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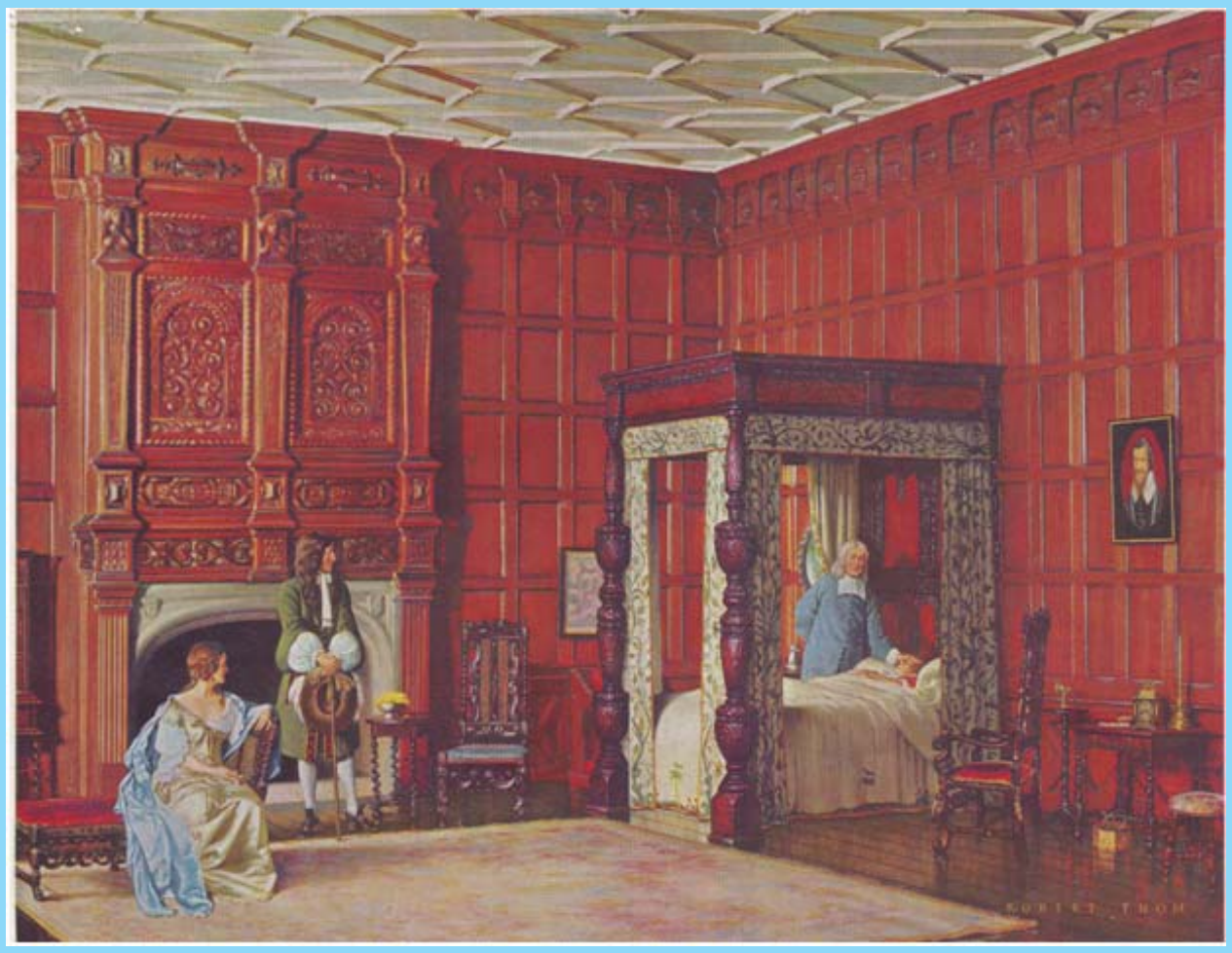

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Cover picture

SYDENHAM: PROPONENT OF CLINICAL MEDICINE

Thomas Sydenham (1624-1689), seventeenth-century London physician, at the bedside of a patient – the only place, he believed, where doctors could learn about disease. Sydenham's plain Puritan costume contrasts markedly with high-fashion raiment worn by his lifelong friend, John Locke, physician-philosopher, who frequently accompanied him on his rounds of patients. Sydenham's honest and straightforward observations, accepted and published in many countries, earned him such posthumous titles as that of the "English Hippocrates,'' and also the "Father of Clinical Medicine in Britain."

