Medicines Adverse Reactions Committee

Meeting date	13/06/2024	Agenda item	3.2.1
Title	**Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) with systemic antibiotics and systemic antifungals**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Products Systemic antibiotics Systemic antifungals			
PHARMAC funding	As listed in the pharmaceutical schedule		
Previous MARC meetings	No		
International action	No		
Prescriber Update	Dec 2023: Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)		
Classification	Prescription medicines, except for fluconazole which is available from a pharmacist (restricted medicine) for a single 150mg dose to treat vaginal candidiasis.		
Advice sought	**The Committee is asked to advise:** • whether there is an association between systemic antibacterials or systemic antifungals with SDRIFE. This can be considered on an individual medicine level or in medicine groups (eg, beta-lactams, non-beta-lactams, penicillins, tetracyclines, triazoles etc.)		

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1 PURPOSE

Over the last 18 months, Medsafe and the Centre for Adverse Reactions Monitoring (CARM) have received three case reports of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). Following signal detection activities of cases reported to the New Zealand pharmacovigilance database, Medsafe reviewed a case of SDRIFE reported with the use of metoprolol and noted another case reporting terbinafine as the suspect medicine. Subsequently, an article on SDRIFE was published in the December 2023 edition of *Prescriber Update*.

In the published scientific literature, the most common medicines associated with SDRIFE are beta-lactam antibiotics. Based on this and the terbinafine case report, we have expanded this review to include systemic antibiotics and systemic antifungals.

The purpose of this paper is to review information on SDRIFE with a particular focus on systemic antibiotics and systemic antifungals.

2 BACKGROUND

2.1 Hypersensitivity reactions [1]

Hypersensitivity is an exaggerated immune reaction to an allergen or antigen following sensitisation. There are four main types of immunologically mediated hypersensitivity reactions to medicines, and these are summarised in Table 1. These immunological adverse drug reactions (ADRs) make up approximately 20% of ADRs [2].

Table 1: Summary of types 1 to IV hypersensitivity reactions

Type		Antibodies or mediators	Immunologic reaction	Examples
I	immediate	IgE	IgE recognises and attaches to foreign antigen activating a chain of reactions resulting in widespread release of chemicals, including histamine. Occurs in minutes.	urticaria, angioedema, anaphylaxis
II	autoimmune	IgG, IgM	IgG and IgM antibodies activate the complement cascade causing inflammation and damage to tissues.	bullous pemphigoid, pemphigus vulgaris
III	immune complex	IgG	IgG antibodies bind to foreign antigens forming complexes that precipitate and get stuck in certain locations (eg, skin, kidneys, joints) causing local inflammation.	Henoch-Schönlein purpura, small-vessel vasculitis, systemic lupus erythematous, serum sickness
IV	delayed	T-cells	T cells are activated by the antigen. CD4+ T helper cells recognise the antigen and release cytokines that activate the immune system with CD8+ T killer cells. Occurs 48-72 hours after allergen exposure.	morbilliform reactions, DRESS, erythema multiforme, lichenoid drug eruptions, SJS, TEN

Source: DermNet Allergies explained [1] (accessed 16 May 2024)
DRESS = Drug reaction with eosinophilia and systemic symptoms
SJS = Stevens-Johnson syndrome
TEN = Toxic epidermal necrolysis

2.1.1 Type IV hypersensitivity reactions [1]

SDRIFE is considered a type IV hypersensitivity reaction, therefore, type IV reactions are described in more detail here.

Type IV hypersensitivity or delayed hypersensitivity reactions occur 48-72 hours after exposure to an allergen. This reaction does not involve antibodies. Instead, eosinophils, monocytes or T cells are activated by the antigen. The helper CD4+ T cells initially recognise the antigen and release cytokines. The cytokines activate the immune system with killer CD8+ T cells to destroy the target cells on contact, and macrophages to wall off the antigen and prevent further damage.

Common examples of cutaneous type IV hypersensitivity reactions include:

- Allergic contact dermatitis: for example, hair dye, nickel in jewellery, poison ivy.
- The Mantoux test for detecting active tuberculosis.
- Delayed drug reactions including:
    - Morbilliform drug reactions
    - Drug reaction with eosinophilia and systemic symptoms (DRESS)
    - Erythema multiforme
    - Lichenoid drug eruptions
    - Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN).

Diagnosis

Thorough history and examination are needed to identify the likely causative agent. Diagnosis is confirmed through patch testing where small quantities of potential allergens are applied to the skin and left for two days. A patch of eczema at the site of an allergen indicates a positive reaction.

Treatment

Avoiding contact with the causative agent is the mainstay of treatment. Emollients and topical steroids can provide symptomatic relief.

2.2 Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)

2.2.1 Introduction

In 1984, Baboon syndrome was first described by Andersen et al [3] who reported on 3 patients with intertriginous and flexural erythemas primarily involving the buttocks after systemic administration or absorption of contact sensitisers such as nickel, mercury and ampicillin. The distribution of the rash was localised to the buttocks and inner thighs, representing the red-bottomed baboon. Baboon syndrome was classified as a form of *systemically induced allergic contact dermatitis* subsequent to previous skin sensitisation with identical contact allergens.

Ten years later, Menné et al [4] proposed the term *systemic contact dermatitis* for baboon syndrome and other types of dermatitis caused by systemic administration of substances either with or without previous topical exposure. Baboon syndrome was classified as 1 of 5 clinical reaction patterns within the group of systemic contact dermatitis without previous skin sensitisation.

In 2003, Lachapelle [5] proposed the term *allergic contact dermatitis syndrome* (ACDS) to distinguish all clinical types of allergic contact dermatitis with previous skin sensitisation from other immunologically related skin ADRs that lacked prior cutaneous sensitisation to the allergen. In this classification, baboon syndrome was considered an ACDS stage 3 reaction, thus assumption of previous skin sensitisation was again made.

Up until this point, many sometimes confusing terms had been proposed to describe baboon syndrome, a heterogeneous group of systemically induced contact dermatitis (Table 2).

Table 2: Skin reactions related to or imitating baboon syndrome

In 2004, Häusermann et al [6] noted the term baboon syndrome was problematic for several reasons, including:

- Being associated with a reaction induced by systemic absorption of a substance often after previous skin sensitisation with the same substance
- Doesn't reflect the entire range of clinical signs and symptoms of mercury-induced baboon syndrome
- Incorporates a broad spectrum of diseases encompassing allergic contact dermatitis syndrome, drug eruptions and a variety of other intertriginous dermatoses such as intertriginous candidiasis
- Fails to respect ethical and cultural sensitivities.

Therefore, Häusermann et al proposed the term SDRIFE in line with commonly used and easily remembered abbreviations such as fixed drug eruption (FDE), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS).

2.2.2 Clinical presentation

SDRIFE is a drug-induced rash involving the skin folds [7, 8]. It presents as a well-defined symmetrical V-shaped erythematous rash of the gluteal region or groin. There is often involvement of at least one other skin fold or flexural area, such as the armpit and behind the knees [7, 8]. Additional findings along with the macular eruption may include bullae, papules or pustules, and it may also be pruritic [9].

The lack of systemic symptoms is a key characteristic of SDRIFE. Aside from the rash, the person is generally well with no other symptoms [7].

There is usually no mucosal involvement, and involvement of the face and palmoplantar surfaces is rare [10].

A comparison of clinical features of SDRIFE with acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and fixed drug eruption (FDE) is shown in Table 3.

