholesterol from plasma.

Conversely, other PCSK9 mutations result in unusually low concentrations of plasma LDL cholesterol and a reduced risk of atherosclerotic disease.

Blocking the activity of PCSK9 with monoclonal antibodies reduces the degradation of LDL receptors and increases the clearance of LDL cholesterol.

An injection of PCSK9-specific antibody suppresses LDL-cholesterol concentrations for several weeks.

Introduction

The 1985 Nobel Prize for Physiology or Medicine was awarded to Michael Brown and Joseph Goldstein for their research into the link between cholesterol metabolism and coronary artery disease.[1] This research increased our understanding of the pathophysiology of disorders such as familial hypercholesterolaemia, and paved the way for important therapies like statins (HMG-CoA reductase inhibitors). They found that the low-density lipoprotein (LDL) receptor, expressed primarily in the liver, was responsible for clearing LDL particles from plasma.

Statins decrease the intracellular concentration of cholesterol in the liver. This increases the expression of LDL receptors and more LDL cholesterol is removed from the circulation (Fig. 1).

Proprotein convertases

Proprotein convertases are a family of enzymes involved in converting precursors of secretory proteins, such as hormones, enzymes and receptors, into bioactive molecules at their intended target tissue. These enzymes are part of regulatory pathways that help the body to maintain homeostasis.

PCSK9

PCSK9 (proprotein convertase subtilisin/kexin type 9) was first described in 2003 (Fig. 2).[2] In its active form, PCSK9 regulates cell surface receptors, in particular the LDL receptor. The enzyme encoded by the PCSK9 gene is primarily expressed in the liver.

Most cases of familial hypercholesterolaemia are due to mutations resulting in defective LDL receptors, with others caused by defects in the ligand for the LDL receptor, apolipoprotein-B100. Inherited 'gain-of-function' mutations in the PCSK9 gene have recently also been found to cause familial hypercholesterolaemia. This is characterised by very high plasma concentrations of LDL cholesterol and associated with premature atherosclerotic cardiovascular disease.[3] Conversely, 'loss-of-function' PCSK9 mutations result in unusually low concentrations of plasma LDL cholesterol. People with these mutations have a markedly reduced lifetime risk of atherosclerotic cardiovascular disease.[4]

PCSK9 circulates in three main forms:

- mature, monomeric protein, which circulates exclusively in an LDL-bound form
- multimeric, self-associated form, which probably has increased activity
- furin-cleaved, inactive fragment.

Some PCSK9 mutations result in changes to the self-association or furin-mediated cleavage of PCSK9. These mutations lead to gain or loss of function.[5]

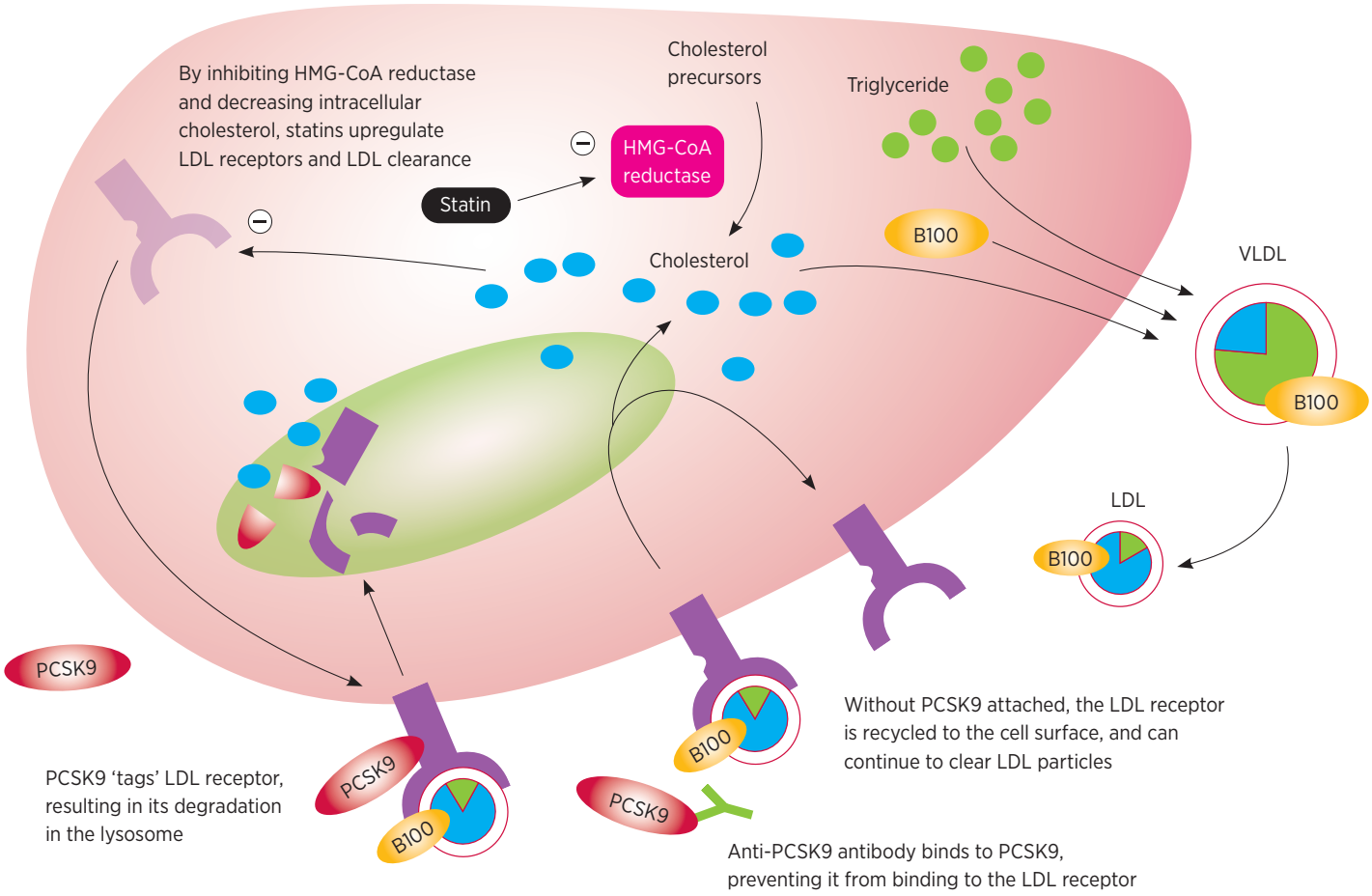
PCSK9 is cleared from the circulation by the LDL receptor. It is then cleaved inside hepatocytes (Fig. 1).

Role of PCSK9

PCSK9 regulates the degradation of the LDL receptor in response to cholesterol concentrations within the cell (Fig. 1). PCSK9 binds to an extracellular part of the LDL receptor. Apolipoprotein-B100, the structural protein of LDL and ligand for the LDL receptor, binds to a different site on the LDL receptor.

Fig. 1 Mechanism of action of statins and anti-PCSK9 monoclonal antibodies

VLDL is secreted by the liver and converted to LDL, which delivers cholesterol to peripheral tissues and is atherogenic. LDL particles are taken up via LDL receptors, primarily on hepatocytes, and degraded. The production of LDL receptors is decreased by intracellular cholesterol, so lowering intracellular cholesterol with statins results in increased LDL receptors and LDL uptake. LDL-receptor degradation is enhanced by PCSK9, so inhibiting PCSK9 with antibodies increases LDL-receptor recycling and LDL uptake.