Conducting clinical trials: Practice essentials

Introduction

Clinical trials are conducted to evaluate the efficacy and safety of an investigational product (IP) in human beings. These are usually done after pre-clinical trials to determine efficacy and toxicity in animals and in vitro studies. Human studies are undertaken only if safety of introducing the IP to humans is established during the preclinical studies. Development of the IP can be stopped at any stage if it is considered not efficacious or safe for human use. Since clinical trials could pose risks to humans and result in approval of medicines for human use, the conduct of clinical trials are tightly regulated by law in most developed countries to ensure their safety. In Sri Lanka a new Act to regulate the conduct of clinical trials is being drafted and provisions for it are given in the new National Medicines Regulatory Authority (NMRA) Act 5 passed in Parliament in 2015 [1].

Phases of trials

Typically clinical trials are conducted over 4 phases but now very early human dosing is done during phase 0 (zero) studies using very low doses (microdosing), and with few healthy volunteers (Panel 1). Phase 0 trials allow an early evaluation in humans of pharmacokinetic (PK) and pharmacodynamics (PD) of IP by microdosing given for a short period to a small number of humans [2, 3]. The phase 1 trials are generally conducted in healthy volunteers to identify PK and PD in healthy people and to identify a suitable dose for use in humans. In phase 2 studies PK and PD is studied in patients with disease (eg. diabetes), and identify the doses to be used in such patients. Phase 3 studies typically evaluate the efficacy and safety of IP compared to a control group using randomized controlled clinical trial (RCT) design. RCTs are the "gold standard" in the assessment of a treatment effect. The product will be registered after phase 3 trials and evaluation of safety of the marketed drug is undertaken during phase 4 studies.

Panel 1

Approvals needed to conduct a clinical trial in Sri Lanka

1. Ethics approval from an ethics committee recognized by the National Medicines Regulatory Authority (NMRA)
2. Sub-Committee on Clinical Trials (SCOCT) of NMRA approval
3. Registration at Sri Lanka Clinical trials registry (SLCTR)
4. Administrative approval from hospitals where trial is conducted

Types of trials

The clinical trials submitted for approvals in Sri Lanka are either investigator initiated studies of academic interest or pharmaceutical company sponsored clinical trials of a new chemical entity (NCE), which are often international multicentre trials.

Investigator initiated clinical trials

The investigator initiated clinical trials may be for an already registered pharmaceutical product that is evaluated for a new clinical indication (eg. metformin for obesity), or a non-registered product (eg. a herbal product used in Aurveda, tested according to accepted scientific methodology in a clinical trial for treatment of diabetes), or a new herbal extract, or any other products tested in a clinical trial. If the tested product has not been used in humans in the same dosages and in same combinations, or an extract is used, preclinical trials are required before undertaking clinical trials. However, if it is a traditional medicinal product used over the years in any other systems of medicine (eg. Aurveda, Sidha or Unani or homeopathy) and is going to be tested in the same doses and compositions, conducting preclinical trials are not necessary. For clinical trials using herbals, robust methodologies and reporting according to recommended guidelines should be used [4].

Industry sponsored trials

The other category of clinical trials conducted in Sri Lanka are the pharmaceutical company sponsored, often international multicentre trials. Although only a few such studies are currently conducted in Sri Lanka, compared to the other countries, now clinical trials are having their presence in Sri Lanka. These trials generally are originated in a developed country and Sri Lanka is included as one of the trial centres. Often a Clinical Research Organization (CRO) based locally or overseas coordinates the trial on behalf of a sponsor, and they approach prospective investigators who are consultants managing the patients with the disease condition for which the IP is developed as treatment. In Sri Lanka sponsored phase 1 studies of NCE are not allowed unless it is a drug developed for a specific disease condition only prevalent locally (eg. antivenom for snake bite). Phase II or III trials are allowed only if the trial is also conducted in a reference country (eg. USA, European Union, Australia, Singapore) with a stringent regulatory process as identified by the NMRA.

