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Telephone: + 94 11 2695300 Ext 315 and
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Telephones + 94 11 2320356-9
Fax: + 94 11 447118
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Cover Picture

LOUIS HÉBERT, FIRST CANADIAN APOTHECARY (1605 A.D.)

Parisian Apothecary Louis Hébert in 1605 helped Champlain establish Canada's first settlement at Port Royal (Nova Scotia); cared for its sick, and cultivated drug plants. Later, at Quebec, he established the first farm in Canada

One of a series: A History of Pharmacy in Pictures, presented by Parke, Davis & Company.
George A. Bender, Director © 1955 Robert A. Thom, Artist

The Sri Lanka Prescriber

Prescribing in acute kidney injury

Acute kidney injury is a sudden, but usually reversible decline in the glomerular filtration rate (GFR). It is a dynamic state in which the patient follows a trajectory through injury towards organ dysfunction, followed, in most cases, by recovery.

Definition

AKI is defined and stratified according to the Kidney Disease Improvement Global Outcomes (KDIGO) criteria using serum creatinine- or urine output-based criteria. Accordingly, AKI is defined as a rise in serum creatinine of 0.3mg/dl or an increase of 50% from baseline or as a reduction in urine output to <0.5ml/kg/hour for more than 6 hours. AKI can be staged further depending on its' severity. (Table 1)

Table 1: Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

Risk factors for AKI

While any patient may manifest AKI in the presence of a severe insult, certain characteristics make patients more vulnerable. Such patients need special consideration for preventing and identifying AKI.

Risk factors for AKI include:

- Dehydration or volume depletion
- Advanced age
- Female gender
- Black race
- Chronic Kidney Disease
- Chronic diseases (heart, lung, liver)
- Diabetes mellitus
- Cancer
- Anaemia

Identification of AKI

Early detection of AKI in a hospitalised patient is essential for prevention of further worsening. The monitoring for AKI by serial assessments of urine output and serum creatinine is advisable for those at risk. The frequency of monitoring may be determined by the severity or acuity of illness and other risk factors such as the administration of potentially nephrotoxic drugs.

It is worth noting that baseline serum creatinine can be misleading as an indicator of kidney function and is unreliable at extremes of muscle mass. As for example a serum creatinine within the "normal" range in a malnourished and wasted patient may give the false impression of good kidney function. Similarly, in patients with low or low-normal creatinine failure to note a *rise* in serum creatinine may preclude detection of AKI when serum creatinine is still within the normal reference range for the laboratory. Importantly, the degree of renal injury is related to the proportional change in serum creatinine rather than the absolute change. A rise in serum creatinine from 0.6mg/dl to 0.9mg/dl represents a larger loss of GFR (~50%) than arise from 3.0mg/dl to 3.3mg/dl (~10%). In patients who are on potentially nephrotoxic agents, it is important to be aware of this, to ensure AKI is detected early and these agents are discontinued in a timely manner.

Principles of prescribing in AKI

Panel 1
AKI is defined as a rise in serum creatinine of 0.3mg/dl or an increase of 50% from baseline or as a reduction in urine output to <0.5ml/kg/hour for more than 6 hours.

- A patient with AKI can have a serum creatinine within the normal range
- Proportional rather than absolute changes in serum creatinine indicate the severity of acute kidney injury

Because AKI is a dynamic status the strategies towards prescription will differ across the course of illness. Daily review of the drug chart and serum creatinine results is advisable to ensure that the treatment is as *non-nephrotoxic* as possible and is being prescribed at the appropriate dose.

1. Minimising nephrotoxicity

Nephrotoxic drugs can either be the primary cause of AKI or may secondarily worsen or contribute to AKI brought on by other conditions. Many causes of AKI in the hospitalised setting are multifactorial. It is reasonable to avoid prescription of drugs with renal toxicity in patients as risk of AKI, such as patients with established CKD. Some commonly prescribed agents which one should be wary of include non-steroidal anti-inflammatory agents, and anit-infective agents such as aminoglycosides, amphotericin B, and colistin. In all cases consideration of risks and benefit should be made before selecting the appropriate treatment.