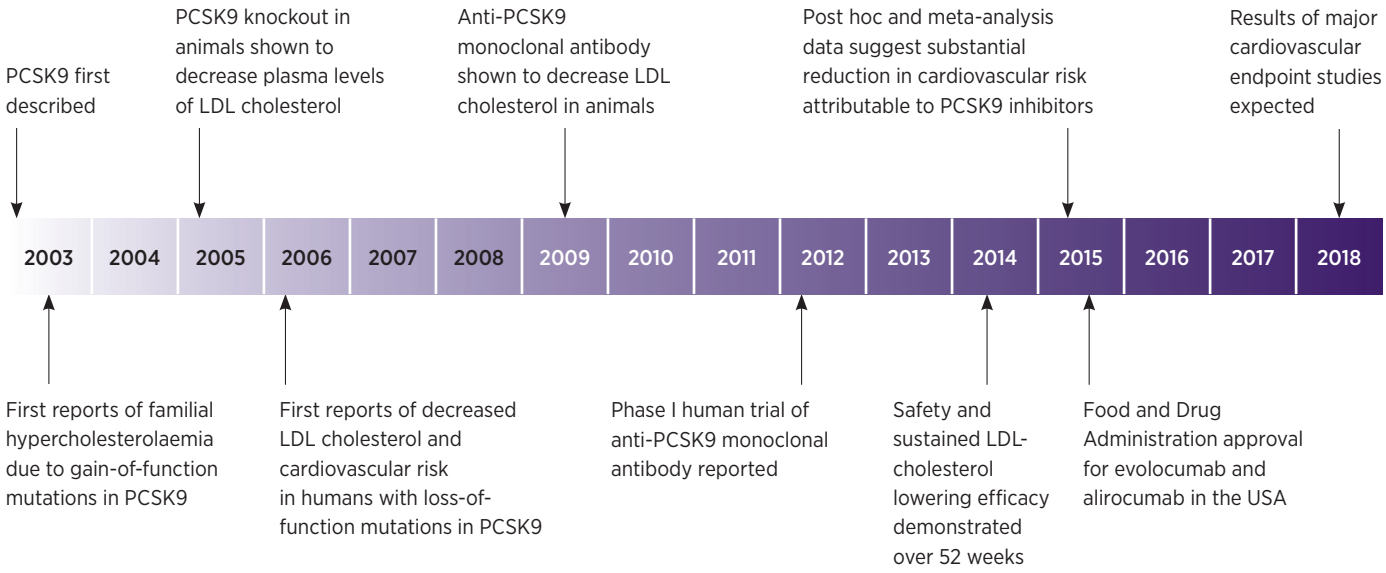
B100 apolipoprotein-B100 PCSK9 proprotein convertase subtilisin/kexin type 9 LDL low-density lipoprotein VLDL very low-density lipoprotein

After the LDL receptor is internalised into the hepatocyte, it is trafficked to a lysosome, where it can be either degraded or recycled back to the surface of the hepatocyte. PCSK9 prevents the LDL receptor from forming a closed conformation, making the receptor susceptible to enzymatic degradation.[6] LDL receptors without PCSK9 bound to them are therefore more likely to be recycled to the cell surface.

Although animal models suggest that PCSK9 has other roles in cholesterol metabolism aside from the regulation of LDL-receptor recycling, this has not been borne out in the clinical setting in humans. In LDL-receptor knockout mice, LDL-cholesterol concentrations are increased by PCSK9 administration or overexpression, despite the absence of LDL receptors as a clearance pathway.[7,8] However, this finding is inconsistent with that in humans with LDL-receptor-negative familial hypercholesterolaemia, in whom blocking the action of PCSK9 does not decrease plasma concentrations of LDL cholesterol.[9]

Animal studies have suggested roles for PCSK9 in non-hepatic tissue. These include intestinal and adipocyte lipid metabolism, development of atherosclerotic plaques and inflammation, apoptotic cell death, and regulation of blood pressure and glycaemia.[5] Clinically significant roles of PCSK9 other than in cholesterol metabolism have not been identified or emerged in the form of unexpected adverse effects despite thousands of patients being treated with anti-PCSK9 antibodies.

Fig. 2 **Timeline of developments in the history of PCSK9**



LDL low-density lipoprotein

PCSK9 inhibition

Inhibiting PCSK9 means that more LDL receptors will be recycled to the surface of the cell. This should increase the clearance of LDL cholesterol from the circulation.

Various approaches to the pharmacological inhibition of PCSK9 have been investigated. Molecules that prevent the formation of PCSK9 include antisense oligonucleotides and small interfering RNAs. Molecules that bind to mature PCSK9, preventing it from interacting with LDL receptors, include the small adnectin polypeptides and monoclonal antibodies.[5]

The anti-PCSK9 monoclonal antibodies are of most therapeutic interest and are currently in phase III trials. Details of their binding sites have not been fully disclosed, but earlier monoclonal antibodies are known to bind at or near PCSK9's binding site for the LDL receptor. In pre-clinical studies this sterically inhibits the interaction of PCSK9 with the LDL receptor.[10] Blocking the binding of PCSK9 to the LDL receptor reduces the degradation of the receptor. This markedly increases the clearance of LDL and substantially lowers plasma LDL cholesterol, as well as apolipoprotein-B100 (Fig. 1).

Consistent with the long plasma half-life of monoclonal antibodies, a single dose of an anti-PCSK9 antibody can suppress the plasma LDL-cholesterol concentration for several weeks. Repeated injections cause a sustained reduction of about 50–70% from baseline, as monotherapy or when added to a statin.[11-13]

Lipoprotein(a)

PCSK9 inhibition also decreases the plasma concentrations of lipoprotein(a) (Lp(a)) by around 20–30%.[11,13] This particle is similar in size and cholesterol content to LDL. Unlike LDL, its apolipoprotein-B100 moiety is covalently linked to apolipoprotein(a), a potentially prothrombotic apolipoprotein with sequence similarity to plasminogen. Genetic and epidemiological studies suggest a causal association between Lp(a) and the risk of atherosclerotic cardiovascular disease.[14]

How PCSK9 inhibitors lower Lp(a) concentrations is unknown and warrants further research. Lp(a) is not currently understood to be cleared by the LDL receptor, and statins, which upregulate the LDL receptor, do not substantially lower plasma concentrations of Lp(a). However, recent in vitro studies have suggested that the LDL receptor may indeed have a role in Lp(a) clearance.[15]

Conclusion

The story of PCSK9 since its discovery just over a decade ago is an important case study in translating research into practice. PCSK9-inhibiting therapies have efficacy in lowering LDL cholesterol which could

decrease the risk of atherosclerotic cardiovascular disease, particularly in high-risk patients. They could reduce the need for radical therapies such as lipoprotein apheresis in patients with severe heterozygous familial hypercholesterolaemia, and homozygous familial hypercholesterolaemia with residual LDL-receptor function.

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EXPERIMENTAL AND CLINICAL PHARMACOLOGY

PCSK9 inhibitors – clinical applications

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Keywords
alirocumab, bococizumab, evolocumab, ischaemic heart disease, LDL cholesterol, proprotein convertase subtilisin/kexin type 9

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SUMMARY

The enzyme PCSK9 has an important role in regulating low-density lipoprotein (LDL) receptors and concentrations of LDL cholesterol. Inhibiting this enzyme could therefore reduce the incidence of ischaemic heart disease.

The monoclonal antibodies alirocumab, evolocumab and bococizumab are directed against PCSK9 and inhibit its activity. Phase II trials have shown alirocumab and evolocumab to be effective at lowering LDL cholesterol.

Preliminary results of these phase II trials show potential benefits in ischaemic heart disease. Reports of adverse effects, including muscular symptoms and neurocognitive changes, were low.

Large phase III cardiovascular outcome trials of these monoclonal antibodies will determine their safety and efficacy. These drugs may have a role in the management of patients at very high risk of cardiovascular events such as those with familial hypercholesterolaemia.

Introduction

The incidence of deaths from ischaemic heart disease in Australia has reduced since the 1960s. While about half of this reduction is due to interventions such as coronary revascularisation and secondary prevention, the remainder is due to addressing risk factors such as smoking, lipids and hypertension. However, ischaemic heart disease remains the leading cause of death in Australia, being responsible for over 20 000 deaths in 2011.[1]

There is ample evidence that statins (HMG-CoA reductase inhibitors) are effective and relatively safe drugs for the management of patients at high risk of cardiovascular events. However, there are limitations to their use. Drug intolerance is a major impediment, with muscular symptoms estimated to occur in around 10% of patients.[2] Although these symptoms are usually mild, they are a major cause of discontinuation and poor adherence to therapy. A large proportion of patients at high risk do not reach the recommended target concentration of low-density lipoprotein (LDL) cholesterol.[3]

Second-line treatments are less efficacious than statins. Ezetemibe was recently shown to reduce cardiovascular events, but the trial needed over 18 000 people at very high risk to be followed up for a median time of six years to show a significant advantage.[4] Fibrates such as fenofibrate have little effect on ischaemic heart disease, unless dyslipidaemia (increased triglycerides, decreased high-density lipoprotein (HDL)) and type 2 diabetes are present.[5] Torcetrapib, a drug that raises HDL, was associated with an increased rate of cardiovascular morbidity and mortality.