Table 3: Comparison and typical clinical features of distinct cutaneous drug eruptions

Source: Häusermann et al [6]

2.2.3 Epidemiology

SDRIFE is rather uncommon with a limited number of cases reported in the literature [11]. Since 1984, over 100 cases of drug-related baboon syndrome or SDRIFE have been reported [10].

SDRIFE can affect all age groups but it is rare in children [7]. It has been reported in an 18-month-old as a side effect of erythromycin for sore throat [12] and in a 5-year-old patient treated with co-amoxiclav for acute otitis media [13].

There is a male predominance of 3:1 [7].

2.2.4 Causes

The most common medicines associated with SDRIFE are beta-lactam antibiotics which are implicated in about 50% of SDRIFE cases [7]. There are many other medicines associated with SDRIFE, including non-beta-lactam antibiotics, analgesics, antifungals and iodine-containing contrast agents [7, 8].

2.2.5 Pathophysiology

SDRIFE is a type IV delayed hypersensitivity reaction to a systemic medicine, appearing a few hours to a few days after medicine exposure [7, 8]. This is supported by immunohistochemical evidence for CD4+ T cell infiltration and the increased endothelial and keratinocyte expression of CD26P-selectin, which recruits type 1 helper T (Th1) cells to the sites of inflammation [14].

According to some authors, SDRIFE likely involves both a type IVa reaction involving CD4+ Th1 cells, macrophages, and also a type of IVc reaction with cytotoxic CD4 and CD8 T cells [15].

Pathophysiological mechanisms might also include a recall phenomenon due to reactivation of tissue toxicity at the intertriginous sites, direct interactions of the medicines with immunoreceptors, and anatomical features of the large folds (abundance of eccrine sweat glands, occlusion) [6, 16].

2.2.6 Histology

The histologic presentation of SDRIFE often indicates superficial dermal oedema and perivascular lymphocytes and histiocytes [17]. The dermis may also contain lymphocytes, neutrophils and eosinophils along with necrotic keratinocytes in the epidermis and bulla [9].

2.2.7 Diagnosis

In 2004, Häusermann et al proposed the following diagnostic criteria for SDRIFE [6]:

1. Exposure to a systemically administered medicine either at the first or repeated dose (excluding contact allergens)
2. Sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perigenital area
3. Involvement of at least one other intertriginous/flexural area
4. Symmetry of affected areas
5. Absence of systemic symptoms and signs.

2.2.8 Treatment

SDRIFE is self-limiting and should completely resolve within 3 weeks after the suspect medicine is withdrawn [7, 18]. Re-exposure to the suspect medicine usually causes SDRIFE to recur [7]. Topical steroids may help to resolve the rash more quickly [7].

2.3 Systemic antibacterials

Beta-lactam antibiotics include penicillins, cephalosporins, carbapenems and the monocyclic-beta lactam aztreonam. The remainder of the systemic antibiotics are referred to as non-beta-lactam antibiotics in this paper.

Rashes due to antibiotics are most often morbilliform (exanthematous) or urticarial. It usually takes 7-10 days to become allergic to a medicine. Therefore, a rapid reaction is either non-immunological or it is due to a previous encounter with the same medicine or chemically similar substance [2].

As with other antibiotics, morbilliform rash is the most common rash due to beta-lactam antibacterials [19]. Other skin reactions to beta-lactam antibacterials include erythema multiforme, Stevens-Johnson syndrome (SJS), exfoliative dermatitis, toxic epidermal necrolysis (TEN) and hypersensitivity angiitis [19]. Allergic reactions to beta-lactam antibacterials are the most common cause of immunological adverse drug reactions (ADRs). This is thought to be due to the structure of beta-lactams [2].

Information on each antibacterial is briefly described below. The New Zealand Formulary (NZF) antibacterial drugs chapter [20] was predominantly used as the reference text. Information from other sources have been added where relevant and these are referenced.

2.3.1 Penicillins

Penicillins are bactericidal and act by interfering with bacterial cell wall synthesis. They diffuse well into body tissues and fluids, but penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. They are excreted in the urine in therapeutic concentrations.

The most important adverse effect of penicillins is IgE-mediated hypersensitivity, including anaphylaxis. Allergic reactions to penicillins are reported by 5-10% of patients.

Penicillin use is also associated with delayed skin reactions which can occur days or weeks after administration. These reactions are often T cell-mediated and commonly include maculopapular and morbilliform rashes, but more serious reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) can also occur.

Delayed cutaneous maculopapular eruptions to amoxicillin classically start on day 7 to 10 of treatment and may even begin 1 to 3 days after cessation of treatment. Symptoms typically begin several hours after the last administered dose, although this timing can be variable. However, symptoms should not begin within one hour of the initial dose. Delayed reactions are not IgE-mediated [21].

Amoxicillin is a broad-spectrum penicillin and is preferred as the first-line antibacterial for susceptible infections. It is active against gram-positive and gram-negative microorganisms. Amoxicillin is well absorbed orally. Maculopapular rashes commonly occur with amoxicillin but are not usually related to true penicillin allergy.

Amoxicillin + clavulanic acid (co-amoxiclav) is a combination product. Clavulanic acid has no significant antibacterial activity but it inactivates beta-lactamases, which makes the combination with amoxicillin active against beta-lactamase-producing bacteria.

Benzylpenicillin sodium (penicillin G) remains an important and useful antibiotic but is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal) and meningococcal infections, gas-gangrene and leptospirosis.

Phenoxymethylpenicillin (penicillin V) has a similar antibacterial spectrum to benzylpenicillin, but is less active. It is gastric acid-stable, so is suitable for oral administration. It should not be used for serious infections because absorption can be unpredictable and plasma concentrations variable.

Most staphylococci are now resistant to benzylpenicillin because they produce penicillinases. However, **flucloxacillin** is not inactivated by these enzymes and is therefore effective in infections caused by penicillin-

resistant staphylococci. Flucloxacillin is acid-stable and can therefore be given by mouth and injection. It is well absorbed from the gastrointestinal tract.

Piperacillin is only available in combination with the beta-lactamase inhibitor tazobactam. It has a broad spectrum of activity against a range of gram-negative bacteria, gram-positive bacteria and anaerobes. Piperacillin is used in the treatment of severe or complicated infections such as hospital-acquired pneumonia.

2.3.2 Cephalosporins

Cephalosporins are broad-spectrum antibiotics used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis and urinary tract infections (UTIs). Their pharmacology is similar to penicillins. As with penicillins, cephalosporins penetrate the cerebrospinal fluid poorly unless the meninges are inflamed; ceftriaxone is suitable for infections of the CNS (eg, meningitis).

The main adverse effect of cephalosporins is hypersensitivity and about 0.5-0.6% of penicillin-sensitive patients will also be allergic to cephalosporins.

Cefazolin is a first-generation cephalosporin. It has good activity against a wide spectrum of gram-positive bacteria and modest activity against gram-negative bacteria.

Cefuroxime is a second-generation cephalosporin that is less susceptible than the earlier cephalosporins to inactivation by beta-lactamases.

Cefotaxime sodium, **ceftazidime** and **ceftriaxone sodium** are third-generation cephalosporins with greater activity than the second-generations against certain gram-negative bacteria. Ceftriaxone has a longer half-life and is therefore given once daily.

Ceftolozane in combination with tazobactam enhances its activity against gram-negative bacilli producing beta-lactamases.