Angiotensin converting enzyme inhibitors and Angiotensin-receptor blockers may aggravate the manifestation of AKI in hypovolemic or hypotensive patient by abrogating the neurohormonal responses which maintain glomerular filtration in these states. However, routine de-prescription of these agents has been recently questioned. It has been hypothesized that the vasodilatation mediated at the efferent arteriole allows a better perfusion of the peritubular capillaries by reducing the filtration fraction, and renders the tubules less vulnerable to ischaemic injury. However, there are still practical concerns about hyperkalaemia which can become challenging to manage medically if patients are kept on these agents, particularly in the absence of definite proof of renoprotection in AKI.

Eventually each prescription is an assessment of risk versus harm. For example, in a critically ill septic patient, one may be keen to be treat infection aggressively at the outset. Sepsis *per se* can cause AKI and controlling sepsis well and early is one strategy to reduce risk and aid early resolution of AKI. Having considered the pros and cons in patients at risk, if a potentially nephrotoxic agent is selected for treatment, strategies must be in place to minimise toxicity. These include using the lowest effective dose, the least nephrotoxic formulation and dosing regimen, minimising the co-prescription of several nephrotoxic agents (eg. vancomycin and gentamicin) and preventive strategies such as pre-hydration when appropriate. (Table 2)

Table 2: Strategies to reduce risk of AKI with drugs with dose-dependent nephrotoxicity

Drug	Reno-protective strategies
Aminoglycosides	Extended dosing intervals Reduce dose according to eGFR Therapeutic drug monitoring Avoidance of combination with drugs which increase toxicity (eg. loop diuretics) Limit duration of course
Vancomycin	Extended dosing intervals Adjustment for eGFR Therapeutic drug

	monitoring Avoidance of combination with drugs which increase toxicity Limit duration of course
Amphotericin	Use of the liposomal formulation Pre-hydration with intravenous crystalloids

2. Minimising systemic toxicity arising from reduced renal clearance

The other important point to consider is that renally cleared drugs can accumulate in AKI and lead to increased toxicity. This is of particular concern for drugs with a narrow therapeutic index. Drug dosing in AKI is mainly adapted from studies done in chronic kidney disease.

Estimating GFR in AKI

One of the greatest challenges in AKI, is determining kidney function. Serum creatinine-based equations which are used to estimate glomerular filtration rate (eGFR) such the Cockcroft-Gault equation, rely on the patient being in a steady state. As patients in acute kidney injury are not in a state of equilibrium, their serum creatinine is an unreliable indicator of kidney function. Unfortunately, there is no direct measure of eGFR in AKI. The rate at which serum creatinine values change and the trends in urine volume can be used to make a reasonable judgement. In general, a patient with declining kidney function has a worse eGFR than which would be estimated by the above-mentioned equations used in CKD, and the opposite is true as the patient begins to recover.

Other factors worth considering are that pharmacokinetics may vary in a critically ill patient leading to unpredictable drug levels. Unfortunately, there are large gaps in knowledge of drug metabolism and disposition in patients with MSOF/MODS as well as AKI, and thus patients may be at significant risk for underdosing as well as overdosing.

Panel 2
Estimating GFR in AKI

- Serum creatinine-based equations require the patient to be in the steady state.
- In the worsening phase of AKI eGFR derived by these equations *over*estimate kidney function.
- In the recovery phase these equations *under*estimate kidney function
- The trends of serum creatinine and urine output will give you a sense of the speed at which the patient's condition is changing.
- As the eGFR changes over the course of the illness drug doses may need to change as well.

Dosing in AKI

It is good practice to refer a renal formulary to decide on drug dosing in patients with renal impairment. Some drugs may need to be withheld in AKI (eg metformin) while others may require adjustment in dosing. Dosing adjustments can take the form of a reduction in dose, increase in dose interval, or both. Dose reductions lower peak concentrations but maintained trough levels, and are preferred when constant exposure required, e.g. many antibiotics. Increases in dose intervals maintain peak concentrations but allow lower trough levels. Typically, this approach is used in aminoglycoside dosing, high peak concentrations deliver bactericidal activity while low troughs avoid toxicity. Loading doses do not usually need adjustment in AKI.

