CHAPTER 4

DERMATOLOGY

Extemporaneous compounding of some of the preparations listed should only take place at institutions where the competencies and equipment are available.

4.1 ACNE

L70.0-5/L70.8-9

DESCRIPTION

Acne is an inflammatory condition of the pilosebaceous unit. Secondary changes can lead to scarring and pigmentation.

Mild acne:
Predominantly consists of non-inflammatory comedones.

Moderate acne:
Consists of a mixture of non-inflammatory comedones and inflammatory papules and pustules.

Severe acne:
Characterised by the presence of widespread nodules and cysts, as well as a preponderance of inflammatory papules and pustules.

GENERAL MEASURES

» Do not squeeze lesions.
» Avoid greasy or oily topical products such as moisturisers that block the hair follicle openings.
» Discourage excessive facial washing.

MEDICINE TREATMENT

For the primary management of acne, see Primary Health Care Standard Treatment Guidelines and Essential Medicine List, section 5.3: Acne vulgaris.

Women who have inflammatory acne and also require oral contraception can be initiated on a cyproterone acetate-containing combined oral contraceptive pill, provided that they have no personal or family history of breast cancer or venous thrombosis.

- Cyproterone acetate 2 mg plus ethinyl estradiol 35 mcg, oral daily.

LoE:Ia[i]

Note: Discuss all severe cases with a dermatologist.

4.2 CELLULITIS AND ERYSIPELAS

L03.0-3/L03.8-9 + (L04.0-3/L04.8-9/B95.0-8) and A46

DESCRIPTION

These are skin and subcutaneous infections with pain, swelling, and erythema, usually caused by streptococci and staphylococci, and occasionally other organisms. Regional lymphadenitis may be present. Erysipelas has a raised demarcated border, whilst the border is indistinct in cellulitis.

The presence of areas of necrosis, haemorrhage, or pain out of proportion to the physical signs should raise suspicion of necrotising fasciitis which requires aggressive surgical debridement and broad-spectrum antibiotics (e.g. amoxicillin/clavulanic acid) as these infections are often polymicrobial.

GENERAL MEASURES

» Elevate the affected limb to reduce swelling and pain.
» Hydrate.

MEDICINE TREATMENT

Non-severe infection
Antibiotic therapy:

- Cefalexin, oral, 500 mg 6 hourly for 5 days.

OR

- Flucloxacillin, oral, 500 mg 6 hourly for 5 days.

LoE:IVb[ii]

Severe penicillin allergy: (Z88.0)

- Macrolide, e.g.:
- Azithromycin, oral, 500 mg daily for 3 days.

Note: Severe cases may require parenteral antibiotics.

Severe infection
The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period.

LoE:IIIb[iii]

- Cefazolin, IV, 1 g 8 hourly.

When there is clinical improvement, change to: *LoE:IIIb[iv]*

- Flucloxacillin, oral, 500 mg 6 hourly.

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly.

When there is clinical improvement, change to:

- Clindamycin, oral, 450 mg 8 hourly.

Note:
» If patients are treated with intravenous antibiotics, they should be switched to oral agents as soon as there is clinical improvement.
» Intravenous antibiotics are preferred in the setting of rapid progression of erythema.

Pain control:
- NSAID, oral: e.g.
- Ibuprofen, oral, 400 mg 8 hourly with meals.

OR
- Paracetamol, oral, 500 mg–1 g, 4–6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

Note:
» If the patient is admitted and bed-bound with lower limb cellulitis, consider deep venous thrombosis prophylaxis (See section 2.8 Venous thrombo-embolism).
» If Tinea pedis is suspected to be the predisposing cause, treat accordingly. see section 4.10: Fungal infections.

REFERRAL
Urgent
» For debridement if necrotising fasciitis is suspected, i.e. gangrene, gas in the tissues or haemorrhagic bullae.

Non-urgent
» To surgeon for non-response.
» For further investigation and potential biopsy if cellulitis is associated with wounds exposed to aquatic environments**,** (salt water, brackish water, or fresh water), or if there is a lack of response to treatment.

4.3 IMPETIGO
L01.0-1A + (B95.0-8)

DESCRIPTION
Superficial skin infection, starting as vesicles with an inflammatory halo. Later a characteristic honey-coloured crust on erythematous base develops which heals without scarring. Usually caused by group A streptococci or staphylococci. Post-streptococcal glomerulonephritis is a potential complication.

GENERAL MEASURES

» Good personal and household hygiene to reduce carriage of organisms and spread of infection.
» Wash and soak lesions in soapy water to soften and remove crusts.

MEDICINE TREATMENT

Antibiotic therapy

- Flucloxacillin, oral, 500 mg 6 hourly for 5 days.

Severe penicillin allergy: (Z88.0)

- Macrolide, e.g.:
- Azithromycin, oral, 500 mg daily for 3 days.

4.4 FURUNCLES AND ABSCESSES

L02.0-4/L02.8-9/H00.0/H60.0/N76.4/J34.0 + (B95.6-8)

DESCRIPTION

Localised bacterial skin infection of hair follicles (furuncle/boil) or dermis (abscess), usually with *S. aureus*.
The surrounding skin becomes:

» swollen
» red
» hot
» tender to touch.

Note:

» Boils in diabetic, malnourished, or other immunocompromised patients are more likely to develop complications.
» Check blood glucose levels and HIV status if the boils are recurrent.

GENERAL MEASURES

Treatment will depend on the abscess size:

» Small furuncles should be managed with a moist, warm compress applied to the infected area, several times per day to promote drainage.
» Large fluctuant lesions should be treated with incision and drainage.

The following sites should be drained by a surgeon:

» Peri-rectal abscess
» Anterior and lateral neck abscess
» Abscess adjacent to nerves or blood vessels e.g carotid artery, facial nerve, central triangle of face (formed by the corners of the mouth and the nasal bridge).

Note:

» Needle aspiration is insufficient for adequate abscess drainage.
» Systemic antibiotics are used only as indicated below.

MEDICINE TREATMENT

Antibiotic therapy

Systemic antibiotics are seldom necessary, except for facial abscesses, or abscesses associated with tender draining lymph nodes, fever, or extensive surrounding cellulitis.

Antibiotics should usually be given for 5–10 days, depending on clinical response.

- Cefazolin, IV, 1g 8 hourly.

LoE:IIIb[v]

When there is clinical improvement, change to:

- Flucloxacillin, oral, 500 mg 6 hourly.

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly.

When there is clinical improvement, change to:

- Clindamycin, oral, 450 mg 8 hourly.

4.5 ATOPIC ECZEMA/ DERMATITIS

L20.0/L20.8-9

DESCRIPTION

Eczema is a pruritic, inflammatory skin condition characterised by vesicles, weeping, and crusting in the acute phase; and thickened, scaly skin with increased skin markings known as lichenification in the chronic phase.

Assessing severity

1% of body surface is equal to the size of one hand (including the fingers) of the patient.

Mild

» Less than 5% body surface involved.
» No acute changes.
» No significant impact on quality of life.

Moderate

» 5–30% body surface involved.
» Mild dermatitis with acute changes.
» Mild dermatitis with significant impact on quality of life.

Severe

» More than 30% body surface involved.
» Moderate dermatitis with acute changes.
» Moderate dermatitis with significant impact on quality of life.

GENERAL MEASURES

» Avoid exposure to trigger or precipitating factors, where applicable.
» Avoid irritants such as strong detergents, antiseptics, foam (especially hot) baths, soaps, and rough occlusive clothing (silk is better than cotton, which is better than nylon, which is better than wool).
» Good personal hygiene with once daily washing to remove crusts and accretions and avoid secondary infection.
» Keep fingernails short to minimise trauma from scratching.
» Respect patient preference for cream or ointment topical treatment.
» Wet wraps may help control eczema and pruritus but should not be used for infected eczema.
» Diet modification has no role in atopic eczema treatment unless double blind challenge testing proves food sensitivity.
» Avoid smoking.

LoE:IIIb[vi]

MEDICINE TREATMENT

To relieve skin dryness:

- Aqueous cream topical, to wash or bath.

AND

- Emulsifying ointment (UE), topical, applied daily to dry areas as a moisturiser.

LoE:IIIb[vii]

Note:
Maintenance treatment with moisturising soap, creams, and ointments as described above should be continued, even if the dermatitis is controlled.

To control wet or weepy dermatitis:
Creams are preferred to ointments on open or oozing lesions and in intertriginous folds.