Cefepime hydrochloride is considered a fourth-generation cephalosporin and has a broad spectrum of activity.

Ceftaroline fosamil acetate is a fifth-generation cephalosporin with bactericidal activity similar to cefotaxime. However, ceftaroline has an extended spectrum of activity against gram-positive bacteria.

Orally active cephalosporins include **cefalexin** (first-generation) and **cefaclor** (second-generation) and they have similar antimicrobial spectrums. Cefuroxime is also orally active but is poorly absorbed; taking with food improves its absorption.

2.3.3 Monocyclic beta-lactams

Aztreonam is a monocyclic beta-lactam (monobactam) antibiotic with an antibacterial spectrum limited to gram-negative aerobic bacteria. Adverse effects are similar to other beta-lactams but aztreonam may be less likely to cause hypersensitivity in penicillin-sensitive patients.

2.3.4 Tetracyclines

Tetracyclines are active against a wide range of pathogens, particularly respiratory pathogens and chlamydia. They have anti-inflammatory effects making them useful for dermatological indications such as acne, rosacea and perioral dermatitis.

Tetracyclines, particularly minocycline, are associated with potentially serious hypersensitivity reactions including rash, exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and anaphylaxis. Compared to other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome.

Tetracyclines, particularly doxycycline, are the most common antibiotic cause of photosensitive rashes [2].

Doxycycline is usually the tetracycline of choice for acne as dental staining appears to be least and it is taken once or twice daily.

Minocycline has a broader spectrum than other tetracyclines.

Tigecycline is a glycylcycline antibacterial structurally related to tetracyclines. It is active against gram-positive and gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes.

2.3.5 Aminoglycosides

Aminoglycosides have a hexose ring with amino group substituents to which various amino sugars are attached via glycosidic linkages [22, 23]. Aminoglycosides are bactericidal and inhibit protein synthesis by binding to the 30S ribosomal subunit [23]. They are active against some Gram-positive and many Gram-negative organisms.

Aminoglycosides are not absorbed from the gastrointestinal tract, although there is a risk of absorption in inflammatory bowel disease and liver failure. They must therefore be given by injection for systemic infections.

Aminoglycosides may cause urticarial reactions [2].

Gentamicin is the aminoglycoside of choice in NZ and is used widely for the treatment of serious infections. It has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. When used for empiric treatment of undiagnosed serious infections, it is usually given in conjunction with a penicillin, metronidazole, or both.

Amikacin is more stable than gentamicin to enzyme inactivation. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli.

Tobramycin has similar activity to gentamicin. It is slightly more active against *Pseudomonas aeruginosa* but shows less activity against certain other Gram-negative bacteria.

Streptomycin is another aminoglycoside which is active against *Mycobacterium tuberculosis and* therefore almost entirely reserved for tuberculosis. Streptomycin is not reviewed any further in this paper because there are no approved products in NZ.

Neomycin is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure. Oral administration may lead to malabsorption. Neomycin is excluded from this review because it is not used systemically.

2.3.6 Macrolides

Macrolides have an antibacterial spectrum that is similar but not identical to that of penicillin. Therefore, they are an alternative for penicillin-allergic patients.

Morbilliform and urticarial rashes, and rarely SJS/TEN, have been reported with macrolides [2].

Erythromycin is recommended as an alternative in penicillin allergy for the management of suspected Strep A throat infections, secondary prevention of acute rheumatic fever/rheumatic heart disease and treatment of Legionella.

Roxithromycin has similar properties to erythromycin but gastrointestinal adverse effects are less frequent.

Azithromycin has slightly less activity than erythromycin against gram-positive bacteria but enhanced activity against some gram-negative organisms. Plasma concentrations are very low but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is therefore recommended.

Clarithromycin is an erythromycin derivative with slightly greater activity than the parent compound. Tissue concentrations are higher than with erythromycin.

2.3.7 Carbapenems

Carbapenems are beta-lactam antibacterials with broad-spectrum activity which includes many aerobic gram-positive and gram-negative bacteria and anaerobes.

Meropenem and **imipenem** are used for the treatment of severe hospital-acquired infections and polymicrobial infections. Imipenem is partially inactivated in the kidney by enzymatic activity and is therefore administered in combination with cilastatin, a specific enzyme inhibitor which blocks its renal metabolism.

Ertapenem is indicated for abdominal and gynaecological infections and for community-acquired pneumonia.

2.3.8 Metronidazole and ornidazole

Metronidazole is an antimicrobial with high activity against anaerobic bacteria and protozoa. It is a prodrug which diffuses across cell membranes and is then partially reduced by anaerobic bacteria and protozoa generating toxic free radicals and disrupting nucleic acid synthesis [24]. It is well absorbed orally and the intravenous route is normally reserved for severe infections. It is also used intravenously for surgical and gynaecological sepsis in which its activity against colonic anaerobes, especially *Bacteroides fragilis*, is important. Metronidazole may cause fixed drug eruption [2].

Ornidazole is an antimicrobial related to metronidazole. It is more commonly used in protozoal infections and is also active against anaerobic bacteria.

2.3.9 Sulfonamides and trimethoprim

Cross-reactivity occurs between different antibiotic sulfonamides such as sulfamethoxazole in cotrimoxazole, sulfadiazine, sulfacetamide (eye drops), silver sulfadiazine (cream) and sulfasalazine. When people react to cotrimoxazole, it is difficult to distinguish whether this is due to sulfamethoxazole or trimethoprim, so both antibiotic sulfonamides and trimethoprim should be avoided.

There is no established cross-reactivity between antibiotic sulfonamides and non-antibiotic sulfonamides such as thiazides, loop diuretics, sulfonylureas or triptans. However, some individuals allergic to antibiotic sulfonamides have a heightened risk of hypersensitivity and can react to other drug classes including non-antibiotic sulfonamides.

Observed skin reactions with sulfonamides include SJS/TEN, anaphylaxis, fixed drug eruption, serum sickness-like reaction and drug hypersensitivity syndrome [2].

Cotrimoxazole (sulfamethoxazole + trimethoprim) is associated with rare but serious adverse effects (eg, Stevens-Johnson syndrome and blood dyscrasias) especially in the elderly.

Trimethoprim alone is mainly used for the treatment of UTIs.

2.3.10 Quinolones

Quinolones should only be prescribed for serious and/or difficult to treat infections for which other antibiotics are considered inappropriate.

Quinolones are associated with increasing resistance in New Zealand, and rare but potentially irreversible severe adverse reactions.

Skin reactions with quinolones include hypersensitivity vasculitis, serum sickness-like reaction, morbilliform or urticarial rashes, AGEP, SJS/TEN [2].

Norfloxacin is effective in uncomplicated chronic relapsing UTIs but should be reserved for isolates resistant to empiric choices (trimethoprim or nitrofurantoin).

Ciprofloxacin is active against both gram-positive and gram-negative bacteria. It can be used for infections of the respiratory tract (except pneumococcal pneumonia), gastrointestinal system, bone and joint infections, gonorrhoea and septicaemia caused by sensitive organisms.

Moxifloxacin is active against gram-positive and gram-negative organisms. It should be reserved for treating community-acquired pneumonia, intra-abdominal infections and skin and soft-tissue infections which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials.