PCSK9 inhibitory antibodies

Studies of uncommon mutations, such as the LDL-receptor mutations in familial hypercholesterolaemia, have led to important therapeutic advances in the study of lipids and cardiovascular disease. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme involved in the regulation of LDL receptors and LDL cholesterol. By tagging LDL receptors for destruction in the liver, PCSK9 increases concentrations of LDL cholesterol.[6] Plasma PCSK9 concentrations are raised by statins and this could attenuate the effect of these drugs.

Research has focused on PCSK9 as a therapeutic target because blocking its action could reduce LDL cholesterol. The first candidates for therapies were humanised monoclonal antibodies. Currently alirocumab, evolocumab and bococizumab are in commercial development. These are all given by subcutaneous injection and reach a maximal effect 5–7 days after the dose, which lasts for about two weeks.

Phase I trials started in 2012, and showed large reductions in LDL cholesterol. The antibodies were well tolerated, including in patients intolerant of statins. In addition to the effect on LDL cholesterol, PCSK9 inhibition also reduces lipoprotein(a) and has favourable effects on other lipoproteins such as triglycerides, HDL and Apo B.[7] Lipoprotein(a) is a recognised risk factor for atherosclerotic disease and, to date, has not been shown to respond to any conventional therapies.

Clinical studies

One of the first studies of PCSK9 antibody therapies was the RUTHERFORD study. This involved 167 very high-risk patients with heterozygous familial hypercholesterolaemia, treated with evolocumab every four weeks for 12 weeks. These patients were on stable lipid-lowering treatment with a statin with or without ezetemibe. The highest dose of evolocumab resulted in a drop in LDL cholesterol from 3.8 to 1.7 mmol/L (55%, p<0.001 vs placebo).[8]

The phase II OSLER-1 and phase III OSLER-2 studies were two open-label trials of evolocumab in combination with standard therapy. They involved more than 4000 patients for a median of 11.1 months. In patients treated with evolocumab, there was a fall in median LDL-cholesterol concentration from 3.1 mmol/L to 1.24 mmol/L (61%) with little change seen in the control group. Although the study design only allowed cardiovascular events to be analysed as an exploratory analysis, the event rate was 0.95% in the study group, compared with 2.18% in the control group (relative risk reduction 56%, p=0.003).[9]

The ODYSSEY phase III double-blind trial of alirocumab versus placebo involved 2341 patients at very high risk. Following injections every two weeks there was lowering of LDL cholesterol after 24 weeks. Major cardiovascular events were lower in the alirocumab group compared with controls (1.7% vs 3.3%, p=0.02). Lipoprotein(a) was also observed to fall by 26%.[10]

Adverse effects

Arthralgia, headache, limb pain and fatigue were more frequent in the OSLER studies of evolocumab than in controls, but liver function and creatine kinase were unchanged. Injection site reactions led to six patients (0.2%) stopping treatment. Neurocognitive changes were more common with evolocumab, but were infrequent (0.9%, compared with 0.3% in the placebo group) and were not related to the concentration of LDL cholesterol.[9] A dedicated neurocognitive substudy of evolocumab is under way to give a more definitive assessment. The occurrence of adverse effects may have been confounded by the open-label method of the study, as patients treated with evolocumab were examined more frequently than controls. Evolocumab-binding antibodies were found in 0.3% of treatment and control patients, and were transient on repeat testing. No neutralising antibodies were observed.

In the ODYSSEY trial overall adverse event rates were similar in the alirocumab and placebo groups. Discontinuation due to adverse events was 7.2% in the alirocumab group and 5.8% in the control group. Myalgia was more frequent with alirocumab than with placebo (5.4% vs 2.9%, p=0.006). Other adverse events included injection site reactions, neurocognitive events related mainly to memory, ophthalmologic events, and changes in transaminase and creatine kinase concentrations. The rate of diabetes development was not significantly different between groups.[10]

Therapeutic use

To date, studies of anti-PCSK9 antibodies have examined the lowering of LDL cholesterol, with cardiovascular outcomes being analysed post hoc based on a relatively small number of events. Much larger trials are in progress, which should determine cardiovascular outcomes and less common adverse effects. The FOURIER study of evolocumab involves 27 500 high-risk patients with cardiovascular disease on background statin therapy. Similar trials of alirocumab and bococizumab are in progress.

Alirocumab was approved by the Food and Drug Administration in July 2015 for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolaemia or patients with clinical atherosclerotic cardiovascular disease. Alirocumab is available as a 75 mg/mL pre-filled pen or syringe and is given every two weeks by subcutaneous injection at a dose of 75–150 mg.[11] Shortly afterwards, evolocumab was approved for a similar group of patients. The recommended dose is 140 mg two-weekly or 420 mg once monthly.

Evolocumab is available in a 140 mg/mL single-use prefilled syringe or autoinjector.[12] The monthly dose of evolocumab is more than double the dose of two-weekly injections because the drug has non-linear pharmacokinetics. Its plasma concentrations do not increase in proportion to the administered dose.[13]

Evolocumab has been recently approved in Australia for use in combination with diet and exercise in adults with primary heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease in combination with a statin, or in combination with other lipid-lowering therapies in patients who are statin-intolerant. It is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia, in combination with other lipid-lowering therapies.[14,15]

These new drugs for lowering LDL cholesterol may become a valuable addition to, or a substitute

for, current lipid-lowering therapies. Until the results from large phase III trials are able to clearly delineate harms and benefits, their role is likely to be restricted to patients with a high cardiovascular risk who do not reach targets for LDL cholesterol with oral therapy.

These trials may also uncover rare adverse effects. Hyperlipidaemia is an asymptomatic condition, and minor adverse effects may lead to discontinuation. The need for subcutaneous injection may also make patients reluctant to use the antibodies, and some patients may need to have their doses administered by health professionals. Biological drugs are expensive and cost is initially likely to be a barrier to their use.

Conclusion

PCSK9 inhibitory antibody therapies target a novel pathway in LDL-cholesterol metabolism, and early phase I and II trials show highly promising results. Results of large-scale and longer term phase III trials are awaited and these will yield better information about efficacy and adverse effects. Until the results of these trials are known, the use of antibodies is likely to be restricted to high-risk patients who have inadequate responses to, or are intolerant of, statins.

Conflicts of interest: none declared

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Non-culture methods for detecting infection

SUMMARY

Culture-independent diagnostic techniques are increasingly used in clinical laboratories. They have improved turnaround times and are generally more sensitive than culture.

Their relative ease of use may increase the numbers of patients being tested.

These tests allow detection of organisms that are currently difficult or impossible to culture.

The main non-culture methods are immunoassays, which detect antibody or microbial antigen, and nucleic acid amplification testing, which detects microbial RNA or DNA.

For some infections, culture may need to be combined with these tests to determine antibiotic susceptibility.

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Key words
immunoassay, infection, microscopy, polymerase chain reaction, serology

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Introduction

Traditional methods for diagnosing infection have relied largely on clinical microbiology laboratories selecting, isolating and then identifying pathogenic organisms via culture. This can be very time consuming. For some fastidious or slow-growing organisms, the delay to definitive microbiological diagnosis can stretch to weeks, while some organisms cannot be cultured at all. Other drawbacks with culture methods include problems with sensitivity, cost (resource intensive) and potential safety concerns with pathogenic organisms such as *Mycobacterium tuberculosis* or *Coxiella burnetii* (the causative organism of Q fever).

Non-culture-based diagnostic methods (see Table) can have significant advantages over traditional culture methods. For example, nucleic acid amplification testing has drastically reduced turnaround times for many routine diagnostic tests and enabled high throughput testing for multiple organisms, many of which were previously very difficult to diagnose. However, rapid changes in this area make it difficult for practitioners to keep abreast of available methods.