Renal replacement therapy (RRT)

RRT in AKI (RRT-AKI) may be delivered as intermittent haemodialysis, continuous renal replacement therapies, a hybrid of these two modalities, or as acute peritoneal dialysis. Drug dosing in these patients has additional challenges. The amount of drug removed by

extracorporeal therapies will be determined by the molecular weight and charge of the substrate of interest and by blood flow rate, dialysate flow rate, dialyser size and membrane, clearance modality (haemodialysis vs hemofiltration vs hemodiafiltration) and dialysis duration. Some renal clearance by native kidneys can be expected if the patient continues to pass urine. Further complicating matters, clearance of other uremic solutes can have unrecognised effects on the non-renal clearance of drugs. Therapeutic drug monitoring, including measurement of the dialyzer clearance, is advisable for drugs with a narrow therapeutic range, such as, aminoglycosides and vancomycin. Serum creatinine is not useful to gauge kidney function in patients on dialysis, and the eGFR is generally considered to be <10ml/min. Dosing should be determined by reference of a renal formulary.

For intermittent RRT (eg. intermittent HD), it is best to administer drugs after HD, wherever possible, and to consider a supplemental dose after HD based on the expected clearance during dialysis, if not. Much of the, albeit limited, data on prescribing in RRT comes from the 1990s. Since then, dialyser membranes have evolved, and low flux membranes have been replaced by intermediate or high flux membranes in most settings. Supplemental doses may need to be increased by about 50% of what has been recommended for low-flux membranes in patients receiving dialysis via high flux membranes.

Panel 3
Patients on RRT
Assume patients have an eGFR of <10ml/min
Drugs may be cleared on dialysis; therefore dose *post*-dialysis whenever possible.
Use a formulary to guide your dosing

Identifying recovery

The first indication of renal recovery is an improvement in urine output. Often this precedes a reduction in serum creatinine. As described above, serum creatinebased equation will underestimate renal function in this stage. This is of special relevance for dosing of antibiotics, which will need to be adjusted according to trends, to avoid underdosing.

Conclusions

AKI is a dynamic process which requires frequent review of the patient's clinical and laboratory parameters to understand and respond to the patient's trajectory. Vigilance is necessary to detect AKI early in those at risk. Decisions to use potentially nephrotoxic. It is wise to refer to a renal formulary in patients with renal impairment to decide on appropriate dosing of drugs.

Further Reading

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Dr Dilushi Wijayaratne MBBS MD MRCP
Specialist Nephrologist & Senior Lecturer in Clinical medicine
Department of Clinical Medicine
University of Colombo
dilushi.w@clinmed.cmb.ac.lk

Safeguarding medical schools from undue influence of the pharmaceutical industry

Summary

In this article, we discuss the current context in which the pharmaceutical industry influences medical schools and undergraduate medical education, and the new challenges posed due to the financial crisis in the country. To face this situation, we propose the following concepts and basic guidelines for the local medical schools on interacting with the pharmaceutical industry. It is hoped that this article will provide a platform to discuss this crucial issue further and develop more specific guidelines and regulations covering broader and specific areas.

1. Background

1.1 Global level

The influence of the pharmaceutical industry on undergraduate medical education has been assessed around the world, both in developed and developing regions. According to a study conducted in Germany, medical students encounter pharmaceutical promotion early in their training, and there is limited awareness of the associated conflicts of interest among them [1]. This lack of awareness is a pressing issue that needs immediate attention. The interactions between clinical students and pharmaceutical companies have increased between 2012 and 2016 in Japanese medical schools [2]. In a study covering Finish medical schools, most students did not favour pharmaceutical promotion and felt that it would negatively affect their future prescribing behaviour. The awareness of these students about such influence increased over the course of studies [3]. In a study conducted in France in 2019, it was noted that exposure of medical students to pharmaceutical promotion and incentives remained considerable and started early during medical training [4]. In a survey among the US medical schools in 2005, only 10 out of 120 schools had a policy regarding relationships between medical students and pharmaceutical company representatives [5].