2.3.11 Other antibacterials

Clindamycin is a lincosamide and has similar antibiotic activity to macrolides. It inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit [25]. Clindamycin is active against Gram-positive cocci including streptococci and penicillin-resistant staphylococci, and has additional activity against many anaerobes, especially *Bacteriodes fragilis*. Clindamycin has high oral bioavailability and good penetration into a wide range of tissues. The oral route is preferred, but intravenous clindamycin can be considered for patients unable to take or absorb it orally or those with life-threatening infections.

Chloramphenicol is a potent broad-spectrum antibiotic. Systemic administration is associated with serious haematological adverse effects and it should be reserved for treating life-threatening infections after expert assessment.

Sodium fusidate and fusidic acid are narrow-spectrum anti-staphylococcal antibiotics. There are limited indications for their use and they should never be used alone due to rapid development of resistance.

Vancomycin and teicoplanin are glycopeptide antibiotics with bactericidal activity against aerobic and anaerobic gram-positive bacteria including multi-resistant staphylococci. 'Red man' syndrome is a histamine-mediated reaction to the rapid infusion of vancomycin and is not an allergic reaction [2]. Drug hypersensitivity is also seen with glycopeptides [2]. Vancomycin is used IV for treating serious infections caused by gram-positive cocci, and by mouth for treating C. diff infection. Teicoplanin is similar to vancomycin but has a significantly longer half-life allowing once-daily administration.

Daptomycin is a lipopeptide antibacterial with a spectrum of activity similar to vancomycin. It should be reserved for complicated severe infections caused by resistant gram-positive bacteria, including MRSA.

Fosfomycin is a bactericidal usually used in the treatment of acute uncomplicated infections of the urinary tract.

Linezolid is an oxazolidinone antibacterial active against Gram-positive bacteria including MRSA and vancomycin-resistant enterococci. Linezolid inhibits protein synthesis by binding to the 50S ribosomal subunit and preventing the formation of the 70S initiation complex [26]. It should be reserved for infections caused by Gram-positive bacteria when the organisms are resistant to other antibacterials or when patients cannot tolerate other antibacterials.

Nitrofurantoin is a nitrofuran antibacterial. It is used in the treatment of uncomplicated lower UTIs, including prophylaxis or long-term suppressive treatment in recurrent infection. Nitrofurantoin can cause fixed drug eruption and drug-induced lupus erythematosus [2].

Colistimethate sodium (colistin) is active against gram-negative organisms. It is not absorbed by mouth. IV use should be reserved for multi-drug resistant gram-negative organisms.

2.3.12 Antituberculosis agents

Many medicines used to treat tuberculosis are unapproved (ethambutol, cycloserine, para-aminosalicylic acid, protionamide, ethionamide, streptomycin, clofazimine, terizidone, delamanid) or are being used outside their approval status (amikacin, moxifloxacin). Approved medicines indicated for tuberculosis include isoniazid, pyrazinamide, rifabutin, rifampicin and bedaquiline.

Isoniazid only has antibacterial activity against mycobacteria. It has bacteriostatic activity against *Mycobacterium tuberculosis* and is one of the first line chemotherapeutic agents in treating tuberculosis. It is given with other antitubercular agents to reduce resistance which develops after a few weeks if used alone [27].

Pyrazinamide is a highly specific agent having a bactericidal effect on *Mycobacterium tuberculosis* but no activity against other mycobacteria or micro-organisms in vitro [28].

Rifabutin inhibits DNA-dependent RNA polymerase in susceptible strains of prokaryotic organisms but not in mammalian cells. It inhibits incorporation of thymidine into DNA of rifampicin-resistant *Mycobacterium*

tuberculosis suggesting it may also inhibit DNA synthesis which may explain its activity against rifampicin-resistant organisms [29].

Rifampicin has bactericidal activity intracellularly against slow and intermittently growing *Mycobacterium tuberculosis*. It inhibits DNA-dependent RNA polymerase activity in susceptible cells [30].

Bedaquiline is a diarylquinolone. It specifically inhibits mycobacterial ATP synthase, an enzyme essential for the generation of energy in *Mycobacterium tuberculosis*. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli [31].

2.3.13 Antileprotics

The WHO has made recommendations to overcome the problem of dapsone resistance and to prevent the emergence of resistance to other antileprotics.

Dapsone has an action similar to that of sulfonamides, which involves inhibiting folic acid synthesis in susceptible organisms [32]. Dapsone may cause fixed drug eruption [2].

Rifampicin is also indicated for the treatment of leprosy [30].

Clofazimine is an unapproved medicine used in the treatment of multibacillary leprosy [32].

2.4 Systemic antifungals

Systemic antifungal medicines may be required to treat a fungal infection if it is extensive or severe, resistant to topical antifungal treatment, or if it affects hairy areas. The choice of antifungal and its dose and duration of treatment depends on the type of fungus, the affected site, other co-existing diseases and interaction with other medicines [33].

Information on each antifungal is briefly described below. The New Zealand Formulary (NZF) antifungal drugs chapter [34] was predominantly used as the reference text. Information from other sources have been added where relevant and these are referenced.

2.4.1 Triazole antifungals

Triazoles inhibit an enzyme needed for the conversion of lanosterol to ergosterol, thereby disrupting the biosynthesis of ergosterol leading to increased cell membrane permeability and damage [35].

Triazoles are generally well tolerated. Gastrointestinal symptoms are most frequently reported and include nausea, abdominal pain, vomiting and diarrhoea [35].

Fluconazole is very well absorbed after oral administration. It can be used to treat mucosal candidiasis where topical treatment has failed.

Itraconazole is active against a wide range of fungi, particularly dermatophytes. Itraconazole capsules require an acid environment in the stomach for optimal absorption.

Posaconazole is used for the treatment of invasive fungal infections unresponsive to conventional treatment. It may also be used for prophylaxis of fungal infections in high-risk immunocompromised patients, and for the treatment of unresponsive infection in these patients.

Voriconazole is a broad-spectrum antifungal which is approved for use in life-threatening infections. It is considered first-line treatment for invasive aspergillosis.

2.4.2 Polyene antifungals

Polyene antifungals include amphotericin and nystatin. They are not absorbed when given orally [34].

Nystatin tablets and capsules are indicated for intestinal candidiasis. Nystatin is well tolerated even with prolonged administration. Large oral doses have occasionally produced diarrhoea, gastrointestinal distress,

nausea and vomiting. There have been reports of allergic reactions to orally administered nystatin, although these are rare [36].

Amphotericin B by intravenous infusion is used to treat systemic fungal infections and is active against most fungi. It is highly protein bound and penetrates poorly into body fluids and tissues. When given parenterally, amphotericin is toxic and adverse effects are common. Lipid formulations of amphotericin are significantly less toxic than the conventional formulation.

There is a lozenge formulation of amphotericin B which is not included in this review due to negligible absorption from the gastrointestinal tract even with very large doses [37].

2.4.3 Other antifungals

Caspofungin is an echinocandin antifungal. It is only active against Aspergillus and Candida. Echinocandins are not effective against fungal infections of the CNS.

Terbinafine is the medicine of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate.

2.5 Data sheets

2.5.1 Beta-lactam antibacterials

All the beta-lactam NZ data sheets (innovator and generic) and international data sheets (one for each active ingredient) were searched. International data sheets include Australia, UK, EU, US and Canada.