Mild eczema

- Hydrocortisone 1%, topical, applied 12 hourly to body and face until control is achieved.
  - Can be used on face and in skin folds.
  - Apply sparingly to the face.
  - Use with caution around the eyes.

Moderate and severe eczema

- Potent topical corticosteroids, e.g.:
- Betamethasone 0.1%, topical, applied daily for 7 days to the affected areas.
  - Apply sparingly to face, neck and flexures.

Note: There is no clear benefit for more than once daily application.

LoE:Ia[viii]

If non-responsive:
Refer for dermatologist opinion, and whilst awaiting referral, initiate:
- Prednisone, oral, 0.5 mg/kg daily, for ≤ 2 weeks (Specialist initiated)

Maintenance therapy
Once eczema is controlled, wean to the lowest potency topical corticosteroid that maintains remission and continue applying twice a week.

- Emulsifying ointment (UE), topical, applied daily.
  - Apply moisturiser as needed.

Infected eczema
This is usually due to staphylococcal infection.

Antibiotic therapy
- Flucloxacillin, oral, 500 mg 6 hourly for 5 days.

Severe penicillin allergy: (Z88.0)
- Clindamycin, oral, 450 mg 8 hourly for 5 days.

For sedation and relief of itch:
- Chlorphenamine, oral, 4 mg at night as needed.

Eczema herpeticum (B00.0)
Therapy should be initiated without delay:
- Aciclovir, oral, 400 mg 8 hourly for 7 days.

LoE:IIIb[ix]

If patient is unable to swallow due to odynophagia:
- Aciclovir, IV, 5 mg/kg/dose, 8 hourly for 7 days.
  - Infuse over 1 hour.

LoE:IIIb[x]

REFERRAL
» Severe, non-responsive, or complicated cases.
» Cases with uncertain diagnosis (e.g. severe infection including disseminated herpes simplex).

4.6 ERYTHEMA MULTIFORME, STEVENS JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS

L51.0-2/L51.8-9

DESCRIPTION
Erythema multiforme
An acute, self-limiting, and commonly recurrent inflammatory skin eruption with variable involvement of the mucous membranes, and without systemic symptoms.

Symmetrically distributed crops of target lesions (dark centre, an inner, pale ring surrounded by an outer red ring) often involving palms and soles are characteristic. This condition is usually due to an infection, commonly herpes simplex or mycoplasma.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Life-threatening acute hypersensitivity reactions with systemic upset, epidermal necrosis, and mucous membrane involvement. TEN and SJS are different ends of the same spectrum: in SJS, the involvement is <10%, while in TEN, epidermal necrosis involves >30% of body surface area. Non-specific prodromal symptoms, often mistaken as an upper respiratory tract infection, may occur before skin lesions become apparent.

Cutaneous lesions may start as a dusky red macular rash, progressing to confluence with epidermal necrosis and large, flaccid blisters which rupture, leaving large areas of denuded skin. Mucous membrane erosions are common and multi-organ involvement may be present.

This condition is usually due to medication, e.g. sulfonamides, non-nucleoside reverse transcriptase inhibitors (especially nevirapine), anti-epileptics (phenytoin, phenobarbitone, carbamazepine, lamotrigine), allopurinol, and laxatives (phenolphthalein).

Complications include:
» Dehydration, electrolyte disturbances, and shock
» Hypoalbuminaemia
» Hypo- and more commonly hyperthermia
» High output cardiac failure
» Secondary infection and sepsis
» Adhesions and scarring

Stop all medicines, where safely possible, including complementary, alternative, and self-medication.

GENERAL MEASURES

Immediate in hospital evaluation

» The foundation of management is supportive care, good nursing, and the prevention of dehydration and sepsis.
» Stop all potentially implicated medicines.
» Patients usually require care in a high or intensive care unit with dedicated nursing.
» Attempt to identify causative agent as early withdrawal of agent improves prognosis.

Monitoring
» Monitor vital organ function.
» Examine daily for infection and swab infected lesions. Do blood cultures if fever persists or suspicion of infection.

Dressings
Ensure skin hygiene routines with daily cleansing and bland, non-adherent dressings as needed.

Do not use silver sulfadiazine if SJS/TEN is thought to be due to co-trimoxazole or other sulfonamides.

Mucous membranes:
» Regular supervised oral, genital, and eye care to prevent adhesions and scarring.
» Two-hourly mouth washes with bland mouth wash, e.g. glycothymol.
» Examine daily for ocular lesions and treat 2-hourly with eye care and lubricants (see section 18.9: Dry eye) and break down adhesions.
» Treat genitalia 6-hourly with Sitz baths and encourage movement of opposing eroded surfaces to prevent adhesions.

Fluids:
» Oral rehydration is preferred but intravenous fluid therapy may be required to treat significant dehydration.
» Encourage oral fluids to prevent pharyngeal adhesions.
» Provide soft, lukewarm food. Restrict nasogastric feeds to those patients that are unable to eat, as they may lead to additional trauma with bleeding, secondary infection, and adhesions.

Note: All patients should receive a notification bracelet/necklace on discharge.

MEDICINE TREATMENT

Corticosteroids
The use of systemic corticosteroids is not supported by evidence and is therefore not recommended.

Antibiotic therapy
» Systemic antibiotics may be indicated, depending on results of appropriate cultures. They should not be administered routinely, nor be given prophylactically.
» Organisms identified on skin swabs are not a good indicator of systemic infection.

Analgesia
Appropriate and adequate analgesia for pain should be given at least half an hour before dressing changes (see section 12.4.1: Perioperative analgesics).

REFERRAL/CONSULTATION

» Discuss with a specialist, if considering re-initiation of medication.
» Consult a specialist immediately where there is ocular involvement.

4.7 LEG ULCERS, COMPLICATED

L97

DESCRIPTION

A chronic, relapsing disorder of the lower limbs. It has many causes and is often associated with lipodermatosclerosis (bound-down, fibrosed skin) and eczema. It is mainly associated with vascular (predominantly venous) insufficiency and immobility. It is also associated with neuropathy, and, occasionally, with infections, neoplasia, trauma, or other rare conditions.

GENERAL MEASURES

» The aim of management should be to:
  – Treat underlying conditions, e.g. heart failure, diabetes mellitus, and venous stasis.
  – Limit the extent of damage.
  – Encourage rapid healing to minimise scarring and fibrosis.
  – Prevent recurrences.
» Avoid all topical irritants and allergens, e.g. lanolin, neomycin, bacitracin, parabens, fusidic acid, clioquinol, antihistamine creams, etc.
» If the ulcer is oedema- or stasis-related, rest the leg in an elevated position.
» In venous insufficiency, compression (bandages or stockings) is essential to achieve and maintain healing, provided the arterial supply is normal.
» In patients with arterial insufficiency, avoid pressure elevation and compression bandages or stockings on bony prominences and the toes.
» Counsel the patient on meticulous foot care and avoidance of minor trauma.
» Encourage walking and exercise.
» Encourage patients with neuropathy not to walk barefoot, to check their shoes for foreign objects, examine their feet daily for trauma, and to test bath water before bathing to prevent getting burnt.
» Avoid excessive local heat.
» Indications for surgical procedures include:
  – slough removal
  – arterial insufficiency
  – surgery for varicose veins
  – skin grafting

MEDICINE TREATMENT

Antibiotic therapy

Systemic antibiotics are seldom required for ulcers and should be considered only if there is surrounding cellulitis. These infections are typically polymicrobial and broad-spectrum antibiotics are recommended.

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 7 days.

Local wound care

Topical cleansing

Use bland, non-toxic products to clean the ulcer and surrounding skin.

For clean uninfected wounds:

- Sodium chloride 0.9% or sterile water.

Dress frequently with:

- Moistened dressing, e.g. gauze with sodium chloride 0.9%.

LoE:IIIb[xi]

For exudative, infected wounds:

- Povidone-iodine 5% cream, topical, apply daily.

4.8 PSORIASIS

L40.0-5/L40.8-9

DESCRIPTION

This is an inflammatory condition of the skin and joints of unknown aetiology. Scaly, red papules and plaques over extensor surfaces and on the scalp are common. The nails and skin folds are often involved. In exceptional cases, it is localised to palms and soles and pustular skin lesions are seen, especially following rapid treatment withdrawal, e.g. steroids or systemic agents.

GENERAL MEASURES

» Counsel regarding precipitating factors and chronicity.
» Encourage sun exposure as tolerated.