In the late 20th century and early 21st century, physicians and medical students across the globe developed groups focusing on educating health professionals about the promotion of medicines and medical devices. 'No Free Lunch,' was one such group founded in 2000 by internist Bob Goodman in the United States. It had a membership of 500 physicians and other healthcare professionals who signed an agreement not to meet medical representatives [1]. Some student associations have been at the forefront of developing policies governing corporate sponsorship for their own organisations [2]. A review has reported that a substantial proportion of students (13%–69%) believed that gifts from the industry influenced prescribing and certain attitudes appeared to change during medical school; For example, clinical students (53%–71%) were more likely than preclinical students (29%–62%) to report that promotional information helps them to study about new medicines [3]. The Association of American Medical Colleges recommended that medical schools and academic health centers develop policies to manage interactions between academic medicine and the pharmaceutical industry [4]. At a global level, it has been observed that residents who graduated from schools with restrictive policies are less likely to accept industry gifts or industry-sponsored meals, speak with a marketing representative about drug products, attend industry-sponsored lecture, or prefer brand-name medications than residents who graduated from schools with less restrictive policies [5]. As per a study conducted in Pakistan medical students, more than one-third of the students were comfortable receiving gifts from drug companies. Overall, the results of this study offer an interesting comparison between the students of a private medical school and a public medical school; private medical school students exhibited a greater degree of mistrust towards drug information provided by pharmaceutical companies compared to public medical school students

($p = 0.040$). Furthermore, when asked if there was a need to incorporate guidelines in the undergraduate curriculum with regard to interaction with drug companies, 84.2% of students at private medical schools agreed, compared to 54.9% of public medical school students [6]. The above information shows that the pharmaceutical industry influences medical undergraduates worldwide and that concise policy recommendations and guidelines are necessary to counteract their adverse influences.

1.2 Country level

In Sri Lanka, the influence of the pharmaceutical industry on the healthcare sector and medical schools has been observed at multiple levels. With the current financial crisis, the economic burden on both the health sector and medical education has intensified, opening new space for the pharmaceutical industry to execute its marketing strategies targeting specific groups. In the past, their involvement with medical and paramedical undergraduates was limited. However, in the current context, it was observed that they are trying to extend their influence over the critical needs of medical and paramedical undergraduates. This observation leads us to explore the situation and come up with a comprehensive plan to minimise the negative impact of such influences.

Faculty of Medicine, University of Colombo, has a long history of challenging the pharmaceutical industry over undue financial and other influences from the era of Professor Senaka Bibile. He pioneered the concept of Essential Medicines, which was later adopted by the World Health Organisation and subsequently by many countries worldwide [7]. Later, other academics of the faculty continued strong resistance to the influences of the pharmaceutical industry in many ways, sensitising generations of medical students to this issue. At one time (1990-2015 approx.), the Faculty had a student organisation titled Students Involved in Rational Health Activities (SIRHA) with objectives to counter the adverse industry influence. With this background, the Department of Pharmacology, Faculty of Medicine, University of Colombo, decided to propose these concepts and generic guidelines to address any adverse influence of the pharmaceutical industry on medical schools.

2. Current and future challenges

The current financial crisis has caused a shortage of funds not only for academic conferences but also for the development and maintenance of infrastructure of academic institutions. Therefore, medical institutions have opened up for donations enabling the pharmaceutical industry to link up with them strategically. The absence of guidelines in the medical schools, exposes the students to pharmaceutical industry influences with adverse long term impact. Coming to a consensus among a group of people on this topic is also a challenge.

2.1 Overcoming challenges

It is accepted that medical educators have a duty of care to protect their students from the adverse influences of the pharmaceutical industry [8] Medical schools have a role in ensuring that their students are protected from undue financial influence during their training and are educated about profession-industry relations [9] Policymakers should pay greater attention to medical schools to review policies regulating medical students-industry interactions, receipt of funds, gifts and meals, and participation in academic events [10] Putting in place rules and regulations that regulate ties between physicians/students and the pharmaceutical industry is a mandatory first step. Further, complementary strategies should be implemented within medical schools, highlighting the conflicts of interest issues in medical training [11].

Table 1: Generic Guidelines and suggestions on interacting with the pharmaceutical industry and obtaining sponsorships by the medical school.

Principles underlining the guidelines
1.Develop institutional-level guidelines to avoid adverse influence of the pharmaceutical industry In this process ensure that the long-term educational objectives of the medical school is not affected by the influence of the pharmaceutical industry. 2.Have financing plans in medical school that is independent of funding by pharmaceutical companies. 3.Implement policies and action plans to prevent unethical behaviour and conflicts of interest that could arise during interactions with the pharmaceutical industry. 4.Promote transparency and integrity in educators and researchers by mandating disclosure of conflicts of interest. 5.Discourage the advertisement of any pharmaceutical product, company, or brand within medical school premises. 6.Do not allow pharmaceutical industry personnel within the medical school premises to engage in promotional activities.