Of the NZ data sheets, SDRIFE is only listed in the Augmentin (amoxicillin + clavulanic acid) data sheet under Section 4.8 Undesirable effects (not listed in the generic data sheets):

Skin and subcutaneous tissue disorders:

Uncommon:	Skin rash, pruritus, urticaria
Rare:	Erythema multiforme
Very rare:	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and symmetrical drug-related intertriginous and flexanthema (SDRIFE) (baboon syndrome) (see also Immune system disorders). If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued. Linear IgA disease.

As with NZ, in Australia, SDRIFE is only listed in the Augmentin (amoxicillin + clavulanic acid) product information under Section 4.8 Undesirable effects (generic data sheets were not checked):

Hypersensitivity and skin

common:	skin rashes, pruritis, urticaria
rare:	angioneurotic oedema, anaphylaxis, serum-sickness-like syndrome, erythema multiforme, Stevens-Johnson syndrome, hypersensitivity, vasculitis, toxic epidermal necrolysis, bullous exfoliative dermatitis ,acute generalised exanthematous putulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (baboon syndrome) have been reported rarely. Whenever such reactions occur, AUGMENTIN DUO should be discontinued, unless in the opinion of the physician no alternative treatment is available and continued use of AUGMENTIN DUO is considered essential. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillins (See **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).
not known:	Linear IgA disease

SDRIFE is not listed in any beta-lactam UK, EU, US or Canadian data sheets.

2.5.2 Non-beta-lactam antibacterials

All the non-beta-lactam NZ data sheets (innovator and generics) were searched. International non-beta-lactam data sheets were not searched due to the number of antibacterials in this category.

None of the non-beta-lactam NZ data sheets contain information on SDRIFE.

2.5.3 Systemic antifungals

There is no information on SDRIFE in any of the systemic antifungal NZ or international (Australia, UK, EU, US, Canada) data sheets.

Information relating to skin reactions in systemic antifungal NZ data sheets is shown in Table 4.

Table 4: Information relating to rash in systemic antifungal data sheets

Medicine	4.4 warnings and precautions	4.8 undesirable effects
Triazoles		
fluconazole (capsule, powder for oral suspension, infusion)	Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis, during treatment with fluconazole. Drug reaction with eosinophilia and system symptoms (DRESS) has been reported. AIDS patients are more prone to the development of serious cutaneous reactions to many medicines. Fluconazole should not be used again if a rash develops which is attributable to fluconazole.	Pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria
itraconazole (capsule, oral solution)		Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, urticaria, alopecia, photosensitivity, rash, pruritus.
posaconazole (oral suspension, tablet)		rash, pruritus
voriconazole (tablet, injection, infusion, powder for oral suspension,	Dermatological adverse events Severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported with the use of voriconazole. If a patient develops a suspected SCAR, voriconazole should be discontinued immediately and an alternative treatment should be considered. Also, photosensitivity/phototoxicity is described in more detail.	Rash, dermatitis exfoliative, alopecia, purpura, rash maculopapular, pruritus, Stevens-Johnson syndrome, photosensitivity reaction, urticaria, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema, pseudoporphyria, erythema multiforme, psoriasis, drug eruption, eczema. Also, dermatological reactions are included in the description of adverse reactions subsection.

Medicine	4.4 warnings and precautions	4.8 undesirable effects
Polyenes		
nystatin (capsule, tablet, oral drops)		Rash, urticaria, Steven-Johnson Syndrome. [Note: Nilstat has no information]
amphotericin B (injection)		Rash, folliculitis, rash erythematous, rash follicular, rash maculopapular, sweating increased, urticaria acute
Other antifungals		
Terbinafine (tablet)	Dermatological effects: There have been rare observations of serious skin reactions (for example, Stevens-Johnson Syndrome and toxic epidermal necrolysis). Treatment using terbinafine tablets must be discontinued if a skin rash develops. Patients with pre-existing psoriasis may be at risk of an exacerbation.	Rash, urticaria, pruritus, erythema (non-serious forms of skin reactions). Hair loss (no causal relationship has been established), dermatitis exfoliative, dermatitis bullous, psoriasiform eruptions or exacerbation of psoriasis, serious skin reactions (for example, acute generalised exanthematous pustulosis, anaphylactoid reactions including angioedema, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis). In the occasion of an allergic or severe skin reaction, oral terbinafine treatment should be discontinued. Photosensitivity reactions (for example, photodermatosis, photosensitivity allergic reaction and polymorphic (light eruption) drug rash with eosinophilia and systemic symptoms (DRESS).
caspofungin (infusion)	Possibly histamine-mediated adverse reactions, including rash, facial swelling, angioedema, pruritus, sensation of warmth, or bronchospasm have been reported and may require discontinuation and/or administration of appropriate treatment. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported after post marketing use of caspofungin. Caution should apply in patients with history of allergic skin reactions.	Rash, pruritus, sweating, erythema, toxic epidermal necrolysis, Stevens-Johnson syndrome.

Source: New Zealand data sheets (extracted 13 May 2024)

Comments:

General: The only NZ data sheet that includes information on SDRIFE is the Augmentin (amoxicillin + clavulanic acid) data sheet where it is listed as a very rare undesirable effect. This was recently added during the last data sheet update in Feb 2024. SDRIFE is also listed in the Augmentin Australian data sheet.

Systemic antifungals: Generally, there is information on skin reactions in all systemic antifungal NZ data sheets. These include non-serious reactions such as rash, urticaria and erythema and serious cutaneous reactions such as SJS and TEN. The posaconazole, nystatin and amphotericin B data sheets contain the least information on skin reactions.

2.6 Usage

Due to the number of systemic antibacterials available, usage data for each active ingredient was not retrieved. However, according to PHARMAC's year in review 2023, amoxicillin ranked fourth on the list of the number of funded community medicines dispensed (1,230,000 prescriptions). There were no other systemic antibacterials on this list.

The number of people in NZ with initial dispensings of a systemic antifungal from a community pharmacy by year is shown in Table 5. According to PHARMAC's year in review 2023, amphotericin B was ranked 16th ($2.38 million) on the hospital medicines (by gross spend) list.

Table 5: Number of people with initial community dispensings of a systemic antifungal, by year

	2018	2019	2020	2021	2022
azoles					
fluconazole	26,901	27,470	34,838	43,143	44,809
itraconazole	5,229	5,228	7,857	10,868	11,416
posaconazole*	116	140	144	165	150
voriconazole*	99	96	86	118	135
polyenes					
nystatin#	38,255	38,582	35,923	36,122	35,484
amphotericin B	Funded on HML only (usage data not available)				
other					
caspofungin	Funded on HML only (usage data not available)				
terbinafine	26,413	26,585	24,451	24,479	23,822

Source: Pharmaceutical Data web tool (extracted 13 May 2024)
* PHARMAC funded subject to special authority criteria
# Vaginal cream is also funded and is included in these figures
HML = Hospital medicines list

3 SCIENTIFIC INFORMATION

3.1 Published literature

A search in PubMed of SDRIFE with systemic antibacterials and systemic antifungals was conducted. Review articles retrieved from this search are summarised in this section.

3.1.1 Häusermann et al 2004 – Baboon syndrome resulting from systemic drugs: is there strife between SDRIFE and allergic contact dermatitis syndrome? [6]

These authors proposed renaming baboon syndrome to SDRIFE, and criteria for diagnosis of SDRIFE (see section 2.2 of this report). A presentation of 2 case reports and review of literature cases was also conducted by the authors and these are described here, with a full copy of the article provided as Annex 1.