Investigational products and placebos

The IPs and placebos used in the trial should be manufactured according to Good Manufacturing Practices

standards [5]. This is important for investigator initiated trials as well. The investigators should ensure that the IP used in the trial meets quality requirements. When herbal products are used, quality controls during manufacture adhering to GMP standards is necessary to ensure uniform quantities of ingredients used [6]. Any placebos used in the trial for effectuive blinding should also be manufactured under the same GMP conditions to appear very similar to the IP. Placebos should not contain any pharmacologically active materials, such as vitamins or minerals, which have the potential to influence the outcomes evaluated.

Approvals needed

Several approvals are necessary to conduct a trial in Sri Lanka (Panel 2). Firstly, ethics approval should be obtained from an ethics review committee (ERC) recognized by the National Medicines Regulatory Authority (NMRA) for approval of clinical trials. The ERCs of Medical Faculties, SLMA, and Medical Research Institute are recognized by NMRA for this purpose. The trial protocol, investigators brochure giving all the information on the IP going to be used in the trial, informed consent forms in all 3 languages, approvals obtained from any overseas ethics committees and regulatory authorities, insurance certificates, funding information, details of payments to research subjects, clinical trials agreements are usually required along with the duly filled application form by the ERCs for perusal. Approval should then be obtained from the Sub-Committee on Clinical Trials (SCOCT) of NMRA. The same documents submitted to ERC are required by the SCOCT for review along with ERC approval. However, simultaneous applications could be submitted pending ethics approval to the SCOCT, which grants approval after submission of Ethics Committee approval. A clinical trial also requires mandatory registration at a national clinical trials registry [7]. The trials conducted in Sri Lanka should be registered at Sri Lanka Clinical Trials Registry (SLCTR), a publicly accessible clinical trials registry, maintained by Sri Lanka Medical Association (www.slctr.lk) [8]. Approval from the chief administrative officer of the hospital is required for trials (or any other research) conducted in state or private sector hospitals or healthcare institutions.

Panel 2

Phases of clinical trials

1. Phase 0 (zero) trials – Microdosing in very few healthy volunteers for early identification of pharmacokinetics (PK) and pharmacodynamics (PD)
2. Phase 1 trials – PK and PD and dosing studies in healthy humans.
3. Phase 2 trials – PK and PD and dosing studies in patients.
4. Phase 3 trials – Evaluation of efficacy and safety using randomized controlled clinical trial design.
5. Phase 4 trials – Post marketing evaluation of safety.

Adherence to Good Clinical Practice (GCP) guidelines

A clinical trial should be scientifically valid and conducted adhering to robust methodology and ethical standards. For this purpose all trials should be conducted in accordance with the recommendations given in Good Clinical Practice (GCP) guidelines [9]. The International Conference on Harmonization GCP (ICH-GCP) guidelines developed in 1996 is adopted by almost all regions in the world and by the World Health Organisation (WHO) as uniform requirements in the conduct of clinical trials in all regions in the world [10]. Adherence to the guidelines will provide an assurance to the public that the trial was conducted adhering to ethical principles stated in the Helsinki Declaration, and that the reported results are credible. Sri Lanka does not have a separate version of GCP guidelines.

Clinical trial methodology

Protocol

Clinical trials should be conducted according to robust methodology if reliable results are to be obtained. These should be detailed in the clinical trial protocol The SPIRIT 2013 Statement provides guidance for minimum protocol content [11]. Good guidance is provided on how to provide detailed information in a clinical trial protocol which would improve the scientific validity of the trial [12]. The objectives of the study should be clear and trial design should be appropriate to achieve the objectives.

Literature search

A good literature search is required to identify what is known about the disease studied, any tools used to assess the disease or recommended for use in clinical trials of that disease. Careful evaluation of what is known about the IP from previous preclinical and clinical studies on efficacy and safety of the product should also be done. Investigators should be satisfied on these before embarking on a clinical trial, even for a sponsored trial for which protocol has been developed by the sponsors and other overseas investigators.