Suggestions for way forward

• Improving knowledge and awareness of staff and students of medicine and allied health sciences regarding ethical and professional interactions with the pharmaceutical industry.

• Strengthen the content related to interacting with the pharmaceutical industry in the undergraduate curricula and improve awareness among students on pharmaceutical promotion.

• Establish campaigns against unethical pharmaceutical marketing and promotional activities by students and staff via institutional websites, webinars, discussions, etc. Publicise mottos such as “No free lunch”

• Promote open access and open educational resources to share the most up-to-date information to prevent the need to seek financial or educational support from third parties such as the pharmaceutical industry.

• Establish a monitoring mechanism at an institutional level to safeguard against the influence of the pharmaceutical industry on medical education.

• Establishing a culture of full disclosure of conflicts of interest at medical schools.

• Inculcate the principle that continuing professional education is the responsibility of the individual professional and that he/she should be prepared to pay for it rather than seek funds from the pharmaceutical industry.

• Create awareness that money spent on product promotion by the pharmaceutical industry is recovered in full with profit from the sale of their products. This all adds up to the escalating costs of pharmaceuticals.

Educating medical students about the marketing strategies of pharmaceutical companies is important [12]. As the knowledge and attitudes toward the pharmaceutical industry are formed earlier in student life, professional curricula should address the influences of the industry and sales representatives, including the strategies within medical school [13] Education about marketing practices and adaptation of restrictive policies about the medical profession-industry interaction should increase students' awareness about the appropriateness of such marketing practices and the benefits of restricting industry representatives in the learning environment [14] Medical humanities and ethics modules, courses in communication skills, ward teaching,

pharmacology tutorials, integrated ward classes, etc., are other platforms to discuss this issue [15]. In an interventional study conducted among Nepalese medical students, a nine-hour module held over a four-month period effectively improved respondents' knowledge, skills and attitudes about pharmaceutical promotion [16]. The module has used resources already available in the institution. Similar modules can be considered in other medical and health professional schools in South Asia and other developing countries. Sri Lanka should follow a well-designed programme in all its medical schools to inculcate the necessary knowledge, skills, and attitudes on this subject to students of medicine and paramedical professions.

3. Conclusions

The pharmaceutical industry has strategies to promote its products to medical and paramedical students, and this is an insidious process. It is essential that responsible groups formulate national level guidelines and regulations to counteract the adverse influences and implement them with the help of all stakeholder groups. More emphasis should be given in the medical curriculums to incorporate information on pharmaceutical promotion and steps taken to ensure that students of the professions develop a critical, evidence-based approach towards the numerous products advertised and promoted by the pharma industry.

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Dr. Vipula Bataduwaarachchi
MBBS (Col). MD (Med). MRCP (UK) (Res). HERMES (ERS). Pg Cert Med Edu.
Senior Lecturer and Specialist in Respiratory Medicine, Department of Pharmacology, Faculty of Medicine, University of Colombo.
Email: vipula@pharm.cmb.ac.lk

AND

Professor Chamari Weeraratne
MBBS (Col). MD (Med). FCCP
Professor in Pharmacology and Specialist Physician, Department of Pharmacology, Faculty of Medicine, University of Colombo.
Email: chamariweera@pharm.cmb.ac.lk

On behalf of the Department of Pharmacology, Faculty of Medicine, University of Colombo

Treatments for atopic dermatitis

Summary

Atopic dermatitis usually develops in childhood but can occur in adults. Management involves drug and non-drug treatments to clear the skin.

Not all patients with atopic dermatitis have allergies. Most patients have trigger factors that can be avoided.

All patients should use soap substitutes and bath oils. Moisturisers are important for improving the condition of the skin.

Topical corticosteroids are the main drug treatment. The choice of corticosteroid depends largely on the site of the atopic dermatitis.

Topical calcineurin inhibitors can be considered for sensitive sites such as the face where potent topical corticosteroids are potentially harmful.

Adjunctive treatments given during flares of dermatitis include bleach baths and wet dressings. Antihistamines may help to relieve itch.

Phototherapy may be considered by a specialist for adults if there is inadequate response to treatment.

Severe cases of atopic dermatitis may require systemic treatment. Immunosuppressants, such as ciclosporin, have been used and now dupilumab and upadacitinib are available for severe chronic atopic dermatitis.