Microscopy

Light microscopy is the oldest non-culture-based diagnostic method in microbiology. Its use can be enhanced using various staining techniques. For example, calcofluor white is used to detect fungal hyphae of dermatophytes that may take up to three weeks to culture. Despite being challenged by recent advances in molecular techniques, microscopy remains a central tool in laboratories. It is relatively cheap and results can be generated within minutes of receiving a sample. Microscopy can also provide important ancillary information about the likelihood of clinical infection, such as the presence, nature and differential of inflammatory cells in a specimen. Microscopy can also be highly specific for some infections, and it is the diagnostic gold standard for detecting parasitic pathogens of the blood (e.g. malaria) or gastrointestinal tract (e.g. giardiasis).

Microscopy has several clear drawbacks. Even for parasitic enteropathogens the sensitivity of a single specimen is poor,[1] and for most common bacterial and fungal infections it is neither sensitive nor specific.

Microscopy is labour intensive and requires highly skilled scientists for optimal diagnostic performance. For most pathogens, microscopy is best used as an adjunct to traditional culture or molecular methods.

Immunoassays

Immunoassays use antibodies to detect either antibody or antigen in a patient's sample (usually serum but also nasopharyngeal swabs, throat swabs and urine).

Testing for antibodies

Antibody immunoassays – usually referred to as serology – have the particular advantage over other non-culture diagnostic methods in their ability to retrospectively diagnose infection long after viable microorganisms or recoverable nucleic acid have disappeared. Other advantages include a high degree of specificity where seroconversion has occurred, fast turnaround times and improved safety compared to culture methods for some organisms (e.g. *Coxiella burnetii*). They can also rule out acute infection based on serological evidence of previous exposure and immunity.

Table **Laboratory tests for commonly encountered infections**

Syndrome and potential cause	Culture	Non-culture methods			Notes
		Serology	Antigen	Nucleic acid amplification testing	
Pharyngitis					
Group A streptococci	✓	●	✓	×	
Epstein-Barr virus and cytomegalovirus	×	✓	×	×	Epstein-Barr virus and cytomegalovirus NAAT is *not* useful in diagnosing acute pharyngitis in the immunocompetent patient.
Ocular infection					
Herpes simplex virus and adenovirus	×	×	×	✓	
Chlamydia trachomatis	×	×	×	✓	
Neisseria gonorrhoeae	✓	×	×	✓	Culture should be performed with NAAT where possible.
Other bacteria e.g. *Bartonella henselae* (granulomatous conjunctivitis)	●	✓	×	●	
Lower respiratory tract infection					
Respiratory viruses	×	●	✓	✓	Antigen testing on sputum is available for some pathogens, but is insensitive. PCR testing is preferred.
Mycoplasma pneumoniae	×	✓	×	✓	
Chlamydia pneumoniae	×	✓	×	✓	
Bordetella pertussis	×	✓	×	✓	
Legionella species	✓	✓	✓	●	Urinary antigen is only available for *Legionella pneumophila* serogroup 1.
Mycobacterium tuberculosis	✓	×	×	●	
Streptococcus pneumoniae	✓	×	✓	●	Pneumococcal urinary antigen is highly specific, but insensitive. It is useful as a rapid adjunct to culture.
Gastritis					
Helicobacter pylori	●	✓	✓	×	Culture is performed from gastric biopsies only. Diagnosis is most commonly made by urea breath test and faecal antigen. When an invasive procedure is performed endoscopy and biopsy urease testing can be used on tissue.
Gastroenteritis					
Bacteria (e.g. *Salmonella*)	✓	●	×	✓	
Parasites	×	●	✓	✓	Serology is available for selected parasitic causes, e.g. *Entamoeba histolytica*
Viruses (e.g. noro, rota, adeno)	×	×	✓	✓	Antigen testing for these pathogens is relatively insensitive. NAAT (PCR) testing is preferred.
Toxigenic *Clostridium difficile*	●	×	✓	✓	

NAAT nucleic acid amplification testing PCR polymerase chain reaction
✓ routine use ● useful in special circumstances × not routine use or unavailable

Table **Laboratory tests for commonly encountered infections (continued)**

Syndrome and potential cause	Culture	Non-culture methods			Notes
		Serology	Antigen	Nucleic acid amplification testing	
Sexually transmitted infection					
Neisseria gonorrhoeae	✓	✗	✗	✓	Culture should be performed with NAAT testing where possible.
Chlamydia trachomatis	✗	✗	✗	✓	
Mycoplasma genitalium	✗	✗	✗	✓	
Trichomonas vaginalis	✗	✗	✗	✓	
Syphilis	✗	✓	✗	✓	NAAT is useful for primary ulcers. Serology is the screening method of choice.
Systemic syndromes					
HIV	✗	✓	✓	●	P24 antigen and NAAT may be useful in early seroconversion – discuss with laboratory.
Ross River virus and Barmah Forest virus	✗	✓	✗	✗	
Rickettsia and Q fever	✗	✓	✗	●	Some laboratories may offer NAAT. But nucleic acid is usually only detectable early in acute infection (first 7 days).
Leptospirosis	●	✓	✗	●	Leptospira can be cultured, but requires direct inoculation from blood into special media.
Viral exanthems					
Parvovirus, measles, mumps, rubella	✗	✓	✗	✓	NAAT is useful for measles (urine and blood), mumps (buccal swab) and rubella (pharyngeal swab).
Fever in the returned traveller					
Malaria	✗	✗	✓	●	
Dengue	✗	✓	✓	✓	
Salmonella typhi	✓	●	✗	✗	Culture is the mainstay of diagnosis. Serology can be of some use in retrospective diagnosis.

NAAT nucleic acid amplification testing PCR polymerase chain reaction
✓ routine use ● useful in special circumstances ✗ not routine use or unavailable

However, immunoassays have a number of disadvantages. Most serological diagnoses rely on the early detection of specific IgM at the time of acute infection, with subsequent seroconversion for specific IgG. There are several pitfalls to this approach. First, during an acute infection serology may be negative as the patient has not yet generated an antibody response. Second, cross reactions with unrelated IgM can occur. Although specific IgM is classically detectable for six weeks to three months following acute infection, it occasionally persists for months to years, or may reappear as an anamnestic response due to another infection. This response is particularly common for IgM against *Toxoplasma gondii*, and when diagnosing the arbovirus infections such as Barmah Forest virus and Ross River virus, and may lead to false positive results and spurious diagnoses. Such errors can be reduced by measuring acute- and convalescent-phase antibody concentrations to look for changes in response to infection. This is the preferred method for definitive serological diagnosis but obviously slows down the time to confirm diagnosis. Seroconversion often takes two weeks or more to occur.

The sensitivity of serological diagnosis can be reduced by a variety of factors, including age and immunodeficiency. Serology is only useful for

diagnosis when there is a clear relationship between antibody concentrations and infection. It is less useful for infections where antibodies may persist but do not provide protection against repeat infection or reactivation, such as herpes simplex, cytomegalovirus and varicella zoster virus, or for infections caused by commensal organisms.

Waning immunity and reinfection commonly occur with *Bordetella pertussis*, which causes whooping cough. The detection of IgG specific for *B. pertussis* toxin greater than 100 IU/mL is suggestive of acute infection, and in older children and adults this may be supported by the presence of IgA to *B. pertussis* toxin.

Infections for which serology remains the mainstay of diagnosis in general practice include syphilis, Epstein-Barr virus, cytomegalovirus, toxoplasmosis, parvovirus, Barmah Forest virus, Ross River virus, dengue, chikungunya and Zika virus. Historically, detection of polyclonal antibody (Monospot test) has been used to diagnose acute glandular fever. It lacks sensitivity and specificity and has generally been replaced by the detection of specific IgM/IgG to Epstein-Barr virus capsid antigen in combination with the absence of IgG to nuclear antigen which develops six weeks to three months after acute infection and remains positive lifelong.

Testing for microbial antigens

An antigen is a component of a pathogen that stimulates an immune response. Immunoassays can measure this in various sample types. Many of these tests are in current use, including urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1. These are useful to identify the causative organism of acute community-acquired pneumonia, and the group A streptococcal antigen test of throat swabs for bacterial pharyngitis. Other examples of useful antigen assays include cryptococcal antigen detection in serum and cerebrospinal fluid in both immunocompetent and immunocompromised patients, and galactomannan antigen which is a surrogate marker for invasive aspergillosis, usually in immunocompromised individuals.