MEDICINE TREATMENT

Local plaques

Maintenance therapy:

- Coal tar 5%, topical, apply at night.
  - Avoid use on the face, flexures, and genitalia.

For flares:

- Potent topical corticosteroids, e.g.: *LoE:IVb*[xii]
- Betamethasone 0.1%, topical, apply 12 hourly.
  - Decrease according to severity, reduce to hydrocortisone 1% cream, then stop.

Scalp psoriasis

Maintenance therapy:

- Wash with coal tar containing shampoo.

OR

- Coal tar 1%, topical, apply at night, under occlusion, and wash out the next morning.

For flares:

- Potent topical corticosteroids, e.g.: *LoE:IVb*[xiii]
- Betamethasone 0.1% lotion, topical, apply once daily.

Note:

» Avoid systemic corticosteroids.
» Patient adherence is the greatest barrier to treatment success with topical therapies.

REFERRAL

» Inadequate response to topical treatment.
» Severe disease, especially if there is joint involvement.

4.9 URTICARIA

L50.0-6/L50.8-9

DESCRIPTION

A transient itchy inflammatory skin and mucosal condition recognised by a wheal and flare reaction. There are many causes, and in most chronic cases, the precipitant for the urticaria is never found. Lesions due to insect bites are often grouped, show a central bite mark, are on exposed areas of the body, and are often associated with excoriation, vesicles, pigmentary changes, and secondary infection.

GENERAL MEASURES

» Limit exposure to triggers such as non-immune mast cell degranulators which aggravate and prolong urticaria, e.g. opioids (such as codeine), NSAIDs, salicylates, alcohol, etc.
» Avoid oral corticosteroids.

MEDICINE TREATMENT

Antihistamines

Regular use is recommended until the urticaria is quiescent.

For chronic urticaria, less sedating antihistamines are preferable:

- Cetirizine, oral, 10 mg daily.

REFERRAL
All patients with urticaria that have individual lesions for longer than 48 hours should be referred to a specialist to exclude urticarial vasculitis.

4.9.1 PAPULAR URTICARIA
L50.8

DESCRIPTION
Papular urticaria is a hypersensitivity disorder to insect bites, resulting in recurrent, and sometimes chronic, itchy papules on exposed areas of the body. An initial lesion appears, usually as a red papule, which may blister, become excoriated, and then heal with hyperpigmentation. Lesions usually occur in crops over several months. Chronic, severe, persistent reactions may be seen in immunocompromised patients, e.g. HIV infection, immunosuppressive therapy, and malnutrition.

GENERAL MEASURES
» Reduce exposure to insects by treating pets, using mosquito nets, and fumigating the household regularly.
» Use of insect repellents may be helpful.
» Examine carefully for burrows to rule out scabies.

MEDICINE TREATMENT
New inflamed lesions:
- Potent topical corticosteroids, e.g.: *LoE:IVb*[xiv]
- Betamethasone 0.1%, topical, apply daily for 5 days.

For sedation and relief of itch:
- Chlorphenamine, oral, 4 mg at night as needed in severe cases.

REFERRAL
Non-responsive and chronic cases.

4.10 FUNGAL INFECTIONS
B35.0-6/B35.8-9/B36.0-3/B36.8-9/B40.3/B45.2/B46.3

DESCRIPTION
The skin may be infected by fungi, and the clinical presentation varies with organism, body site infected, and the body's response to the infection.

GENERAL MEASURES
» Manage predisposing factors, e.g. occlusion, maceration, and underlying conditions such as diabetes mellitus, eczema, immunocompromising conditions, etc.

» Advise patient regarding spread of infection and exposure in communal, shared facilities (especially spread of dermatophytes).

MEDICINE TREATMENT

Yeast and dermatophytes (fungal infection of the skin):
- Imidazole, e.g.:
- Clotrimazole 1%, topical, apply 8 hourly until clear of disease (i.e. for at least 2 weeks after the lesions have cleared).

Pityriasis versicolor: (B36.0)
- Selenium sulfide 2.5% suspension, applied once weekly to all affected areas.
  - Allow to dry and leave overnight before rinsing off.
  - Repeat for 3 weeks.

Systemic antifungal therapy
Topical treatment is generally ineffective for dermatophyte hair and nail infections.
Systemic therapy may be indicated for immunocompromised individuals with extensive skin infection.
- Fluconazole, oral, 200 mg once weekly for 6 weeks.
  - For onychomycosis, 200 mg weekly for 6 months.

LoE:IIIb[xv]

Note: Recurrent infections may occur if repeat exposure is not prevented.

REFERRAL
» Non-responsive infections.
» Systemic infections.

4.11 VIRAL INFECTIONS

4.11.1 VIRAL WARTS/ANOGENITAL WARTS
B07/A63.0

DESCRIPTION
Superficial muco-cutaneous infection caused by the human papilloma virus.

GENERAL MEASURES
Patients with anogenital warts are at an increased risk of other STIs.

If the patient has anogenital warts:
» Pap smear should be offered to women to screen for cervical pathology.
» Screen for HIV and other STIs.

MEDICINE TREATMENT

Cutaneous warts

Treatment is seldom indicated.

Anogenital warts

- Podophyllotoxin 0.5% solution (patient application).
  - Wash the affected areas with soap and water, and dry thoroughly with your own towel.
  - Apply petroleum jelly to surrounding skin and mucous membranes for protection.
  - Apply podophyllotoxin 12 hourly for 3 consecutive days until lesions disappear.
  - Treatment may be repeated at weekly intervals for a total of four 3-day treatment courses if necessary.

OR

- Podophyllin 20% in compound benzoin tincture, topical (health care professional application).
  - Apply petroleum jelly to surrounding skin and mucous membrane for protection.
  - Apply at weekly intervals until lesions disappear.
  - Wash the solution off after 4 hours.

LoE:IIb[xvi]

Note:

» Podophyllin and podophyllotoxin are cytotoxic agents.
» Avoid systemic absorption.

CAUTION - Podophyllotoxin
Podophyllotoxin containing agents are contraindicated in pregnancy.

REFERRAL

» Extensive or recurrent anogenital warts.

4.11.2 SHINGLES (HERPES ZOSTER)

See section 9.13: Zoster (shingles).

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SOUTH AFRICAN PRIMARY HEALTHCARE & ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 4: DERMATOLOGY
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4)

The Adult Hospital Level (AHL) Dermatology chapter underwent detailed clinical editing and editorial changes for clarity.

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG) and supporting medicine reviews. *All reviews and costing reports may be accessed at:* https://www.health.gov.za/nhi-edp-stgs-eml/.

A: PREVIOUS MEDICINE AMENDMENTS:
At the NEMLC meeting of the 25 August 2022, the following was ratified.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
4.1 Acne	Cyproterone acetate 2 mg plus ethinyl estradiol 35 mcg, oral	Directions for use not amended
4.2 Cellulitis and erysipelas	Flucloxacillin, oral	Retained
	Cefalexin, oral	Retained
	Amoxicillin, oral	Not added
4.3 Impetigo	Povidone-iodine, topical cream	Not added
4.4 Furuncles and abscesses	Povidone-iodine scrub	Not added
	Chlorhexidine scrub	Not added
4.5 Atopic eczema/ dermatitis	Guidance to avoid Smoking	Retained
- To relieve skin dryness	Emollient	Retained as a therapeutic class
	Emulsifying ointment (UE)	Retained as an example of class (emollient) listed in the STG
	Cetamacrogol	Not added as an example of class (emollient) – already included on the therapeutic interchange database
- Moderate and severe eczema	Corticosteroid, potent, topical	Retained as a therapeutic class
	Betamethasone 0.1%, topical	Retained as an example of class (potent corticosteroid) listed in the STG
	Fluocinolone, topical	Not added as an example of class (potent corticosteroid) – already included on the therapeutic interchange database
- For non-responsive eczema	Prednisone, oral	Retained
	Clobetasol, topical	Not added
- Maintenance Therapy	Emollient	Retained as a therapeutic class
	Emulsifying ointment (UE)	Retained as an example of class (emollient) listed in the STG
	Cetamacrogol	Not added as an example of class (emollient) – already included on the therapeutic interchange database
4.6 Erythema multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis	Management as of burns (debridement)	Deleted
4.7 Leg ulcers, complicated	Hydrocolloid dressings	Not added
	Moistened dressing e.g., gauze with Sodium chloride, 0.9%	Retained
4.8 Psoriasis	Coal tar 6% ointment	Deleted
- Local plaque: maintenance	Coal tar 5%, topical	Added
- Local plaque: flares	Corticosteroid, potent, topical	Retained as a therapeutic class