Keywords
atopic dermatitis, calcineurin inhibitors, corticosteroids, immunosuppression, Janus kinase inhibitors, phototherapy

(Aust Prescr 2023;46:9–12)

Introduction

Atopic dermatitis is a common, multifactorial skin condition that is often managed by GPs. It affects all ages and is heterogeneous in appearance. While there is usually a flexural predominance, it can be localised to the face or hands,or be generalised. Patients complain of itch as well as the rash.

Management of atopic dermatitis is similar in adults and children. It requires a combination of drug and non-drug therapy. Corticosteroids are the mainstay of drug therapy, but biological drugs are now available.

Non-drug treatment

The aim is to manage aggravating factors and improve the condition of the skin. All patients should be instructed to use soap substitutes or bath oils long term.

Avoiding triggers

It is usually possible to identify factors that trigger a flare of atopic dermatitis. Some triggers can be avoided.

Heat

Most patients report that their skin flares in response to heat. Hot baths or showers, bedding, warm clothing or exercise can all be triggers. Patients should be educated to avoid overheating and use cool compresses when their skin is hot or itchy.

Irritants

Soaps, detergents, rough fabrics, seams, clothing labels and exfoliants may all aggravate atopic dermatitis.

Allergens

Not all patients with atopic dermatitis have allergies, but allergens can play a role in some patients.

Fragrance is the most common cause of contact allergy, followed by preservatives in consumer products, for example, methylisothiazolinone. Patients should always use fragrance-free products. Do not use

products containing essential oils (e.g. lavender oil), or food ingredients (e.g. oatmeal, goats' milk, nut oils, pawpaw); these have a high risk for causing sensitisation and consequent food allergy. Sensitisation to contact allergens is more common in atopic individuals due to their impaired skin barrier, but can also occur in those without a known history of atopy. Dietary restrictions are to be minimised, particularly in infants, without input from specialists. Animal dander, house dust mite,[1] pollens and grasses are other potential allergens to recognize and avoid. Skin prick and RAST testing are of limited diagnostic yield in most cases of eczema.

Moisturiser

Moisturiser is the cornerstone of the management of atopic dermatitis. A genetic tendency to dry skin, caused by filaggrin mutations, underlies most cases. Keeping the skin well moisturised ensures the skin barrier remains intact, prevents penetration of pathogens and allergens, and minimises itch. Patients should moisturise at least daily, but more often if their skin is particularly dry, or during flares.

Moisturisers should be tailored to the sites affected and patient preference. For example, a greasy moisturiser containing liquid paraffin may be suitable around the mouth of a dribbly infant but on the face of an adolescent it may cause acne. Lighter moisturisers may be preferable for hairy areas where folliculitis is more common.

The latest advances in moisturisers specifically for atopic dermatitis include the addition of ceramides which help to repair the deficient skin barrier and restore water permeability.[2-5] Some also contain prebiotics and probiotics to assist in homeostasis of the skin flora and minimise the predominance of *Staphylococcus aureus*. These eczema-specific moisturisers should in theory be more efficacious than standard moisturisers, however it is usually acceptable for a patient to use any bland moisturiser rather than nothing at all.

Drug treatment

The goal of drug treatment is to clear the atopic dermatitis completely. Undertreatment is likely to lead to recurrence.

Topical corticosteroids

Topical corticosteroids are the most important pharmacotherapy for atopic dermatitis. However, the correct selections of strength, quantity and duration of use remain major problems for both GPs and patients alike.

Patients should be counselled that topical corticosteroids are effective and safe when used correctly and should not be avoided or used sparingly. One of the common reasons for treatment failure is underuse due to steroid phobia. Patients are often concerned about the risk of skin thinning, becoming reliant on a corticosteroid, or that corticosteroids make things worse in the long term. They should be counselled that if the correct strength is prescribed for the site, then there is unlikely to be any concern with using a corticosteroid until the skin is clear. This can take weeks to months depending on the severity and chronicity of the atopic dermatitis. Treatment can be repeated on and off, for years if necessary. There is no need to taper topical steroids. They can be stopped when the skin is clear, or reduced to twice a week as maintenance in recurrence-prone areas.