Antigen testing can provide rapid results – the *S. pneumoniae* antigen test can be completed within 15 minutes. Many of these tests have very good specificity. For example, a positive group A streptococcal antigen from a throat swab can allow targeted treatment if indicated and obviate the need for culture. Unfortunately, these tests often lack sensitivity in comparison to traditional culture methods and particularly compared to nucleic acid amplification tests. Their usefulness therefore often lies in enabling rapid diagnosis, rather than excluding clinical infection.

Combined immunoassay tests

The drawbacks of using antigen or antibody assays in isolation can be overcome by combining them. Assays that include both antigen and antibody, such as dengue virus NS1 antigen with IgM/IgG, or HIV antigen/antibody screening testing, offer reduced diagnostic window periods and enhanced sensitivity and specificity. Dengue NS1 antigen detection (Fig.) in particular has allowed rapid confirmation of dengue with the ability to initiate public health interventions earlier. Its sensitivity equates to that of a polymerase chain reaction (PCR) test for dengue in the first week of illness.

Nucleic acid amplification testing

Nucleic acid amplification testing involves the detection of pathogen-specific DNA or RNA sequences in patient samples. There are a number of different methods – PCR is one type. Compared to traditional methods, nucleic acid amplification testing offers improved turnaround times and markedly enhanced sensitivity. These techniques are easily adapted to high-throughput testing and can allow multiple pathogen identification within a single test. Nucleic acid amplification testing is currently revolutionising areas where traditional microbiological methods have been complex, costly and time consuming, such as the diagnosis of faecal pathogens.

However, nucleic acid amplification testing is not without its challenges. Loss or changes to the target nucleic acid sequence through mutation can lead to false negative results. Furthermore, because of their extreme sensitivity, contamination can lead to false positives. While strict quality-control measures reduce this risk, nucleic acid amplification testing is not endorsed for screening in critical diagnoses such as HIV.

A positive result reflects the presence of nucleic acid only, not viable organisms. Failure to recognise this can lead to pitfalls in interpretation of results. For example, when infection has resolved (with or without treatment), nucleic acid may persist. Re-testing at an early interval can lead to positive results and false assumptions about reinfection or failure of therapy. For this reason if re-testing for *Chlamydia trachomatis* is required, it is recommended at least three weeks after initial diagnosis. The same applies to other sexually transmitted infections such as *Neisseria gonorrhoeae* and *Trichomonas vaginalis*.

Problems with assay specificity can potentially lead to false positives. Early nucleic acid amplification tests for *N. gonorrhoeae* resulted in significant rates of false positives due to cross reactions with commensal *Neisseria* species.[2] Most testing platforms include both *C. trachomatis* and *N. gonorrhoeae* in multiplex assays. Laboratories report both results despite the generally lower prevalence of *N. gonorrhoeae*. To reduce false

positive results, laboratories invariably confirm initial positive *N. gonorrhoeae* results using a second independent assay.[3,4] This increases the positive predictive value of the reported positive result.

For many pathogens, it is important to pair nucleic acid amplification testing with traditional culture methods for additional information regarding antimicrobial susceptibility, microbial virulence and epidemiology. Currently, these cannot be determined by most molecular assays.[5] For example, around 33% of all notified *N. gonorrhoeae* cases were diagnosed by culture, allowing antimicrobial susceptibility to be performed. With the introduction of faecal bacterial enteropathogen testing (*Campylobacter, Salmonella, Shigella*) the same concerns around availability of isolates for typing and susceptibility are surfacing.

Nucleic acid amplification testing has limitations when applied to organisms that potentially form part of the normal human flora (either transiently or permanently). For example, *Clostridium difficile* may be present in the bowel without causing illness. Its detection alone does not necessarily indicate a disease state,[6] and a positive result in the wrong clinical context can lead to inappropriate diagnosis and therapy.

Nucleic acid is generally robust, so amplification testing on blood and other specimens (including skin swabs, urine, genital swabs, throat swabs, nasopharyngeal swabs, tissue aspirates) are usually stable at room temperature for 24 hours. If processing is delayed, samples should be refrigerated at 4° C. Dedicated samples for nucleic acid amplification testing are desirable to reduce the risk of contamination. Swabs in bacterial transport medium (Amies and Stuarts) may be inhibitory for nucleic acid amplification testing. Dry dacron-tipped or flocked swabs are the preferred sample type. Universal swabs suitable for all types of testing will become routinely available, although it is best to liaise with the local pathology laboratory regarding the preferred specimen types.

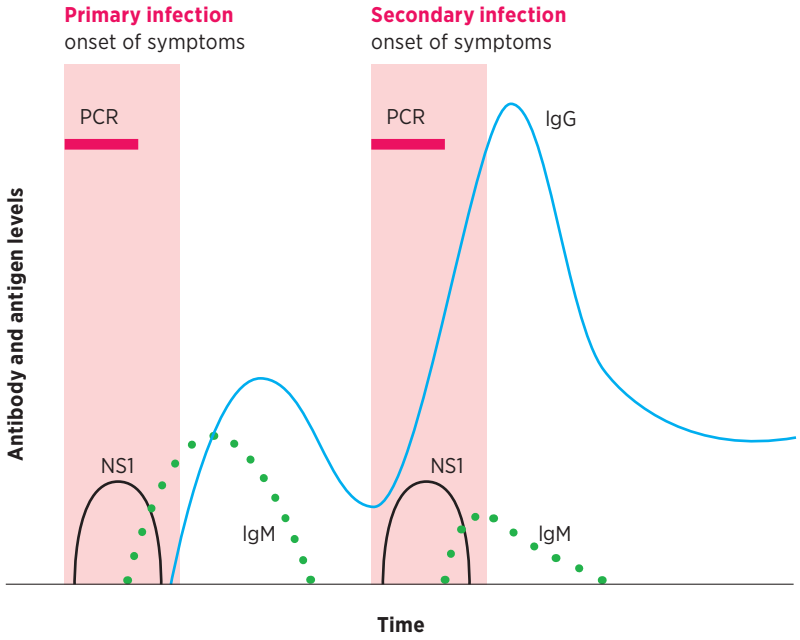
Conclusion

Non-culture-based diagnostic methods, particularly nucleic acid amplification tests, often as multiple PCR tests in a syndromic panel, are revolutionising the modern medical microbiology laboratory. They have enabled or simplified many difficult diagnoses, improved turnaround times and been adapted to allow high-throughput testing. This area will continue to expand and may even replace many traditional culture methods in the future. The optimal use of these diagnostic tests requires recognition of their limitations and judicious use of supporting clinical and laboratory evidence (including culture-based methods). When questions arise regarding the choice or interpretation of non-culture-based diagnostics, it is advisable to liaise with your local laboratory.

Conflict of interest: none declared

Fig. **Immune response with primary and secondary dengue infections**

Dengue NS1 antigen appears first during infection, along with a positive PCR result. Dengue-specific IgM follows, and corresponds with the disappearance of NS1 antigen and a negative PCR result. This is followed by the appearance (primary infection) or rise (secondary infection) of dengue-specific IgG.



PCR polymerase chain reaction

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FEATURE

Medicinal mishap

Paediatric dosing errors with oral prednisolone mixture

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Case 1

The parents of an 18-month-old girl with croup called the Victorian Poisons Information Centre (VPIC) when they realised they had given their daughter three doses of prednisolone mixture during the day instead of one dose. She was also receiving amoxycillin syrup three times daily for an unknown indication.

The child had no symptoms of prednisolone toxicity. The parents were reassured that the child would be fine, although she might experience some mild gastrointestinal upset and be a bit irritable or difficult to settle.

Case 2

The parents of a nine-year-old girl suffering acute asthma phoned VPIC when they realised they had given their daughter three doses of prednisolone mixture daily for the previous two days instead of one dose daily for three days. They realised the error when the 30 mL bottle of mixture ran out. The child had facial flushing and nausea.