Case reports (n=2)

The first case was a 39-year-old man treated with amoxicillin, clarithromycin and omeprazole for *Helicobacter pylori* gastritis. The next day, he developed a pruritic symmetrical erythema with vesicles and small pustules on both inner thighs, cubital fossae, axillae and gluteal area. This reaction was presumably a reaction to amoxicillin. Two weeks after stopping all medicines, the lesions self-resolved without any further treatment. There were no systemic symptoms. The patient's history for previous exposure to amoxicillin or other beta-

lactam antibacterials was not conclusive. Three months later, re-exposure to amoxicillin with one oral dose resulted in an identical reaction 8 hours later.

The second case was a 78-year-old woman who underwent surgery for a bunion. On the day of surgery, she received cefuroxime IV and two days later developed a sharp symmetrical erythema with small pustules on the buttocks and erythema in a V-shaped pattern on the inner upper thighs, popliteal folds and submammary areas. A baboon-type drug reaction was diagnosed. Skin biopsy showed a superficial perivascular dermatitis with a dominant involvement of mainly CD3+/CD4+ lymphocytes and some neutrophils. Subcorneal pustules were present consistent with a pustular variant of a baboon-type eruption. The reaction spontaneous cleared within 8 days. There were no systemic symptoms. The patient denied previous drug eruptions and was uncertain about previous intake of antibiotics.

Literature cases

Of about 100 cases classified as baboon syndrome, 50 were found to be drug-induced. Of these, 8 were considered representative of systemically induced allergic contact dermatitis or allergic contact dermatitis syndrome, and 42 were assessed as examples of drug eruptions elicited by systemic administration of oral or IV medicines.

The main clinical findings included sharp demarcation of a V-shaped erythema in the inguinal/genital and gluteal/perianal areas and in most cases, additional involvement of at least one other flexural or intertriginous fold. Of the 42 cases, amoxicillin was the eliciting medicine in 14 cases, 30 of the patients were men, and the latency periods were short (between hours and a few days). The main histological pattern was non-specific and showed a superficial perivascular mononuclear cell infiltrate with some neutrophils and eosinophils.

Comments:
The authors proposed separating systemically induced drug-related baboon syndrome *without* known previous cutaneous sensitisation and systemically induced cases *with* previous cutaneous sensitisation into two distinct subgroups. The term SDRIFE was proposed to describe systemically induced cases without known previous cutaneous sensitisation.

3.1.2 Schuler et al 2021 – Symmetric drug-related intertriginous and flexural exanthema: Clinicopathologic study of 19 cases and review of literature [38]

The authors describe 19 new cases of SDRIFE and review the literature to better define the clinical and histopathologic spectrum of SDRIFE.

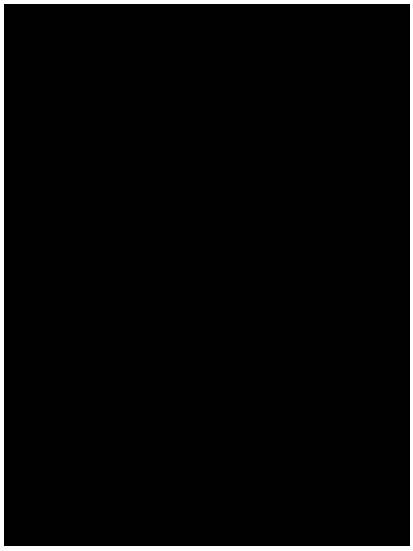
Cases (n=19)

The strict SDRIFE criteria proposed by Häusermann et al were applied and the authors identified 19 patients with SDRIFE who had undergone biopsies to allow for histopathologic characterisation. Over half (53%) of the 19 cases were triggered by antibiotics with cotrimoxazole being the most frequent culprit (16%) (Table 6). Six new causative medicines were identified: ciprofloxacin, metoprolol, dapsone, lenalidomide, methylphenidate and enfortumab vedotin.

Median onset was 7 days. Pruritus was a common symptom (89%). There were no cases with systemic signs or symptoms. Primary morphology ranged from plaques (89%), papules (68%), to patches (11%), some with overlying scale (47%). The colour of lesions was described as erythematous (89%), dusky (21%), hyperpigmented (11%) or violet (5%). Vesicles/bullae, erosions and pustules were relatively infrequent.

The most common histopathologic finding was superficial perivascular lymphocytic infiltrate followed by dermal eosinophils, spongiosis and orthokeratosis. Basal vacuolisation and apoptotic keratinocytes were less common. Interstitial histiocytes were present in almost half of the cases. Other findings included atypical lymphocytes and “flame figure”.

Table 6: Inciting medicines of the 19 SDRIFE cases



Literature review

A total of 73 cases of SDRIFE with accompanying histopathologic data were identified in the literature. The average age of patients was 51 years. There was a slight male predominance (male-to-female ratio of 1.5:1). Antibiotics were the most common culprits, reported in 33% of cases (Table 7). Less common culprits included chemotherapy, antifungals, NSAIDs, anti-gastroesophageal reflux medicines, IV radiocontrast, antihypertensives, antiepileptics and anti-TNF-alpha medicines.

Average latency period was 5 days. Similar to the authors' case series, a superficial perivascular lymphocytic infiltrate was most common (99%) followed by dermal eosinophils (66%) and spongiosis (44%). Orthokeratosis and parakeratosis (19%) were much less commonly described while basal vacuolisation (33%) and apoptotic keratinocytes (30%) were reported more frequently.

Table 7: Inciting medicines of the 73 literature SDRIFE cases

Comments:

This is the most recent publication that includes a review of cases reported in the literature. Antibiotics were the most common culprits, reported in over half of the case reports and one-third of the literature cases. Of the 19 case reports, 10 were reported with antibacterials: co-trimoxazole (3 cases) and 1 case each for amoxicillin, co-amoxiclav, ampicillin, cephalexin, clindamycin, ciprofloxacin and dapsone.

The main focus of this article was on histopathologic findings to distinguish SDRIFE from other skin reactions. The authors' cases confirmed frequent findings of superficial perivascular lymphocytic infiltrate, dermal eosinophils and spongiosis. Most cases were microscopically indistinguishable from a common eczematous dermatitis.

The authors note SDRIFE is largely a clinical diagnosis but biopsy may be helpful in excluding other reactions as differential diagnoses.

3.1.3 Tan & Tan et al 2011 – Symmetrical drug-related intertriginous and flexural exanthema [10]

The authors review SDRIFE, including its clinical features, histology, causes, causative medicines and differential diagnoses.

SDRIFE is described as a benign and self-limiting type IV hypersensitivity reaction. Histology of skin lesions is variable with a predominance of superficial perivascular inflammatory cell infiltrates. Outcomes of allergy tests are variable with positive delayed intradermal tests reported for penicillin V, allopurinol; positive patch tests for erythromycin, mitomycin, nystatin, pseudoephedrine; positive lymphocyte transformation tests for erythromycin; and positive drug provocation tests for clindamycin, cimetidine, corticosteroids, terbinafine and valaciclovir.

A variety of causative medicines have been reported, the majority from amoxicillin (>15 cases reported). Other medicines reported include IV immunoglobulins, chemotherapeutic agents and biologics. A clinical diagnosis of SDRIFE has also been reported with roxithromycin, ceftriaxone, cefalexin, barium sulphate, mitomycin C and oxycodone but there were no corresponding confirmatory skin or oral provocation tests in these cases. . SDRIFE may also occur on re-exposure to a cross-reactive medicine. A summary is shown in Table 8.