Face

Only the weakest topical corticosteroids, hydrocortisone 0.5% or 1%, are relatively safe on the face and eyelids. If they are effective, they can be used twice a day until the skin is clear. Higher potency topical corticosteroids should be avoided as they commonly cause periorificial dermatitis, a form of steroid-induced rosacea. Other adverse effects such as telangiectasia, acne and erythema can also occur when moderate- and high-potency topical corticosteroids are applied to the face for prolonged periods. Cataracts and glaucoma are the main risks of long-term use of potent topical corticosteroids on the eyelids. If

hydrocortisone is ineffective after two to four weeks, then non-steroid options such as a calcineurin inhibitor, or crisaborole should be considered.

Body and limbs
The body and limbs are more tolerant of topical corticosteroids than the face, with few adverse effects. Patients should be reassured that skin thinning is rare and, if seen, reversible. Suitable strengths include methylprednisolone aceponate 0.1%, or mometasone furoate 0.1%. These are used once daily until the skin is clear, then as needed. Ensure patients have a prescription for at least one to two months supply. An authority prescription may be needed to obtain adequate supply through the Pharmaceutical Benefits Scheme (PBS).

Hands and feet
The thick skin of the palms and soles requires a high- potency topical corticosteroid to achieve clearance of atopic dermatitis. Betamethasone dipropionate 0.05% is the standard strength for these sites. Apply twice a day until clear. These sites take longer to clear than other areas – four weeks is usual.

Calcineurin inhibitors
Pimecrolimus and tacrolimus are useful topical anti-inflammatory drugs for the treatment of atopic dermatitis. They are particularly used on the face and eyelids when mild topical corticosteroids are ineffective and where potent topical corticosteroids are not desirable.

Pimecrolimus 1% cream is available on the PBS (authority prescription) for specified patients over six months of age. It is used twice daily until the skin is clear. It can then be reduced to twice a week as maintenance therapy.

Tacrolimus is only available in Australia on a private prescription, compounded as either cream or ointment in strengths of 0.03% or 0.1%. Tacrolimus 0.03% is equivalent to pimecrolimus 1%.

The main adverse effect of calcineurin inhibitors is a stinging or burning sensation on initial use. This normally subsides after a few days and is not harmful. Discomfort can be minimised by keeping the drug in the fridge and applying moisturiser first.

Crisaborole
Crisaborole 2% cream is approved for mild to moderate atopic dermatitis in patients over the age of two years. It is a phosphodiesterase-4 inhibitor which works by reducing cytokines including tumour necrosis factor alpha.

In clinical trials, 30% of patients were clear or almost clear after 28 days of crisaborole, compared to 18–25% with placebo (vehicle-only).[6] There are no trials comparing its efficacy to topical corticosteroids. The main adverse effect of crisaborole is stinging (4%), followed by flare of atopic dermatitis, pain and skin infection. Apart from the limited efficacy of crisaborole for atopic dermatitis, cost may limit use, with 60 g crisaborole costing approximately $145 on private prescription.

Adjunctive treatments
Bleach baths, oral antihistamines and wet dressings are all potentially helpful adjunctive therapies when patients have a flare of atopic dermatitis. See Box for useful resources that include patient handouts and videos.

Bleach baths
Patients with broken skin, weeping, crusting or sores should be instructed to have bleach baths. Plain, fragrance-free household bleach is added to the bath (¼ cup (62.5 mL) to a child's half-full bath, ½ cup (125 mL) to a full adult bath) for two to five minutes before getting out and patting dry. Oral antibiotics are generally not required unless the patient is systemically unwell or has failed to respond to bleach baths.

Antihistamines
Antihistamines can provide some relief from itch when given regularly. Less-sedating drugs, for example cetirizine or loratadine, are

given during the day. Sedating antihistamines, for example promethazine or cyproheptadine, are given at night if sleep disturbance is a problem. Sedating antihistamines should not be used in children under the age of two years. Less-sedating antihistamines are considered to be relatively safe from the age of six months.

Wet dressings
Soaked clothing, tubular bandages or cloths held in place with crepe bandages can be used overnight or for periods of around four hours. They give relief from itch and aid penetration of moisturiser and topical corticosteroids.

Second-line treatments

Patients should be reviewed several weeks after having a flare of atopic dermatitis to check for response to treatment. If there is no response or response is inadequate based on skin appearance, symptoms of itch, poor sleep, or impact on school, work, family functioning or mental health, then further treatment and specialist referral are required.