Case 3

A GP contacted VPIC for advice about an 18-month-old boy with croup who had been given 2 mL of prednisolone mixture three times a day for two days instead of the prescribed 2 mL daily for three days. His parents had misread the label. The parents described the boy as being restless and difficult to settle to sleep for the last 24 hours. The GP was advised to stop the prednisolone and reassure the parents that the child's symptoms would resolve.

Comment

In all these cases the VPIC was able to advise that the symptoms would resolve with no long-term adverse effects. The cases reflect an increasing number of calls (see Table) involving paediatric dosing errors with oral prednisolone mixture. We believe this is because the dosing directions are misunderstood.

Prednisolone is most commonly prescribed daily, and patients are advised to take it with or after food. If a label is written: 'Give 3 mL daily after food for three days', this could be interpreted as dosing three times a day. This may occur because there are three meals daily, or perhaps because prednisolone is often co-prescribed to children with an oral antibiotic that is given three times a day.

This dosing error does not usually lead to significant clinical consequences. Prednisolone toxicity is low for a single acute overdose or excessive dosing of short duration. However, adverse effects may occur and include gastrointestinal effects (nausea, vomiting, abdominal distension, increased appetite), insomnia, restlessness and increased motor activity.

Recommendations

To reduce dosing errors with prednisolone, we suggest that prescribers explain to parents that this mixture is only given once a day. We also suggest that pharmacists carefully consider the label instructions and reinforce them with verbal counselling. For example: 'Give the child 3 mL once daily in the morning. The dose is best given after breakfast.'

Conflict of interest: none declared

Table **Dosing errors with oral corticosteroids reported to the Victorian Poisons Information Centre**

Year	Calls involving oral corticosteroids	Calls involving paediatric oral prednisolone mixture
2013	130	80 (62%)
2014	147	94 (64%)
2015	157	102 (65%)

FURTHER READING

Lalor D. Medicines labelling. Aust Prescr 2011;34:136-8.
http://dx.doi.org/10.18773/austprescr.2011.072

BOOK REVIEW

Book review

Clinical Pharmacy. 2nd ed.

Gray AH, Wright J, Bruce L, Oakley J
London: Pharmaceutical Press; 2015.
568 pages

The second edition of this book features a revised format from a larger range of contributing authors with a multidisciplinary background. It is pocket-sized with a small font. The book is set out in alphabetical monographs which aim to provide ready information to the pharmacists conducting medication reviews at the bedside or in ambulatory settings. There are different types of monographs including a selection of disease states, drugs, electrolytes, and clinical assessment tools.

This is a UK publication and is designed to complement, rather than replace, existing reference texts such as the British National Formulary. It is therefore not always relevant to Australian practice. For example, a monograph on enoxaparin dosing in unstable angina is present, but not one for dosing in venous thromboembolism. There is, however, a monograph for tinzaparin in venous thromboembolism, a drug not currently marketed in Australia. Similarly, there is an entry for intravenous omeprazole, but no other parenteral proton pump inhibitor. Presumably, these anomalies are intended to complement information readily available in the UK.

The monographs are concise, easy to read, and highly applicable to practice. Entries on electrolytes are very well written and feature reference ranges, signs and symptoms of high and low serum levels and supplementation for each. Other very useful entries include nil-by-mouth management in perioperative patients and pain management.

In short, the monographs are selected to complement references and practice in the UK, and Australian users may be frustrated at missing or irrelevant information. The entries that are relevant, however, are very useful for the practising pharmacist.

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BOOK REVIEW

Book review

Physicochemical Principles of Pharmacy: In Manufacture, Formulation and Clinical Use. 6th ed.

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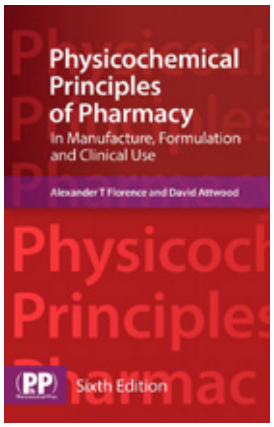

Florence AT, Attwood D
London: Pharmaceutical Press; 2016.
647 pages

This new edition of an established textbook continues to provide comprehensive coverage of physicochemical principles in relation to drug properties, dosage form design, and delivery by various routes to sites of action in the body. As the title indicates, aspects of manufacture, formulation and clinical use have been added to this edition.

The text is highly illustrated throughout and includes key points and appropriate examples, providing clinicians with some easily accessible and relevant information. The clinical points and case studies are of particular use in the chapters on paediatric and geriatric formulations and adverse events.

Greater need for the personalisation of medicines has placed emphasis on the flexibility of dosage forms to deliver tailored dosages. While not a comprehensive guide, the chapter providing insight into dose formulations at different ends of the age spectrum is very useful.

In the chapter on adverse events, the role of formulation and delivery systems highlights the often incorrect assumption that adverse events can only be attributed to the drug. Some examples of adverse events due to excipients, impurities, the influence of dosage forms, materials in delivery devices and even light-induced effects are also included. Although the detection of adverse events is not an easy task, these examples may assist clinicians in asking the right questions to predict or identify adverse effects.

The final chapter contrasts generic medicines with biosimilars. It discusses why biosimilars (macromolecular or protein-based drugs) are often not able to be classified as identical to the brand leader, but 'similar' and not 'equivalent'.

The new focus on applications to clinical practice in this edition has extended its usefulness from pharmacy and pharmaceutical scientist courses to clinicians seeking an understanding of formulations, especially for children and older people, and in identifying the cause of adverse events.

BOOK REVIEW

Book review

Stockley's Drug Interactions. 11th ed.

Edited by Preston CL
London: Pharmaceutical Press; 2016.
1827 pages
(also available online via MedicinesComplete)

The new edition of this extremely valuable resource provides busy clinicians with a concise, in-depth and reliable source of information on drug interactions. This is increasingly important for complex patients with multiple comorbidities and extensive polypharmacy.

Stockley's summarises a broad range of references. Product information is often inherently cautious and incomplete, so this edition reviews these sources (from the UK and USA) alongside extensive primary literature (case reports and clinical papers) and guidance from international regulatory bodies such as the UK Medicines and Healthcare products Regulatory Agency. Occasionally differences in the Australian product information are identified.

Drug–drug, drug–food and a limited number of drug–herb combinations are indexed for both interacting and some non-interacting pairs. The fully referenced monographs (approximately 4500 of them) are clearly laid out with a brief summary of the interaction, clinical evidence, proposed mechanism and importance, and practical management advice. Monographs may also include alternative non-interacting drug options.

Updates to this edition include 350 new monographs (including the oral direct-acting hepatitis C drugs) and revisions to the list of drugs prolonging the QT interval.

The hard copy is limited by its physical size and ongoing currency, but a subscription to the online version, which is updated quarterly, is available and highly recommended. Online access also allows users to plug in unlimited numbers of drugs and search easily for interaction data.

Although mainly a resource used and known by pharmacists, the extensive coverage and ease of use of Stockley's should appeal to all prescribers looking for detailed drug interaction information. Stockley's can be used alongside other valuable drug interaction resources such as the Australian Medicines Handbook and the interaction checkers on MIMS or Lexi-Interact (via Lexicomp).

Australian Prescriber readers receive 20% discount on the printed copy. Simply go to www.pharmpress.com and enter code ap16 at check out, or request a free online two-week trial on MedicinesComplete.

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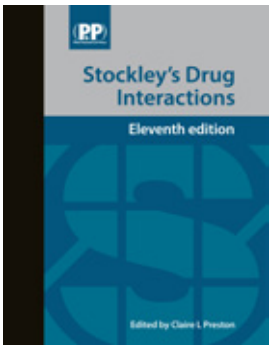

NEW DRUGS

New drugs

Evolocumab

Aust Prescr 2016;39:180–2
http://dx.doi.org/10.18773/austprescr.2016.078

Approved indication: hypercholesterolaemia

Repatha (Amgen)
syringes or pre-filled pens containing 140 mg/mL
Australian Medicines Handbook section 6.5

The enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9) reduces the number of receptors available to bind with low-density lipoprotein (LDL) cholesterol. Inhibitors of this enzyme therefore increase the number of receptors. This results in more LDL cholesterol being removed from the circulation.[1,2] Evolocumab is a PCSK9 inhibitor which has been approved for the treatment of hypercholesterolaemia including familial hypercholesterolaemia.