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
	Betamethasone 0.1%, topical	Retained as an example of class (potent corticosteroid) listed in the STG
	Fluocinolone, topical	Not added as an example of class (potent corticosteroid) – already included on the therapeutic interchange database
- Scalp psoriasis: maintenance	Coal tar 1% ointment	Deleted
	Coal tar 1%, topical	Added
- Scalp psoriasis: flares	Corticosteroid, potent, topical	Retained as a therapeutic class
	Betamethasone 0.1%, topical	Retained as an example of class (potent corticosteroid) listed in the STG
	Fluocinolone, topical	Not added as an example of class (potent corticosteroid) – already included on the therapeutic interchange database
4.9.1 Papular urticaria *- New inflamed lesions*	Corticosteroid, potent, topical	Retained as a therapeutic class
	Betamethasone 0.1%, topical	Retained as an example of class (potent corticosteroid) listed in the STG
	Fluocinolone, topical	Not added as an example of class (potent corticosteroid) – already included on the therapeutic interchange database
- Relief of itch and sedation	Chlorphenamine, oral	Retained
	Coal tar 5%, topical	Not added

Paracetamol[1] dosing has been amended in the chapter with dosage range amended and maximum dose reiterated and aligned to AHL Chapter 25: Pain.

4.1 ACNE

Cyproterone acetate 2 mg plus ethinyl estradiol 35 mcg, oral: *directions for use not amended*

External comment without supporting evidence was received suggesting that an age cut off should be provided for oral cyproterone-containing contraceptive for acne, was not accepted. The Adult Hospital Level STGs and EML provides guidance for women with acne.

4.2 CELLULITIS AND ERYSIPELAS

Flucloxacillin, oral: *retained*

Cefalexin, oral*: retained*

Amoxicillin, oral: *not added*

Similar to the PHC Skin chapter, an external comment to replace flucloxacillin/cefalexin with amoxicillin without supporting evidence was not considered, noting that macrolides are already included as an alternative for severe penicillin allergy and intravenous antibiotics are recommended for severe infection.

The NEMLC recommended at the meeting of the 25 August 2022[2] that the PHC/Adult Hospital Level ERC review the evidence for the retention and recommendation of cefalexin for *S Aureus* infections in relation to other antibiotics. An evidence review[3] was summarized including two Cochrane Reviews[4,5] (low & moderate quality review) and Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America (IDSA)[6].

[1] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

2 Minutes of the NEMLC meeting of 25 August 2022.

3 Cephalexin: National Department of Health: Affordable Medicines, EDP- Primary Healthcare and Adult Hospital Level. Medicine Review: Evidence summary of the use of cephalexin for S Aureus skin infections, September 2022.

4 Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev. 2010 Jun 16;2010(6):CD004299. doi: 10.1002/14651858.CD004299.pub2. PMID: 20556757; PMCID: PMC869318

5 Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC, Berger M, van der Wouden JC. Interventions for impetigo. Cochrane Database Syst Rev. 2012 Jan 18;1(1):CD003261. doi: 10.1002/14651858.CD003261.pub3. PMID: 22258953; PMCID: PMC7025440

6 Intravenous antibiotics (severe cellulitis and erysipelas): Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.idsociety.org/practice-guideline/skin-and-soft-tissue-infections/

In September 2022, an additional search brought up a protocol of a study that is still underway entitled antibiotic therapy for skin and soft tissue infections: a protocol for a systematic review and network meta-analysis (biomedcentral.com)[7]. Remaining, studies date back to the 1990's and early 2000's.

In summary:[3]

- The Cochrane reviews could not definitively recommend one antibiotic treatment over another
- It was unclear if oral antibiotics are superior to topical antibiotics for the management of impetigo.
- Penicillin was not as effective as other antibiotics as an intervention for the management of impetigo.
- Mostly there was no significant difference between cefalexin and other treatments, however cefalexin was the most effective treatment (significantly different versus penicillin) in the treatment of non-bullous impetigo. In this case *S aureus* was the most common cause of impetigo in a paediatric population and cefalexin was the most effective treatment.

Level of Evidence: Low to Moderate certainty evidence (conditional)

4.3 IMPETIGO

Povidone-iodine, topical cream: *not added*
The PHC STG recommends a topical antibacterial cream and referral for severe disease to secondary level of care for management with oral antibiotics.

4.4 FURUNCLES AND ABSCESSES

Povidone-iodine scrub: *not added*
Chlorhexidine scrub: *not added*
External comment without supporting evidence was received for washes with povidone-iodine or chlorhexidine to prevent progression of folliculitis to furuncles and/or abscesses often follow folliculitis, was not considered.

As per IDSA[8] guidelines, narrative review[9] and observational evidence[10] the STG recommends antibiotic therapy for adult hospital level of care.

Level of Evidence: Low certainty evidence (conditional)

progression of folliculitis to furuncles and/or abscesses often follow folliculitis, was not considered.

4.5 ATOPIC ECZEMA/ DERMATITIS

Guidance to avoid smoking: *retained*
Evidence indicates that smoking may cause an increased frequency of hand eczema, particularly in high-risk occupations[11]. Therefore, guidance to avoid smoking was retained in the STG.

To relieve skin dryness
Emollient: *retained as a therapeutic class*

[7] Bartoszko JJ, Mertz D, Thabane L, Loeb M. Antibiotic therapy for skin and soft tissue infections: a protocol for a systematic review and network meta-analysis. Syst Rev. 2018 Sep 11;7(1):138. doi: 10.1186/s13643-018-0804-8. PMID: 30205844; PMCID: PMC6134765.

8 Cefazolin, IV: Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.ncbi.nlm.nih.gov/pubmed/24973422

9 Cefazolin, IV: Loubet P, Burdet C, Vindrios W, Grall N, Wolff M, Yazdanpanah Y, AndremontA, Duval X, Lescure FX. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. ClinMicrobiol Infect. 2017 Jul 8.pii: S1198-743X(17)30358-0.https://www.ncbi.nlm.nih.gov/pubmed/28698037

10 Cefazolin, IV: Bai AD, Showler A, Burry L, Steinberg M, Ricciuto DR, Fernandes T, Chiu A, Raybardhan S, Science M, Fernando E, Tomlinson G, Bell CM, Morris AM. Comparative effectiveness of cefazolin versus cloxacillin as definitive antibiotic therapy for MSSA bacteraemia: results from a large multicentre cohort study. J Antimicrob Chemother. 2015 May;70(5):1539-46. https://www.ncbi.nlm.nih.gov/pubmed/25614044

[11] Sørensen JA, Clemmensen KK, Nixon RL, Diepgen TL, Agner T. Tobacco smoking and hand eczema - is there an association? Contact Dermatitis. 2015 Dec;73(6):326-35.

Emulsifying ointment (UE): *retained as an example of class (emollient) listed in the STG*
Cetamacrogol: *not added as an example of class (emollient) – already included on the therapeutic interchange database*

Moderate and severe eczema
Corticosteroid, potent, topical: *retained as a therapeutic class*
Betamethasone 0.1%, topical: *retained as an example of class (potent corticosteroid) listed in the STG*
Fluocinolone, topical: *not added as an example of class (potent corticosteroid) – already included on the therapeutic interchange database*

Non-responsive eczema
Prednisone, oral: *retained*
Clobetasol, topical: *not added*
An external comment without supporting evidence was received that oral prednisone should only be provided by specialists/dermatologists only, as prednisone was not considered standard. Furthermore, the option of topical clobetasol accessed via telephonic prescription was proposed.
Recommendation: The PHC/Adult Hospital Level Committee recommended that the recommendation be retained, as oral prednisone would be initiated in consultation with a dermatologist, whilst awaiting referral. In addition, clobetasol is only accessible at tertiary and quaternary level, and it was not feasible to access clobetasol via a telephonic prescription.
Level of Evidence: Expert opinion

Maintenance Therapy
Emollient: *retained as a therapeutic class*
Emulsifying ointment (UE): *retained as an example of class (emollient) listed in the STG*
Cetamacrogol: *not added as an example of class (emollient) – already included on the therapeutic interchange database*

4.6 ERYTHEMA MULTIFORME, STEVENS JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS

Management as of burns (debridement): *deleted*
Management includes "no debridement", and thus STG text as updated as follows:

Principles of management
Immediate in hospital evaluation
The foundation of management is supportive care, good nursing, and the prevention of dehydration and sepsis.
~~Management is similar to that of burns.~~
Stop all potentially implicated medicines.
Patients usually require care in a high or intensive care unit with dedicated nursing.
Attempt to identify causative agent as early withdrawal of agent improves prognosis.