Table 8: Summary of medicines reported to have caused SDRIFE and allergy test results

[redacted]

[redacted]

Comments:

The systemic antibacterials/antifungals reported to have caused SDRIFE in the authors' review included amoxicillin, cefuroxime, clindamycin, erythromycin, nystatin and terbinafine.

3.1.4 Winnicki & Shear 2011 – A systematic approach to systemic contact dermatitis and symmetric drug-related intertriginous and flexural exanthema (SDRIFE) [39]

The authors review the different presentations and causes of systemic contact dermatitis (SCD) with a focus on baboon syndrome and SDRIFE.

Systemic contact dermatitis occurs when a person sensitised to a contact allergen is exposed to that same allergen or a cross-reacting molecule through a systemic route. The most common causes of systemic contact dermatitis consist of three groups of allergens:

- Metals including mercury, nickel, gold
- Medicines including aminoglycoside antibacterials, corticosteroids, aminophylline
- Plants and herbal products including the Compositae and Anacardiaceae plant families and Balsam of Peru.

The authors note baboon syndrome caused by systemic medicines without a known history of previous cutaneous sensitisation has been termed drug-related baboon syndrome or SDRIFE. Key differences between baboon syndrome and SDRIFE are shown in Table 9.

The reported causes of SDRIFE are shown in Table 10. There is a wide range of causative medicines but the most common are beta-lactam antibacterials such as amoxicillin, and chemotherapeutic agents such as mitomycin.

Table 9: Differences between baboon syndrome and SDRIFE

[redacted]

Reference: Häusermann et al [6]

Table 10: Reported causes of SDRIFE

[redacted]

The authors note epicutaneous patch testing, though initially described as being positive in up to 50% of cases by Häusermann et al has been found to be negative in more recent reports of SDRIFE. This could be due to reduced absorption of systemically administered medicines when applied to the skin by patch testing. Oral provocation testing or rechallenge is positive in almost all reported cases of SDRIFE and is at this time the most reliable way to confirm a diagnosis. Histopathology is nonspecific and cannot be used alone to confirm a diagnosis of baboon syndrome or SDRIFE. Prick testing and lymphocyte stimulation testing are negative in the majority of reported cases of SDRIFE.

Differential diagnoses of skin reactions at intertriginous sites are shown in Table 11.

Table 11: Differential diagnosis of intertriginous eruptions

[redacted]

Comments:

The authors provide detailed information on how to approach a patient who presents with a rash at an intertriginous site.

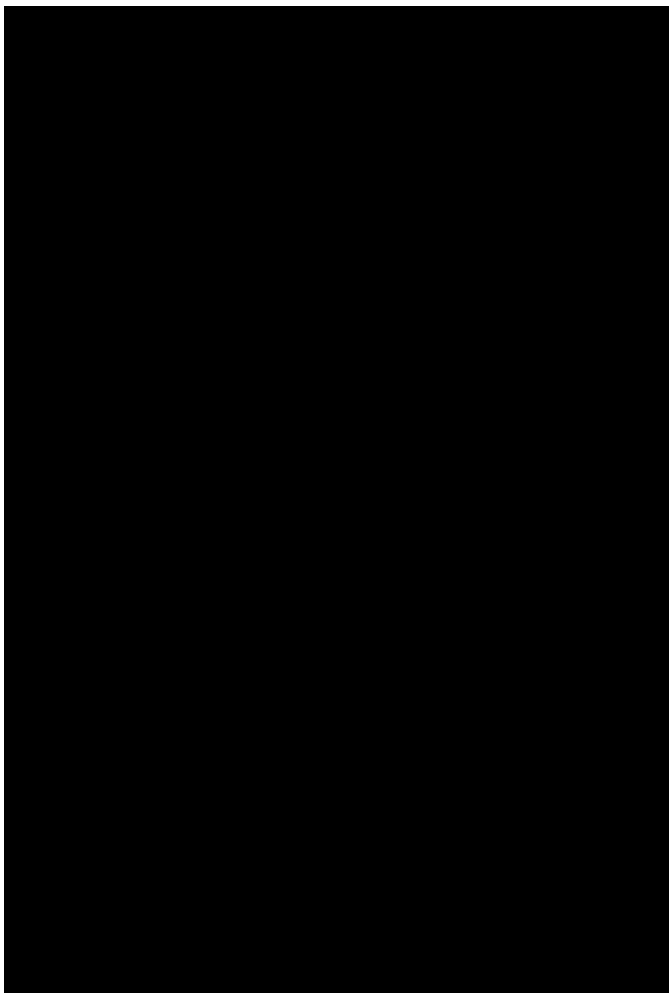
3.1.5 Miyahara et al 2011 – A new proposal for a clinical-oriented subclassification of baboon syndrome and a review of baboon syndrome [40]

The authors retrieved information on baboon syndrome published in the literature. They divided baboon syndrome into 4 subgroups:

- classical baboon syndrome – contact allergen-induced (excluding medicines) baboon syndrome
- topical drug-induced baboon syndrome – allergic contact dermatitis syndrome stage 3A (generalised dissemination of skin lesions form the primary site of application of the allergen via blood vessels).
- systemic drug-induced baboon syndrome – allergic contact dermatitis syndrome stage 3B (systemic reactivation of allergic contact dermatitis with the allergen introduced by systemic administration).
- SDRIFE – non-contact allergenic drug-induced baboon syndrome.

Approximately 50 cases of SDRIFE had been reported at the time. Causative agents of SDRIFE are shown in Table 12. The most common offending medicines were antibiotics, especially beta-lactam antibiotics. Amoxicillin was the leading causative medicine. The likely causative chemical for beta-lactam antibiotics is probably the beta-lactam ring, or less probably the thiazolidine ring, because two penicillins (amoxicillin/sulbactam and phenoxymethylpenicillin) that have different side chains have caused SDRIFE in the same patient [41].

Table 12: Causes of SDRIFE



Comments:

Although SDRIFE was briefly described in this paper, the main focus was on baboon syndrome.

3.1.6 Neri et al 2014 – Baboon-like syndrome in children [42]

The authors present a case of a 4.5-year-old boy who was referred to them for purpuric lesions of the inguinal and axillary folds and pubic area that had appeared 2 days before together with simultaneous high-grade fever. On dermatologic examination, intertriginous lesions of the axillary and inguinal golds, V-shaped involvement of the pubic region and mild involvement of the buttocks were observed. The cutaneous lesions were isolated, nonconfluent, red, purpuric, follicular papules with a diameter of a few millimetres.

Baboon-like syndrome was suspected. The child had not been given any medicines for this condition and had no recent history of contact with mercury. Viral serologic tests highlighted positive IgM against Epstein-Barr virus (EBV) and cytomegalovirus (CMV).

The authors retrieved 38 paediatric cases of baboon syndrome, SDRIFE or baboon-like eruptions reported in the literature (Table 13).

Table 13: Paediatric cases of baboon syndrome, SDRIFE and baboon-like syndrome

Comments:

This article was included because it describes baboon syndrome, SDRIFE and baboon-like syndrome in children.

The paediatric case presented by the authors included high-grade fever at presentation which is unusual for SDRIFE (patients are generally systemically well). The lack of systemic signs and symptoms is also a criterion for the diagnosis of SDRIFE as proposed by Häusermann et al. Therefore, this case is more a baboon-like syndrome case rather than a true case of SDRIFE.