The drug is a monoclonal antibody that binds to PCSK9. It has to be given by subcutaneous injection and it can be injected every two weeks or once a month. The monthly regimen requires several injections to be given simultaneously.

After injection it takes 3–4 days to reach the peak serum concentration. A steady state is reached after about 12 weeks of treatment. The effective half-life is 11–17 days. As evolocumab is an antibody it is cleared like other proteins. Statins increase its clearance, but no dose adjustments are required. Although evolocumab has not been studied in patients with severe impairment, it can be used by patients with hepatic or renal impairment.

Homozygous familial hypercholesterolaemia

Patients with mutations in their LDL receptors have very high concentrations of LDL cholesterol and therefore an increased risk of cardiovascular disease. The TESLA Part B trial randomised 33 patients to add evolocumab and 17 patients to add placebo to their lipid-lowering therapy. At the start of the trial the mean LDL-cholesterol concentration was 9 mmol/L. After 12 weeks of injecting evolocumab 420 mg monthly this concentration fell by 23.1% while there was a 7.9% increase in the placebo group. There was also a significant reduction in apolipoprotein B.[3]

Heterozygous familial hypercholesterolaemia

The RUTHERFORD-2 trial randomised 331 patients who had heterozygous familial hypercholesterolaemia with LDL-cholesterol concentrations of at least 2.6 mmol/L despite lipid-lowering therapy. Two groups of 110 patients injected evolocumab 420 mg monthly or 140 mg every two weeks while 109 patients injected a placebo. After 12 weeks the concentration of LDL cholesterol had declined from a mean of 4.0 mmol/L to 1.8 mmol/L with monthly injections and from 4.2 mmol/L to 1.7 mmol/L with two-weekly injections. Concentrations were largely unchanged with placebo. Both regimens of evolocumab were also associated with significant reductions in apolipoprotein B and triglycerides.[4]

Primary hypercholesterolaemia

Most patients who require drug treatment for raised cholesterol will be prescribed a statin. In some cases this treatment will not achieve the target concentration for cholesterol. The patients may then be given an additional drug such as ezetimibe. The LAPLACE-2 trial looked at adding evolocumab or ezetimibe to treatment with a statin. This trial used evolocumab 140 mg every two weeks or 420 mg monthly. It also used three different statins at different doses so the 2067 patients were randomised to 24 different treatment groups. At the start of the study the patients had LDL-cholesterol concentration around 2.82 mmol/L. After 12 weeks this had reduced to approximately 1.28 mmol/L in patients taking evolocumab with atorvastatin 10 mg. The combination of evolocumab and atorvastatin 80 mg reduced the concentration to approximately 0.93 mmol/L. A primary outcome was the mean percentage change in LDL cholesterol from baseline for weeks 10 and 12 of the trial. For evolocumab these reductions were around 59–66% with moderate or high doses of statins. These changes were greater than those seen in the ezetimibe groups. Combined with atorvastatin, ezetimibe reduced LDL cholesterol by approximately 17–24%. Evolocumab also reduced concentrations of apolipoprotein B and triglycerides.[5]

The DESCARTES trial investigated treatment with evolocumab over a year. There were 905 patients who had an LDL-cholesterol concentration above 1.94 mmol/L despite lipid-lowering therapy. The patients were allocated to be treated with diet alone,

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

atorvastatin 10 mg, atorvastatin 80 mg or atorvastatin 80 mg plus ezetimibe. Within each of these groups the patients were given evolocumab 420 mg monthly or a placebo. After 52 weeks the mean LDL cholesterol fell from 2.69 mmol/L, across all groups, to 1.32 mmol/L with evolocumab, but was almost unchanged in the placebo groups. The largest percentage change (61.6%) was in the group treated with evolocumab and atorvastatin 10 mg in addition to diet. Treatment with evolocumab was also associated with reductions in apolipoprotein B and triglycerides.[6]

The MENDEL-2 trial assessed 615 patients who were not taking a statin. These patients had LDL-cholesterol concentrations averaging around 3.7 mmol/L. They were randomised to take evolocumab, ezetimibe or placebo. After 12 weeks patients injecting evolocumab every two weeks had reduced their LDL-cholesterol concentration by 57% compared with a 17.8% reduction with ezetimibe. The corresponding figures for monthly treatment were 56.1% and 18.6%. There was little change in the placebo groups.[7]

Evolocumab has also been investigated for patients with statin intolerance in the GAUSS placebo-controlled trials.[8] The GAUSS-2 trial enrolled 307 patients who had been unable to tolerate at least two statins. They were randomised to take daily ezetimibe, evolocumab 140 mg every two weeks, or evolocumab 420 mg monthly. At the start of the trial the average concentration of LDL cholesterol was approximately 5 mmol/L. After 12 weeks this had reduced by 53–56% with evolocumab and 15–18% with ezetimibe.

Safety

At the time of its approval in Australia evolocumab had been taken by 5710 patients in clinical trials. There were eight deaths from cardiovascular causes compared with three in the control group. In the one-year trial, two patients taking evolocumab died. Adverse events led to 2.2% stopping treatment compared with 1% of the control group. Common adverse effects that occurred more frequently with evolocumab included upper respiratory infections, influenza, back pain, myalgia, hypertension and erythema at the injection sites. Elevations of creatine kinase were also more frequent than in the control group.[6]

Injecting an antibody can cause allergic reactions. A small number (0.1%) of patients developed antibodies to evolocumab.

There have been no drug interaction studies. The effects of evolocumab in human pregnancy and lactation are unknown.

Discussion

There is no doubt that evolocumab lowers LDL cholesterol in a range of indications (see summary Table). However, this is a surrogate outcome and the drug's benefits on clinical outcomes are still being studied. There were few deaths in the clinical trials, but the proportion due to cardiovascular causes was greater with evolocumab than in the control groups (0.14% vs 0.10%). A meta-analysis of the PCSK9 inhibitors suggests that the cardiovascular mortality rate for the class is 0.19% compared with 0.33% without treatment. However, this reduction in cardiovascular mortality is not statistically significant.[9]

Patients who completed the clinical trials of evolocumab could participate in the OSLER extension studies. In these open-label studies 2976 patients took evolocumab and 1489 took standard therapy. After a median follow-up of 11.1 months, 29 patients taking evolocumab had a cardiovascular event compared with 31 in the control group. The difference in event rates (0.95% vs 2.18%) was statistically significant.[10]

The long-term safety of the class also needs further study. This will include monitoring for any effects on glucose metabolism and neurocognitive function. Over a one-year period neurocognitive events were reported in 0.6% of the patients taking evolocumab and 0.2% of the control group.

Table **Examples of trials of evolocumab efficacy**

Indication	Trial	Duration	Percentage reduction in LDL cholesterol at end of study	
			Evolocumab 420 mg monthly	Evolocumab 140 mg every two weeks
Homozygous familial hypercholesterolaemia	TESLA Part B[3]	12 weeks	23%	–
Heterozygous familial hypercholesterolaemia	RUTHERFORD-2[4]	12 weeks	56%	61%
Hypercholesterolaemia in patients using statins	LAPLACE-2[5]	12 weeks	52–59%	59–66%
Patients intolerant to at least two statins	GAUSS-2[9]	12 weeks	53%	56%

NEW DRUGS

When drug treatment is indicated for hypercholesterolaemia there is much more evidence to support treatment with statins. Injections of evolocumab will therefore be reserved for patients who cannot tolerate statins and when LDL-cholesterol concentrations remain significantly elevated despite treatment.[2]

T manufacturer provided the AusPAR

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The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov), the European Medicines Agency (www.ema.europa.eu) and the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm).

Idarucizumab

Aust Prescr 2016;39:183
http://dx.doi.org/10.18773/austprescr.2016.076

Approved indication: dabigatran reversal

Praxbind (Boehringer Ingelheim)
vials containing 2.5 g/50 mL
Australian Medicines Handbook section 7.4

A limiting factor in the use of the newer oral anticoagulants is that, unlike warfarin, there have been no antidotes. Reversal of anticoagulation may be required if the patient develops severe bleeding or requires emergency surgery. Idarucizumab has been developed to reverse the effect of dabigatran, a direct thrombin inhibitor.