The STG does provide specific guidance on dressings, skin hygiene and daily cleansing.

4.7 LEG ULCERS, COMPLICATED

Hydrocolloid dressings: *not added*
Moistened dressing e.g. gauze with Sodium chloride, 0.9%: *retained*
External comment was submitted without evidence to include hydrocolloid dressings for local wound care. There is no evidence to support the superiority of one dressing type over another when applied under appropriate multilayer compression bandaging[12].

4.8 PSORIASIS

Local plaques: maintenance
Coal tar 6% ointment: *deleted*
Coal tar 5%, topical: *added*

[12] Palfreyman SJ, Nelson EA, Lochiel R, Michaels JA. Dressings for healing venous leg ulcers. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD001103. doi: 10.1002/14651858.CD001103.pub2.

Coal tar 6% ointment is currently not available on the market and thus topical 5% coal tar preparation was added to the STG, as readily available.

Local plaques: flares
Corticosteroid, potent, topical: *retained as a therapeutic class*
Betamethasone 0.1%, topical: *retained as an example of class (potent corticosteroid) listed in the STG*
Fluocinolone, topical: *not added as an example of class (potent corticosteroid) – already included on the therapeutic interchange database*

Scalp psoriasis: maintenance
Coal tar 1% ointment: *deleted*
Coal tar 1%, topical: *added*
Coal tar 1% ointment is not available on the South African market, and a more generic description of coal tar 1%, topical was added to cover currently available products.
Level of Evidence: Expert opinion

Scalp psoriasis: flares
Corticosteroid, potent, topical: *retained as a therapeutic class*
Betamethasone 0.1%, topical: *retained as an example of class (potent corticosteroid) listed in the STG*
Fluocinolone, topical: *not added as an example of class (potent corticosteroid) – already included on the therapeutic interchange database*

4.9.1 PAPULAR URTICARIA

New inflamed lesions
Corticosteroid, potent, topical: *retained as a therapeutic class*
Betamethasone 0.1%, topical: *retained as an example of class (potent corticosteroid) listed in the STG*
Fluocinolone, topical: *not added as an example of class (potent corticosteroid) – already included on the therapeutic interchange database*

For sedation and relief of itch

Chlorphenamine, oral: *retained*

&

For relief of itch

Coal tar 5%, topical: *not added*

External comment without supporting evidence for topical 5% coal tar to relieve itching, was received. Additional review of the literature identified no strong evidence for the use of coal tar 5%, topical.

South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: Skin Conditions/Dermatology

EVIDENCE SUMMARY

Title: Evidence summary of the use of cephalexin for *S Aureus* skin infections

Date: 8 September 2022

Reviewers: Milli Reddy, Halima Dawood, Zahiera Adam

Affiliation and declaration of interests: MR (Right to Care), HD (Grey's Hospital, Caprisa, University of KwaZulu-Natal, Combined Primary Healthcare/Adult Hospital Level Committee, 2021-2023 & National Essential Medicines List Committee, 2021-2023) & ZA (Right to Care) have no interests to declare pertaining to cephalexin.

Background:
At a recent National Essential Medicines List Committee (NEMLC) meeting (August 2022), the inclusion of cephalexin for Staphylococcus Aureus skin infections was deliberated as an external comment was received to replace flucloxacillin/cephalexin with amoxicillin/clindamycin for the management of impetigo and cellulitis, without supporting evidence.

It is noted that during the 2013 review cycle a request was made to replace cloxacillin with amoxicillin. However, cloxacillin was retained. Cloxacillin supply constraints have been experienced by the Department of Health. Macrolides are included in the Standard Treatment Guidelines (STG) as an alternative for severe penicillin allergy.

A summary of the evidence used in reaching the decision to retain cephalexin on the STG was requested by NEMLC. The evidence includes two Cochrane reviews (2010 & 2012)[i],[ii] and Guidelines from the Infectious Diseases Society of America[iii].

In September 2022, an additional search brought up a protocol of a study that is still underway entitled antibiotic therapy for skin and soft tissue infections: a protocol for a systematic review and network meta-analysis (biomedcentral.com)[iv]. Remaining, studies date back to the 1990's and early 2000's. Therefore, the two Cochrane Reviews[i,ii] and IDSA guideline[iii] were reviewed and summarised here.

Meta-Analysis and Systematic Review of Interventions for cellulitis and erysipelas[i]

A Cochrane review included 25 studies (n=2488) published until May 2010 that included adults or children diagnosed with cellulitis. Treatment regimens included antibiotics or antibiotics with anti-inflammatory agents, or physical treatment (such as topical heat, cold, vibration, or elevation). The primary outcomes included symptoms rated by participant or medical practitioner, e.g., duration and intensity of fever, pain, redness of the affected area, swelling of the skin surface and subcutaneous tissue, blister formation, or proportion symptom-free ('cure'), at a time specified by the study authors; proportion with severe complications (such as severe sepsis, multi-organ failure, death) and quality of life scores (including generic and disease-specific items and return to normal activity). Data was screened and independently extracted by two authors. For studies where similar types of interventions were compared and the same primary outcome measures were used, a meta-analysis was conducted.

The age of participants from the included trials ranged from 16 to 90 years old. Of the 25 studies included 17 studies included skin and skin structure infections (such as abscess, impetigo, folliculitis (inflammation of hair follicles), furunculosis (boils), and wound infection). Cellulitis was included as a subgroup. There were eight studies included

where cellulitis or erysipelas was the main inclusion criteria. Three trials compared a cephalosporin with penicillin, six trials compared different cephalosporins and one trial compared a macrolide against a first-generation cephalosporin.

Results:

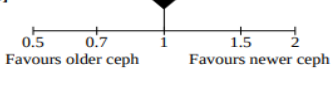
Penicillin versus a cephalosporin: None of the three studies that compared penicillin to a cephalosporin included cephalexin in the comparison. In two studies IV ampicillin/sulbactam was compared with IV cefazolin for the treatment of cellulitis. In the third study IV cefuroxime was compared with IV flucloxacillin. After accounting for heterogeneity, the two studies that reviewed the 1st generation cephalosporins showed no strong evidence of an effect (RR 1.17, 0.91 to 1.50). Similarly, the evidence from the one study using a third-generation cephalosporin also showed no strong effect (RR 0.7, 95% CI 0.48 to 1.00).

Cephalosporin versus cephalosporin

Symptoms rated by participant or medical practitioner (Cure at the end of treatment): Six trials (n=538) compared one cephalosporin with another. Four of these six trials included cephalexin in the comparison. In the meta-analysis comparisons were labelled as new vs old cephalosporin. Overall, no significant differences in treatment effect were noted between the cephalosporins (RR 1.00, 95% CI 0.94 to 1.06).

Analysis 3.1. Comparison 3: Newer vs older generation cephalosporin, Outcome 1: Symptom-free/reduced at the end of treatment

Study or Subgroup	Newer cephalosporin Events	Total	Older cephalosporin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 2nd vs 1st generation						
Iannini 1985	31	35	9	10	6.5%	0.98 [0.78 , 1.25]
Subtotal (95% CI)		**35**		**10**	**6.5%**	**0.98 [0.78 , 1.25]**
Total events:	31		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
3.1.2 3rd vs 1st generation						
Bucko 2002 part 2	50	56	55	66	18.7%	1.07 [0.93 , 1.23]
Grayson 2002	51	59	51	59	18.2%	1.00 [0.87 , 1.15]
Tack 1998	13	17	14	17	3.2%	0.93 [0.66 , 1.31]
Subtotal (95% CI)		**132**		**142**	**40.0%**	**1.03 [0.93 , 1.13]**
Total events:	114		120			
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
3.1.3 3rd vs 2nd generation						
Bucko 2002 part 1	54	66	69	79	18.6%	0.94 [0.81 , 1.08]
Subtotal (95% CI)		**66**		**79**	**18.6%**	**0.94 [0.81 , 1.08]**
Total events:	54		69			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.37)						
3.1.4 4th vs 3rd generation						
Schwartz 1996	49	51	22	23	34.8%	1.00 [0.91 , 1.11]
Subtotal (95% CI)		**51**		**23**	**34.8%**	**1.00 [0.91 , 1.11]**
Total events:	49		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)		**284**		**254**	**100.0%**	**1.00 [0.94 , 1.06]**
Total events:	248		220			
Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 5 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.97)						
Test for subgroup differences: Chi² = 1.13, df = 3 (P = 0.77), I² = 0%						



Miscellaneous (Other) antibiotics: One study which provided an analysis for a cellulitis subgroup showed failure rates of 1/24 (4%) for azithromycin vs 1/23 for cephalexin (4%). In this study oral azithromycin was administered as 1 x 500 mg on day 1 and 250 mg once a day on days 2 to 5. Oral cephalexin was dosed 500 mg 2 times a day for 10 days.