Of the 38 cases of baboon syndrome, SDRIFE or baboon-like syndrome in children that the authors retrieved, 3 cases involved an antibacterial: erythromycin, cefadroxil (a cephalosporin) with paracetamol and a cough mixture as co-suspects, and amoxicillin-clavulanate. Of the 3 antibacterial cases, it is unknown if patients had baboon syndrome, SDRIFE or baboon-like syndrome.

3.1.7 Dilley & Geng 2022 – Immediate and delayed hypersensitivity reactions to antibiotics: Aminoglycosides, clindamycin, linezolid, and metronidazole [26]

The authors note aminoglycosides, clindamycin, linezolid and metronidazole cause hypersensitivity reactions relatively infrequently when compared with beta-lactam antibiotics and sulfonamides. This review covered the

most commonly reported hypersensitivity reaction types including epidemiological data and published evaluation/diagnostic strategies and desensitisation protocols for each of these antimicrobial groups.

Aminoglycosides

Allergic reactions to aminoglycosides occur infrequently but are most commonly found to cause allergic contact dermatitis (type IV hypersensitivity reaction). In the US, neomycin, tobramycin and gentamicin are widely used topically which likely contributes to sensitisation.

Although there is no definitive evidence of IgE-mediated immediate hypersensitivity to aminoglycosides, there are a couple of cases in patients experiencing immediate generalised rashes following administration of IV aminoglycosides. There have been a few reported cases of possible anaphylaxis.

Other cutaneous manifestations like urticaria and DRESS have been reported. There is one case of immediate urticaria following topical nasal application of neomycin and another case of DRESS weeks after starting amikacin.

Clindamycin

The most common type of hypersensitivity reaction to clindamycin is a delayed maculopapular rash usually 7-10 days after initiation. Studies in the 1970s reported an incidence of rashes with clindamycin in about 10% of patients [44]. A more recent and much larger study of 3896 clindamycin administrations from a single US hospital reported a likely more realistic incidence of 0.47% with most of the rashes as delayed cutaneous reactions [45].

Type I IgE-mediated hypersensitivity and anaphylactic reactions to clindamycin are rare with just a few cases described in the literature.

Other immunologic drug reactions include fixed drug eruptions. Other rare hypersensitivity reactions include DRESS, SDRIFE, AGEP and acute febrile neutrophilic dermatosis or Sweet syndrome.

A case of SDRIFE was described by Cabrera Hernandez et al in 2019 [46]. This 63-year-old female patient presented with a systemic allergic contact dermatitis characterised by a pruritic, maculopapular confluent and more intense eruption in the area of the buttocks and major flexures. Clinical symptoms were compatible with SDRIFE caused by clindamycin.

Linezolid

Immediate hypersensitivity reactions have been reported with symptoms including urticaria, skin flushing and angioedema.

Other hypersensitivity reactions include a patient with diffuse confluent non-blanching petechiae and purpura with a punch biopsy showing a perivascular inflammatory infiltrate without noted changes of leukocytoclastic vasculitis, and case reports of reactions such as interstitial nephritis and DRESS.

Metronidazole

Hypersensitivity reactions to metronidazole are rare with only a small number of case reports in the literature.

IgE-mediated reactions including itching, lip swelling, generalised pruritic erythematous lesions and anaphylaxis have been reported in two patients.

Other hypersensitivity reactions include one case report each of allergic contact dermatitis, fixed drug eruption, serum sickness-like reaction, SJS/TEN, AGEP, SDRIFE [47], and a possible case of DRESS.

Comments:
Of the medicines (aminoglycosides, clindamycin, linezolid and metronidazole) included in this review, SDRIFE was reported with clindamycin and metronidazole (1 case each).

3.2 Spontaneous adverse reaction reports

3.2.1 New Zealand

The NZ pharmacovigilance database contains 3 reports coded as symmetrical drug-related intertriginous and flexural exanthema and a further 2 reports describing SDRIFE in the report narrative. These cases are summarised in Table 14.

Table 14: Summary of reports coded as SDRIFE in the NZ pharmacovigilance database

Report ID	Date	Sex	Age	Medicine(s)	Reactions(s) #	Notes
140422	Apr 2021	79	F	metoprolol*, rivaroxaban, furosemide, digoxin	purpura, rash morbilliform	[redacted]
146385	Feb 2023	68	F	metoprolol*, atenolol*	exfoliative dermatitis	[redacted]

Report ID	Date	Sex	Age	Medicine(s)	Reactions(s) #	Notes
147293	Apr 2023	62	M	doxycycline oral*, cetuximab IV*, aqueous cream, hydrocortisone 1% cream	SDRIFE, dehydration, skin infection	[redacted]
147315	Apr 2023	27	M	ceftriaxone IV*, metronidazole oral, paracetamol, ibuprofen	SDRIFE	[redacted]
NZ-Medsafe-153587	Nov 2023	48	M	terbinafine oral*, prednisone, flucloxacillin, tramadol, atorvastatin, miconazole cream, fatty cream, cetomacrogol cream	SDRIFE	[redacted]

Source: NZ pharmacovigilance database (extracted 16 May 2024)
* = suspect medicine as reported by the reporter
# = reaction as coded in database

Comments:

It is possible that there are other cases describing symptoms of SDRIFE in the database that have not been coded as SDRIFE. This is in accordance with coding conventions.

Our adverse reaction dictionary (MedDRA) is hierarchical, therefore when retrieving cases from the database, any cases reporting baboon syndrome would be captured under SDRIFE.

3.2.2 International

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

Hypersensitivity reactions can be grouped into four main types. Type IV hypersensitivity reactions are delayed T-cell mediated reactions and examples include drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SDRIFE.

In 2004, Häusermann et al proposed the term SDRIFE to replace baboon syndrome along with diagnosis criteria. The first criterion for SDRIFE diagnosis is exposure to a systemically administered medicine either at the first or repeated dose, in contrast to baboon syndrome which includes reactions induced by systemic absorption of a substance often after previous skin sensitisation with the same substance.

Systemic antibacterials can cause skin rashes and these are often morbilliform (exanthematous) or urticarial. Beta-lactam antibacterials are the most common cause of immunological adverse reactions, likely because of their chemical structure. Likewise, systemic antifungals can cause skin reactions such as pruritus and urticaria.

Based on the published literature, beta-lactam antibiotics are the most common medicines associated with SDRIFE and are implicated in about half of SDRIFE cases. There are many other medicines that have been associated with SDRIFE, including non-beta-lactam antibiotics and antifungals.

The three NZ cases of spontaneous adverse reaction reports were all received within the last 18 months and the suspect medicine in each included the systemic antibacterials/antifungals doxycycline (tetracycline, non-beta lactam), ceftriaxone (cephalosporin, beta-lactam) and terbinafine (antifungal). [redacted]

[redacted]

The Augmentin (co-amoxiclav) NZ data sheet was updated earlier this year to include SDRIFE as a very rare adverse reaction. No other NZ data sheets include information on SDRIFE.

5 ADVICE SOUGHT

The Committee is asked to advise:

- whether there is an association between systemic antibacterials or systemic antifungals with SDRIFE. This can be considered on an individual medicine level or in medicine groups (eg, beta-lactams, non-beta-lactams, penicillins, tetracyclines, triazoles etc.).

6 ANNEXES

1. Hausermann et al 2004

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