The development of idarucizumab involved genetically engineering a humanised monoclonal antibody fragment. The affinity of this antibody for dabigatran is greater than the affinity of dabigatran for thrombin.

To test the concept that idarucizumab would reverse the effect of dabigatran a trial was carried out in 47 healthy men. They were given dabigatran for a few days then, within two hours of the last dose, they were infused with idarucizumab or a placebo. Idarucizumab immediately bound to dabigatran so unbound dabigatran concentrations fell quickly. After idarucizumab doses of 2 g or more, they remained close to the lower limit of quantification during 72 hours of observation.[1] There was a rapid improvement in clotting studies such as thrombin time and activated partial thromboplastin time.

Idarucizumab is rapidly cleared. It is probably catabolised with 32% of the dose being excreted in the urine within six hours of infusion. There may be a transient proteinuria. Clearance is reduced in patients with renal impairment, but no dose adjustment is currently recommended by the manufacturer.

A prospective cohort study is investigating patients taking dabigatran who present with life-threatening bleeding or require surgery that cannot be delayed. The dose of idarucizumab used in this trial is two infusions of 2.5 g given no more than 15 minutes apart. Interim results on 51 patients with bleeding and 39 surgical patients have been published.[2] Most of these patients had atrial fibrillation and had been using dabigatran for stroke prevention. They had a median age of 76.5 years.

Compared to clotting tests taken before the first infusion, there was a complete reversal of the anticoagulant effect in almost all patients before the second infusion was given. The concentrations of unbound dabigatran had fallen to levels that would have little effect on coagulation. At 24 hours after the second infusion, the thrombin time was within the upper limit of the normal range in 90% of the patients with bleeding and 81% of the surgical patients. Normal haemostasis was reported in 33 of the 36 patients (92%) who had urgent surgery.[2]

The interim analysis reported nine deaths in each group of patients. Most of these were related to the presenting problem, particularly bleeding. Reversing the anticoagulant effect was associated with thrombosis in five patients.[2] While it is difficult to attribute adverse effects to idarucizumab, problems such as fever, rash and pruritus may be signs of hypersensitivity.

The idarucizumab solution contains a large amount of sorbitol and sodium. Patients with hereditary fructose intolerance are potentially at risk of adverse reactions from the sorbitol.

In some patients the anticoagulant effects of dabigatran may re-emerge up to 24 hours after an infusion of idarucizumab. Repeating the treatment may need to be considered. If the anticoagulant effect has been completely reversed, the patient will be at risk of thrombosis. A decision has to be made when to resume anticoagulant therapy. If dabigatran is still indicated, it can be resumed 24 hours after idarucizumab.

Although idarucizumab effectively reverses the anticoagulant effect of dabigatran, patients still require other supportive treatments. In the interim analysis the mortality rate was 20% and, without a control group, it is difficult to know if this was a significant improvement on supportive care. Interestingly, 24% of the patients presented with thrombin times that were within the normal range at baseline, so they would not have derived much benefit from idarucizumab. As these patients were excluded from the analysis, the assessment of effectiveness was limited.[2] More data will be required to define the role of idarucizumab especially in patient populations, such as those with renal impairment. As the drug is specific for dabigatran it should not be used to reverse the effects of other anticoagulants.

T T manufacturer provided additional useful information

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The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov) and the website of the European Medicines Agency (www.ema.europa.eu).

NEW DRUGS

Dust mite allergen extract

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http://dx.doi.org/10.18773/austprescr.2016.077
First published 22 August 2016

Approved indication: allergic rhinitis

Actair (Stallergenes)
sublingual tablets 100 IR and 300 IR

These tablets contain allergen extracts of European house dust mites and American house dust mites in a 1:1 mixture. Tablets come in two concentrations: 100 or 300 index of reactivity (IR). The IR is a defined unit relating to allergenicity of the extract in a skin-prick test.

The exact mechanism of how this product reduces the symptoms of allergic rhinitis caused by dust mites is unclear. It increases the IgG antibody to dust mites which is then thought to compete with specific IgE antibody that mediates the allergy. The extract is also thought to modify the T-cell response to dust mites.

In a trial of 509 adults with confirmed moderate to severe dust mite allergic rhinitis, two doses of the allergen extract (300 IR or 500 IR once daily) were compared to placebo. People with other clinically relevant sensitisations (e.g. hay fever, cat or dog allergy) and those with asthma were excluded. Participants received treatment for one year and were then followed for a further year. During the first year (at 8–12 months), mean scores of rhinitis symptoms were lower with the allergen extract than with placebo (see Table).[1] This difference between groups was maintained during the follow-up year. More patients in the 500 IR and 300 IR groups reported a marked improvement in their symptoms than in the placebo group. However, there was no difference in the use of oral and ophthalmic antihistamines and nasal corticosteroids between the groups after one or two years.

After a year of treatment, serum sampling confirmed that dust mite-specific IgG_4 had increased 2–3-fold with the active treatments. These concentrations were maintained for the one-year follow-up period. IgG_4 concentrations were unchanged with placebo and there were no relevant changes in IgE in any of the groups. The mean diameter of wheals after a skin-prick test with dust mite extract was reduced with the active treatments compared to placebo.

In a similarly designed but unpublished Japanese trial which enrolled adults and adolescents, symptom scores were also lower with a 300 IR sublingual dose compared to placebo. The proportion of patients reporting a marked improvement at the end of treatment was 22.2% with the active treatment and 9.7% with the placebo.

The most commonly reported adverse events with the allergen extract were in the mouth. Over half of people in the active treatment groups reported oral symptoms including oral pruritus and swelling of the mouth, tongue or lips. Throat irritation was also common (21–25%) and some patients reported pharyngeal oedema (4–7%).[1]

More people receiving the 500 IR tablet prematurely discontinued because of an adverse event than those receiving the 300 IR tablet or placebo (11.8% vs 10% vs 2.9%). This was mainly due to pharyngeal oedema, dyspepsia, nausea and mouth

Table **Efficacy of dust mite allergen extract compared to placebo for allergic rhinitis** [1]

Outcome	Daily treatment		
	300 IR tablet	500 IR tablet	Placebo
Average adjusted symptom score‡ (range 0–12):			
- after 1 year	3.18	3.09	3.87
- after 2 years	3.04	2.97	3.67
Proportion of people reporting marked improvement after 1 year	36.9%	33.1%	18%
Average rescue medication score§ (range 0–3):			
- after 1 year	0.33	0.23	0.32
- after 2 years	0.22	0.19	0.28

‡ based on the occurrence and severity of sneezing, rhinorrhoea, nasal pruritus, nasal congestion and ocular itching recorded by participants each day
§ based on the daily self-reported use of oral and ophthalmic antihistamines and nasal corticosteroids

oedema.[1] Eosinophilic oesophagitis has occurred with this type of sublingual immunotherapy. Treatment should be interrupted if persistent or severe dysphagia or chest pain occurs, and only restarted after consultation with a doctor.

This product is contraindicated in people with severe, uncontrolled asthma, an immune deficiency or autoimmune disorder, cancer or oral inflammation such as oral lichen planus, ulcerations or mycosis.

Although initiation of treatment is not recommended during pregnancy or lactation, there was no evidence of fetal harm in animal studies and it is not expected to have effects on breastfed babies.

Tablets should be taken on an empty stomach. They are placed under the tongue and then swallowed after they have completely disintegrated. Treatment should start with one 100 IR tablet on the first day, two 100 IR tablets on the second day and one 300 IR every day after that (maintenance dose). The first tablet should be given under medical supervision and the patient should be monitored for 30 minutes.

This product seems to reduce symptoms in patients with allergic rhinitis but did not decrease their use of symptomatic treatments. The most common treatment-related effects were reactions in the mouth and throat, including irritation and swelling. Some patients developed more serious allergic reactions so administration of the first dose should be supervised.

T T manufacturer provided additional useful information

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The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

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ANSWERS TO SELF-TEST QUESTIONS

1 True 2 True
3 False 4 True

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