Refer to Appendix 1A for AMSTAR review.

Interventions for impetigo (Review)[ii]

Initially 57 trials were included in the review. Following the update of the review, 1 trial was excluded and 12 new trials added. Therefore, the updated review included 68 trials (n=5578), reporting on 50 different treatments, including placebo.

Participants included were diagnosed with impetigo or impetigo contagiosa (preferably confirmed by bacterial culture). Treatments included topical or systemic (oral, intramuscular, or intravenous) antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. Studies that compared different dosages of the same medicine were excluded. Primary outcomes included (1) clearance of crusts, blisters, and redness (i.e., cure as assessed by the investigator), and (2) relief of symptoms such as pain, itching, and soreness as assessed by the participant in the trial.

Topical antibiotics vs oral (systemic) antibiotics (overall n=16 studies, 17 comparisons; n=1 study relevant to cephalexin)

No significant differences were noted between mupirocin and dicloxacillin (n=1 study), cephalexin (n=1 study), or ampicillin (n=1 study). Bacitracin was significantly worse than oral cephalexin in this one small study[v] (n=26 participants), which consisted of three arms.

In this study, cephalexin was reviewed at a dose of 50 mg/kg/day orally in three divided doses (maximum 500mg per dose) plus 30 g of a placebo topical ointment (petrolatum plus glycerin) to be applied to affected areas three times daily in 10 patients, mupirocin ointment 2%, 3 times a day plus an oral liquid placebo matched to oral cephalexin to be given in a dosage comparable with that of cephalexin in 7 patients and bacitracin ointment 500 units/g, three times a day plus an oral liquid placebo matched to oral cephalexin to be given in a dosage comparable with that of cephalexin in three divided daily doses in 9 patients.

S. aureus was cultured from all 22 of 26 patients who had cultures performed of their lesions.

An improvement was noted in 1/10 (1%) participant in the cephalexin group vs 1/7 (14%) in the mupirocin group vs none (n=9 participants) in the bacitracin group. Nine of 10 participants (90%) on cephalexin were cured vs 6/7 (86%) in the mupirocin group vs 3/9 (33%) in the bacitracin group. No treatment failures (0%) were noted for cephalexin and mupirocin groups. However, 6/9 (67%) participants were noted as failing in the bacitracin group.

Comparison of the three treatment groups (Taken from Bass, 1997[v])

Treatment	Initial Lesion(s) Size (cm^2)	Duration of Lesions (Days)	Type of Lesion(s)	Culture Results	Outcome Failure/Improved/ Cured
Cephalexin	6.9 ± 1.8*	7.5 ± 1.8	HC 9, B 1	SA 9	0/1/9
Mupirocin	8.0 ± 3.8	6.1 ± 3.0	HC 4, HC + B1, B1, P1	SA 3, SA + GABHS 2	0/1/6
Bacitracin	4.4 ± 0.9	7.2 ± 1.6	HC 5, HC + B 1, P + B 1, B 2	SA 7, SA + GABHS 1	6/0/3
	6.3 ± 1.3	7.0 ± 1.2	Totals HC 18, HC + B 2, P + B 1, B 4, P 1	Totals SA 19, SA + GABHS 3	Totals 6/2/18

*Mean ± SE.
HC, honey-crusted; NA, not available; GABHS, group A beta-hemolytic streptococci; SA, *Staphylococcus aureus*; B, bullous; S, sensitive; P, pustular; R, resistent.

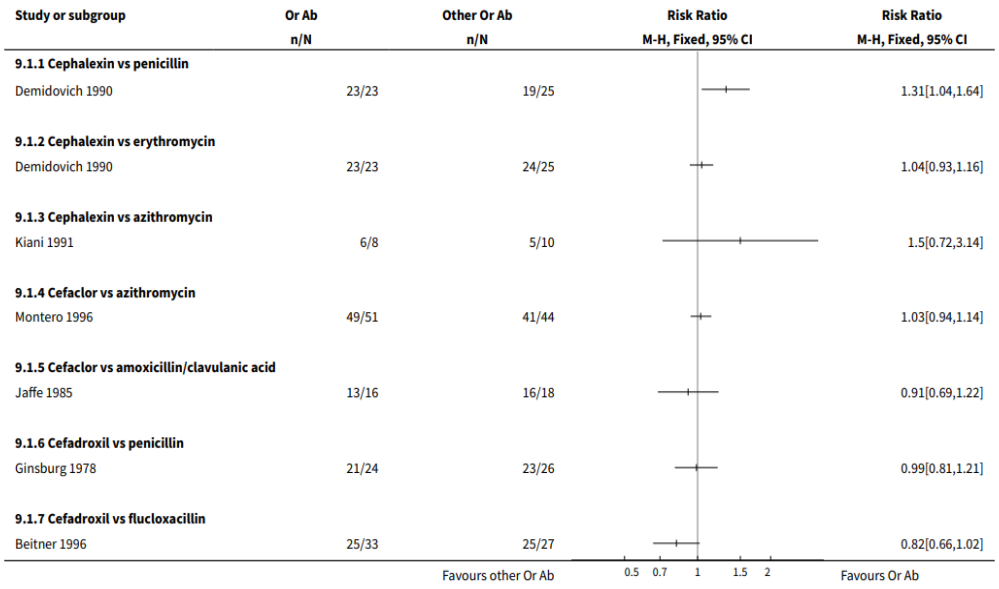
Adverse effects were not reported in the study.

Oral antibiotic vs another oral antibiotic: cephalosporin vs another antibiotic (n=6 studies)

Only one comparison, cephalexin versus penicillin, showed a significant difference in the treatment of non-bullous impetigo (RR 1.31, 95% CI 1.04 to 1.64), favouring cephalexin. Treatment failure occurred in 6/25 (24%) treated with penicillin, 1/25 (4%) treated with erythromycin, and 0/23 (0%) treated with cephalexin. Results showed that *S aureus* was the most common cause of impetigo in this paediatric study population and cephalexin was the most effective treatment. Additionally, erythromycin estolate was nearly equally effective as cephalexin but penicillin was considered

inadequate for treatment of non-bullous impetigo.[vi] There were concerns around randomization, blinding and selective reporting on outcome data and other biases in this study.

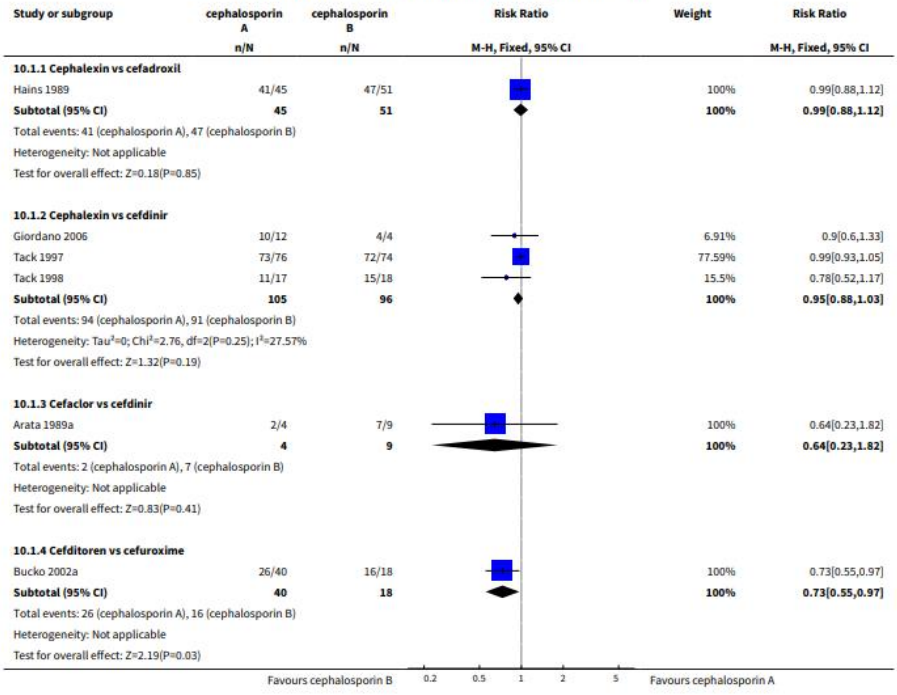
Analysis 9.1. Comparison 9 Non-bullous impetigo: oral (Or) antibiotic (Ab) (cephalosporin) vs another oral (Or) antibiotic (Ab), Outcome 1 Cure/improvement.