Sample size

Proper sample size calculation is required, based on the trial design used (eg. superiority trial or a non-inferiority trial or crossover design) and the outcomes expected in the different arms. Generally the probability of type I error is set at 5% or less and the probability of type II error is set at 10% to 20% giving the trial 80-90% power to detect a difference between outcomes in a superiority trial [13]. Involving a statistician or obtaining help from an investigator with expertise in statistics is essential for proper conduct and analysis of results of a clinical trial. The patients should be recruited with well defined and appropriate inclusion and exclusion criteria.

Randomisation and blinding

Random allocation of patients to different arms is crucial to avoid bias in a clinical trial. Concealment of randomization is also equally important particularly in investigator-initiated trials to avoid any investigators influencing allocation, and details should be reported in the trial, as it assesses methodological quality of the trial. Since there is central randomization for most international multicentre industry sponsored trials, concealment of allocation is ensured.

The interventions should ideally be administered and evaluated in a double-blind manner in a clinical trial where patients and investigators are both unaware of the treatment given. Sometimes blinding may not be feasible and the trial could be single-blinded or an open label trial, where both the patients and investigators are aware of the treatment received. All attempts should be made to have a double-blind trial with the use of placebos in control arms for blinding purposes.

Primary and secondary end points

It is essential for a trial to have clear and objective clinical end-points. Primary clinical end-points such as survival rates or cardiovascular events are preferred over surrogate end-points such as blood pressure or tumour size in assessing real clinical benefit of an intervention. Depending on the duration of the study appropriate primary and secondary end-points need to be identified. There should be also be objective evaluation of end-points which would avoid subjective bias (eg. a pain scoring rather than questioning the patient on degree of pain).

Safety monitoring

Another important aspect of a clinical trial is safety reporting. All serious adverse events (SAE) should be reported to the ERC, SCOCT and the sponsor within a stipulated period (eg. 7 working days) irrespective of whether the SAE is considered related or not related to the study medication. Investigators should however do a causality assessment and report whether the SAE is likely to be related to the IP. A clinical trial of long duration and likely to have significant risks should have an independent Data Safety Monitoring Board (DSMB) to evaluate the efficacy and safety data during the conduct of the study, and advise on continuation of the trial or stopping it because of risks or futility. In sponsored clinical trials, the sponsor will appoint the DSMB. In investigator-initiated trials, it is the responsibility of the investigators to appoint an independent DSMB, and provide data to the members at pre-determined times to decide on continuation of the trial.

Panel 3

Serious adverse events to be reported

1. Death
2. Life threatening illness
3. Hospitalization or extension of hospitalization
4. Permanent disability
5. Birth defects

Monitoring and auditing trials

Properly conducted clinical trials should be monitored at regular intervals to ensure adherence to the approved protocol and meticulous recording of all trial related activities. This is generally undertaken by the CRO in industry sponsored trials. In investigator-initiated trials also regular monitoring by team members should be done to ensure proper conduct and documentation of the trial. Any major deviations from the protocol should be reported to the ERC and the SCOCT. In industry sponsored trials, audits by sponsor as well as the regulatory authority may be done to ensure proper conduct of clinical trials. All trial related documents need to be kept for a designated period at its conclusion for future reference.

Reporting of results

The reporting of results should be according to the Consort Statement [14, 15]. Adhering to this would ensure that all necessary aspects of the trial would be reported, so that readers could decide on the validity of reported results. The trial flow diagram showing the progress through the phases of the trial providing data on screening, enrolment, intervention allocation, follow-up, and data analysis should be provided. The baseline data in all arms of the trial should be presented in a table. Intention to treat (ITT) analysis requires all participants in a clinical trial to be analysed on the arm to which they were assigned at randomization, regardless of any departures from randomised treatment [16]. Reporting magnitude of the effect is better when given as absolute risk reduction (RRR) and number needed to treat (NNT), rather than only as the relative risk reductions (RRR), which does not reflect real benefits of the interventions [17]. Failing to report NNT may influence the interpretation of study results as reporting RRR alone may lead a reader to believe that a treatment effect is larger than it really is. Similar to efficacy, harms also should be appropriately reported following the recommended methods [18].