Oral prednisolone has been used to treat flares of atopic dermatitis. While this may result in short-term improvement, many patients will require recurrent courses of prednisolone due to the long-term genetic tendency to atopic dermatitis. However, prednisolone, rather than topical corticosteroids, is the source of corticosteroid adverse effects, and it should be avoided if possible. There are safer, more effective options than prednisolone to consider in patients requiring more than topical corticosteroid treatment.

Phototherapy
Phototherapy with narrowband ultraviolet B (UVB) results in significant improvement in most patients with atopic dermatitis. A history of exacerbation with sun exposure, melanoma, or very fair skin (skin phototype 1) are contraindications. Lack of access to services in rural areas and not being able to attend due to work commitments are barriers to treatment.

Phototherapy is generally not administered to children until they are able to comply with safety measures such as wearing goggles and standing unaided in the light cabinet.[7]

Immunosuppressants
Ciclosporin is PBS-listed for treating severe atopic dermatitis. This is a medium-term treatment option (up to two years) due to the significant risk of renal impairment, hypertension and the potential for serious infections.
Drugs that have been used off label for atopic dermatitis include methotrexate, mycophenolate mofetil and azathioprine. Immunosuppressive drugs have largely been superseded by newer advanced therapies.

Dupilumab
Dupilumab is a monoclonal antibody that blocks the binding of interleukins 4 and 13, which are key drivers of atopic dermatitis. It is an immunomodulator, not an immunosuppressant.

Dupilumab must be prescribed by a dermatologist or immunologist and is given as a fortnightly subcutaneous injection, for indefinite use. It is administered in conjunction with topical treatments.

The key trials of dupilumab report that two-thirds of patients will achieve a greater than 75% reduction

in severity by 16 weeks and this is maintained out to 52 weeks.[8] Registry data suggest that real-world experience is in fact better than this, with 70–89% of patients achieving 75% skin clearance by week 52.[9,10]

Patients treated with dupilumab should use lubricant eye drops to avoid conjunctivitis, which is seen in around one-third of patients. They may complain of red, itchy, watery or gritty eyes. This is usually allergic conjunctivitis, or blepharitis, which can be exacerbated by dupilumab. It is generally mild to moderate and temporary. General practitioners should advise patients to increase the frequency of lubricant eye drops, add in topical and oral antihistamines, and treat their

eyelids with tacrolimus ointment. A referral to an ophthalmologist may be required if symptoms persist.

Dupilumab is PBS-listed for severe chronic atopic dermatitis with an Eczema Area and Severity Index (EASI score) of 20 or more, or severe involvement of the hands or face. Patients currently must be aged 12 years or older (although it has recently been approved by the Therapeutic Goods Administration for children aged 6–12 years with expected PBS listing to follow) and have failed four weeks of appropriate topical corticosteroids or calcineurin inhibitor therapy.

Upadacitinib

Upadacitinib is a selective Janus kinase 1 (JAK 1) inhibitor, which blocks downstream signalling of multiple cytokines. It is therefore immunosuppressive. Oral upadacitinib has a rapid onset of action, with 70–80% of patients achieving 75% reduction in the severity of atopic dermatitis by 16 weeks.[11]

JAK inhibitors can cause cytopenias and elevation of lipid levels, so blood-test monitoring is required. The most common adverse effect of upadacitinib is acne. Infections, particularly herpes simplex and zoster, are also increased. Patients with suspected infections should be assessed and managed promptly. Consider empiric antiviral drugs if zoster or herpes simplex is suspected. The patients should be advised to withhold upadacitinib until they have fully recovered.

Patients should be fully vaccinated before starting treatment. Live vaccines are contraindicated during treatment.

The PBS criteria for upadacitinib are the same as for dupilumab.

Conclusion

The management of atopic dermatitis combines drug and non-drug therapy. Topical corticosteroids are still the main drug treatment, but other options, such as topical calcineurin inhibitors, may be used at some sites. Immunomodulating and immunosuppressive drugs may be required for severe cases of atopic dermatitis.

Conflicts of interest: Gayle Ross has been a paid speaker and on medical advisory boards for Abbvie, Leo Pharma, Sanofi Genzyme, Lilly, Johnson & Johnson and Ego Pharmaceuticals.

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Gayle Ross Dermatologist, Royal Melbourne Hospital, East Malvern Dermatology, Melbourne

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