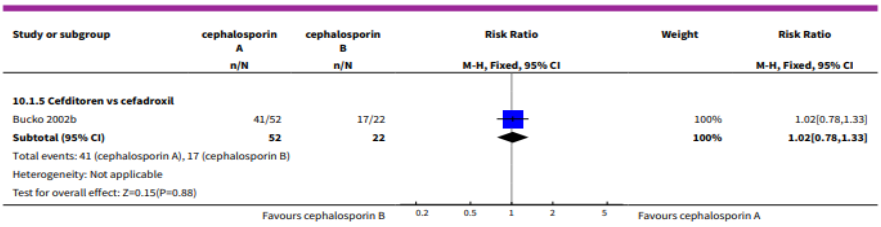


Oral antibiotic vs another oral antibiotic: one cephalosporin vs another cephalosporin (n=7 studies)

No significant differences were noted between cephalexin and cefadroxil, cephalexin vs cefdinir, cefaclor vs cefdinir, or cefditoren vs cefadroxil. The only significant difference for the cephalosporins was noted in the comparison of cefditoren vs cefuroxime, where cefuroxime was more effective (RR 0.73, 99% CI 0.55 to 0.97).

Analysis 10.1. Comparison 10 Non-bullous impetigo: oral (Or) cephalosporin vs other oral (Or) cephalosporin, Outcome 1 Cure/improvement.





Oral antibiotic versus another oral antibiotic (n=1 study)

No significant difference was noted between cephalexin (50 mg/kg/day in 2 divided doses) and dicloxacillin (15 mg/kg/day in 4 divided doses) (RR 1.17, 95% CI 0.95 to 1.45) in the treatment of bullous impetigo.

Topical antibiotic versus oral antibiotic (n=1 study)

No significant difference was noted for cure or improvement between topical mupirocin (44/77 (57%) cured or improved) vs oral cephalexin (52/82; 63%) (RR 1.11, 95% CI 0.86 to 1.43).

Oral antibiotics

In a very small study (n=10), no significant difference was detected between cephalexin and enoxacin for either cure or improvement in secondary impetigo cases (RR 0.75, 96% CI 0.24 to 2.33).

Refer to Appendix 1B for AMSTAR review.

Guidelines

Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America[iii] recommend the following regarding cephalexin and *S Aureus Skin* Infections:

Therapy for Typical Cases of Cellulitis:

- Should include an antibiotic active against streptococci.

- A large percentage of patients can receive oral medications from the start for typical cellulitis, and suitable antibiotics for most patients include penicillin, amoxicillin, amoxicillin-clavulanate, dicloxacillin, cephalexin, or clindamycin.
- In cases of uncomplicated cellulitis, a 5-day course of antimicrobial therapy is as effective as a 10-day course, if clinical improvement has occurred by 5 days
- If coverage for both streptococci and Methicillin-resistant Staphylococcus aureus (MRSA) is desired for oral therapy, options include clindamycin alone or the combination of either sulfamethoxazole and trimethoprim (SMX-TMP) or doxycycline with a β-lactam (e.g., penicillin, cephalexin, or amoxicillin)
- The guidelines mention that a double-blind study showed that a combination of SMX-TMP plus cephalexin was no more efficacious than cephalexin alone in pure cellulitis

Evaluation and Treatment of Impetigo and Ecthyma:

- Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible dicloxacillin or cephalexin is recommended

Impetigo (Staphylococcus and Streptococcus):

- Adults: Cephalexin - 250mg QID po
- Children 25-50mg/kg/d in 3-4 divided doses po

***Methicillin-Sensitive Staphylococcus. Aureus Skin and soft tissue infections* (*MSSA SSTI)*:** (For penicillin allergic patients except those with immediate hypersensitivity reactions. Availability of a suspension and requirement for less frequent dosing)

- Adults: Cephalexin - 500mg QID po
- Children 25-50mg/kg/d in 4 divided doses po

***Streptococcal skin infections*:**

- Adults: Cephalexin 500 mg every 6 h po

***Antibiotics for Treatment of Incisional Surgical Site Infection*:**

- *Surgery of trunk or extremity away from axilla or perineum:* Cephalexin 500 mg every 6 h po

Refer to Appendix 2 for AGREE II Appraisal.

Conclusions

The Cochrane reviews could not definitively recommend one antibiotic treatment over another, and it was unclear if oral antibiotics are superior to topical antibiotics for the management of impetigo. However, penicillin was not as effective as other antibiotics as an intervention for the management of impetigo. Mostly there was no significant difference between cephalexin and other treatments and cephalexin was the most effective treatment (significantly different versus penicillin) in the treatment of non-bullous impetigo. In this case *S aureus* was the most common cause of impetigo in a paediatric population and cephalexin was the most effective treatment. Previously, also due to supply issues, cephalexin was recommended for S aureus skin infections.

Appendix 1 A: Evaluating the methodological quality of the Kilburn et al (2010)[1] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[2])

LOW QUALITY REVIEW

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	No	Comparators were not explicitly explained (grouped with interventions)
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	Report listed deviations from the protocol
3	Review authors explained selection of the study designs for inclusion in the review	Yes	The authors mention that they included studies that allocated participants to groups using randomisation in order to reduce bias.
4*	Review authors used a comprehensive literature search strategy	Partial yes	The authors did not include/consult content experts in the field where relevant
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7*	Review authors provided a list of excluded studies and justify the exclusions	Yes	-
8	Review authors described the included studies in adequate detail	Partial yes	Comparators included as interventions
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	Risk of bias assessed using Cochrane methods – no graphical representation provided
10	Review authors reported on the sources of funding for the studies included in the review.	No	Only mention that a number of drug-company-sponsored studies excluded participants where the bacteria isolated were not sensitive to study antibiotics
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes	-
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	The authors mention that they were not able to conduct sensitivity analyses due to the small number of trials available within each category
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	There was heterogeneity in the results
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No	
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	The authors had no conflicts of interest to disclose

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

[1] Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev. 2010 Jun 16;2010(6):CD004299. doi: 10.1002/14651858.CD004299.pub2. PMID: 20556757; PMCID: PMC8693180.

[2] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

Appendix 1 B: Evaluating the methodological quality of the Koning et al (2012)[3] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[4])

MODERATE QUALITY REVIEW

No.	Criteria	Yes/ Partial Yes/ No	Comment
1	Research questions and inclusion criteria for the review included the components of PICO	No	Comparators were not explicitly explained (grouped with interventions)
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	Report listed deviations from the protocol Inclusion and exclusion were not explicitly stated in the methods but assessed in the results and summary provided in tables
3	Review authors explained selection of the study designs for inclusion in the review	No	The authors mentioned that they included randomized controlled trials but do not provide an explanation
4*	Review authors used a comprehensive literature search strategy	Partial yes	The authors did not apply any language restrictions. Conducted search on 27 July 2010 and published in 2012
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7*	Review authors provided a list of excluded studies and justify the exclusions	Yes	-
8	Review authors described the included studies in adequate detail	Partial yes	Comparators included as interventions
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	Risk of bias assessed using Cochrane methods
10	Review authors reported on the sources of funding for the studies included in the review.	Yes	
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	No meta-analyses conducted	Did not conduct meta-analyses
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	No meta-analyses conducted	Did not conduct meta-analyses
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No meta-analyses conducted	
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	Where there was conflict of interest declared, the authors explained how funds from sponsors were used

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

[3] Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC, Berger M, van der Wouden JC. Interventions for impetigo. Cochrane Database Syst Rev. 2012 Jan 18;1(1):CD003261. doi: 10.1002/14651858.CD003261.pub3. PMID: 22258953; PMCID: PMC7025440.

[4] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

Appendix 2: AGREE II Score Sheet - Evidence-Based Guideline: Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America[iii]

		Reviewer 1 (1 to 7 – Strongly Disagree to Strongly Agree)	Reviewer 2 (1 to 7 – Strongly Disagree to Strongly Agree)
Domain 1	**Scope and purpose**		
Item 1	The overall objective(s) of the guideline is (are) described	5	6
Item 2	The health question(s) covered by the guideline is (are) specifically described	7	7
Item 3	The population (patients, public, etc) to whom the guideline is meant to apply is specifically described	7	4
Domain 2	**Stakeholder involvement**		
Item 4	The guideline development group includes individuals from all relevant professional groups.	6	6
Item 5	The views and preferences of the target population (patients, public, etc.) have been sought.	1	1
Item 6	The target users of the guideline are clearly defined	2	3
Domain 3	**Rigour of development**		
Item 7	Systematic methods were used to search for evidence	4	3
Item 8	The criteria for selecting the evidence are clearly described	4	1
Item 9	The strengths and limitations of the body of evidence are clearly described	3	1
Item 10	The methods for formulating the recommendations are clearly described	6	5
Item 11	The health benefits, side effects, and risks have been considered in formulating the recommendations	4	1
Item 12	There is an explicit link between the recommendations and the supporting evidence	6	6
Item 13	The guideline has been externally reviewed by experts prior to its publication	4	3
Item 14	A procedure for updating the guideline is provided	7	7
Domain 4	**Clarity of presentation**		
Item 15	The recommendations are specific and unambiguous	6	5

		Reviewer 1 (1 to 7 – Strongly Disagree to Strongly Agree)	Reviewer 2 (1 to 7 – Strongly Disagree to Strongly Agree)
Item 16	The different options for management of the condition or health issue are clearly presented	6	5
Item 17	Key recommendations are easily identifiable	6	6
Domain 5	**Applicability**		
Item 18	The guideline describes facilitators and barriers to its applications	1	1
Item 19	The guideline provides advice and/or tools on how the recommendations can be put into practice	4	3
Item 20	The potential resource implications of applying the recommendations have been considered	1	1
Item 21	The guideline presents monitoring and/or auditing criteria	1	1
Domain 6	**Editorial independence**		
Item 22	The views of the funding body have not influenced the content of the guideline	4	4
Item 23	Competing interests of guideline development group members have been recorded and addressed	6	6
Overall assessment	**Assessment**		
	Rate the overall quality of the guideline	5	4
	I would recommend this guideline for use (yes/with modifications/no	Yes, with Modifications	Yes, with Modifications

Appendix 4: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	The Cochrane reviews could not definitively recommend one antibiotic treatment over another for cellulitis. One comparison, cephalexin versus penicillin, showed a significant difference in the treatment of non-bullous impetigo (RR 1.31, 95% CI 1.04 to 1.64), favouring cephalexin Recommendations are based on one trial
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	Overall, no significant differences in treatment effect were noted between the cephalosporins (RR 1.00, 95% CI 0.94 to 1.06). 6 trials (n=538) – only 4 included cephalexin One comparison, cephalexin versus penicillin, showed a significant difference in the treatment of non-bullous impetigo (RR 1.31, 95% CI 1.04 to 1.64), favouring cephalexin (n=1 trial). No significant differences between: • mupirocin, dicloxacillin, cephalexin & ampicillin (n=1 study) • topical mupirocin vs oral cephalexin • cephalexin and enoxacin • cephalosporins
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Failure rates of 1/23 for cephalexin (4%) – 1 trial Concerns around randomization, blinding and selective reporting on outcome data and other biases in the study that favoured cephalexin over penicillin.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☐ None ☐	Unknown - Most trials did not consider adverse effects.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	Most likely favours intervention – as no significant differences with other oral antibiotics and topical treatments. One comparison showed that cephalexin performed significantly better in the treatment of non-bullous impetigo (*S aureus*) compared to penicillin.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	In March/April 2022 – there were some supply challenges experienced with cephalexin syrup. No supply challenges with cephalexin capsules May 2022 – no supply issues noted for cephalexin suspension or capsules

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td></td><td></td><td>June 22 – supply issues on cephalexin suspension

July 2022 – No serious supply issues noted on suspension or capsules</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive: [ ] Less intensive: [x] Uncertain: [ ]</td><td>Price of medicines/ month
<table><tr><th>Medicine</th><th>Price (ZAR)*</th></tr><tr><td>Cefalexin; 250mg; Capsule; 20 Capsules</td><td>14.95</td></tr><tr><td>Cefalexin; 500mg; Capsule; 20 Capsules</td><td>25.88</td></tr><tr><td>Cefalexin; 125mg/5ml; Suspension; 100 ml</td><td>13.69</td></tr><tr><td>Cefalexin; 250mg/5ml; Suspension; 100 ml</td><td>22.68</td></tr></table>Medicine Procurement Catalogue – September 2022</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor: [ ] Major: [ ] Uncertain: [x]

Is the option acceptable to key stakeholders?
Yes: [x] No: [ ] Uncertain: [ ]</td><td>It is uncertain how people value the option. However, cephalexin is available on tender and is used in the public health sector.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes: [ ] No: [x] Uncertain: [ ]</td><td></td></tr>
</table>

<table>
<tr><th colspan="6">PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:</th></tr>
<tr><td>Type of recommendation</td><td>We recommend against the option and for the alternative (strong)</td><td>We suggest not to use the option (conditional)</td><td>We suggest using either the option or the alternative (conditional)</td><td>We suggest using the option (conditional)</td><td>We recommend the option (strong)</td></tr>
<tr><td></td><td></td><td></td><td></td><td>X</td><td></td></tr>
<tr><td colspan="6"><u>PHC/AHL Recommendation: (29 September 2022):</u> The committee suggests that cephalexin be used for management of impetigo as a therapeutic alternative to oral flucloxacillin.
Rationale: Limited evidence showing similar efficacy to alternative antibiotics
Level of Evidence: Low
Review indicator: Completion of an updated Cochrane Review</td></tr>
<tr><td colspan="6"><u>NEMLC RECOMMENDATION: 20 OCTOBER 2022</u>
• The committee suggests that cephalexin be used for management of skin and soft tissue infections as a therapeutic alternative to oral flucloxacillin.</td></tr>
<tr><td colspan="6">Monitoring and evaluation considerations</td></tr>
<tr><td colspan="6">Research priorities</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	8 September 2022	MR, HD, ZA	**Cephalexin be used for management of impetigo as a therapeutic alternative to oral flucloxacillin.** *Rationale:* **Limited evidence showing similar efficacy to alternative antibiotics**

References

[i] Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev. 2010 Jun 16;2010(6):CD004299. doi: 10.1002/14651858.CD004299.pub2. PMID: 20556757; PMCID: PMC8693180.

[ii] Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC, Berger M, van der Wouden JC. Interventions for impetigo. Cochrane Database Syst Rev. 2012 Jan 18;1(1):CD003261. doi: 10.1002/14651858.CD003261.pub3. PMID: 22258953; PMCID: PMC7025440

[iii] Intravenous antibiotics (severe cellulitis and erysipelas): Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. https://www.idsociety.org/practice-guideline/skin-and-soft-tissue-infections/

[iv] Bartoszko JJ, Mertz D, Thabane L, Loeb M. Antibiotic therapy for skin and soft tissue infections: a protocol for a systematic review and network meta-analysis. Syst Rev. 2018 Sep 11;7(1):138. doi: 10.1186/s13643-018-0804-8. PMID: 30205844; PMCID: PMC6134765.

[v] Bass JW, Chan DS, Creamer KM, Thompson MW, Malone FJ, Becker TM, Marks SN. Comparison of oral cephalexin, topical mupirocin and topical bacitracin for treatment of impetigo. Pediatr Infect Dis J. 1997 Jul;16(7):708-10. doi: 10.1097/00006454-199707000-00013. PMID: 9239775.

[vi] Demidovich CW, Wittler RR, Ruff ME, Bass JW, Browning WC. Impetigo. Current etiology and comparison of penicillin, erythromycin, and cephalexin therapies. Am J Dis Child. 1990 Dec;144(12):1313-5. doi: 10.1001/archpedi.1990.02150360037015. PMID: 2244610.