Conclusion

Clinical trials are conducted over 5 phases following preclinical studies to evaluate efficacy and safety of an investigational product. They need to be conducted in accordance with the GCP guidelines to ensure adherence to ethical standards and scientific validity. Several approvals need to be obtained prior to conduct of clinical trials. Proper conduct of clinical trials is essential with adherence to protocol, safety reporting, and documentation which is ensured by monitoring and audits. Results of the study should be reported adhering to recommended guidance. Clinical trials conducted and reported in this manner will transform a molecule in to a medicine for human use.

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Angioedema

Introduction

Angioedema (AE) is defined as pronounced localized and self-limiting oedema of subcutaneous and submucosal tissue, due to a temporary increase in vascular permeability caused by release of vasoactive mediator(s). It was first described by Quincke in 1882 [1].

Epidemiology

The World Allergy Organization (WAO) notes that urticaria and angioedema affect up to 20% of the US population. About 40-50% of patients with chronic spontaneous urticaria have angioedema, and about 10% have angio-edema alone. Hereditary angioedema (HAE) has an estimated prevalence of 1:10 000 to 1:50 000. The prevalence of acquired angioedema (AAE) is very low; until 2006, only about 136 cases had been reported in the literature. The reported incidence of ACE inhibitor-induced angioedema ranges from 0.1% to 6% [2].

Demographic data

Age

AE can affect people of all ages.Allergic reactions to food are more common in children. For patients with HAE, the onset of symptoms is often around puberty. The average age for AE induced by ACE inhibitors is 60 years.

Sex

In HAE, affected women tend to have more frequent attacks and run more severe clinical courses. Oral contraceptives are often linked to exacerbation of swelling attacks. Chronic idiopathic AE is more common in females than in males.

Ethnicity

No specific racial predilection exists for angioedema. However, black individuals are more susceptible to angioedema induced by ACE inhibitors.

Pathophysiology

Angioedema is often caused by the same pathological factors that cause urticaria [3].

It is a result of the fast onset of an increase in local vascular permeability in subcutaneous or submucosal tissue. Histamine and bradykinin are the recognized vasoactive mediators known to be critical in the pathologic process of angioedema; most cases of angioedema are primarily mediated by one of these 2 mediators, though some investigators indicate the possibility that both may be involved in certain cases.

Angioedema with urticaria

Angioedema associated with urticaria may represent hypersensitivity to an offending agent. Histamine is released into the bloodstream, resulting in increased endothelial cell permeability. Angioedema, generalized urticaria, and in severe cases, anaphylaxis will occur.

Angioedema without urticaria

With respect to pathophysiology, angioedema without urticaria may differ substantially from angioedema with urticaria. In many cases, histamine is not involved or only minimally involved.

Bradykinin is known to be the major mediator for HAE, acquired angioedema (AAE), ACE inhibitor-induced angioedema, and certain idiopathic angioedemas.

C_1 esterase inhibitor deficiency/dysfunction

Extravasation of plasma into deeper cutaneous or mucosal compartments as a result of overproduction of bradykinin is the main pathological process. C1 inhibitor helps control bradykinin production by inhibiting plasma kallikrein and activated factor XII. Without enough C1 inhibitor, the contact system is uninhibited and results in bradykinin being inappropriately generated leading to increased vascular permeability.

Panel 1

Causes of angioedema

- Allergic: foods, drugs, insect stings/bites
- Radiocontrast media
- NSAID and ASA
- Associated with anaphylaxis
- Autoimmune
- ACE inhibitors
- Bradykinin-induced with normal C1-inhibitor (HAE-III)
- C1 inhibitor deficiency
- Hereditary – Types I and II
- Acquired
- Systemic diseases (e.g., systemic lupus erythematosis)
- Idiopathic: may be histamine induced or bradykinin induced

Panel 2
Physical causes and common triggers of angioedema

Physical causes	Common triggers of angioedema
• Cold	• Infection
• Cholinergic	• Menstruation
• Solar	• Medication
• Vibratory	• Stress
• Pressure	• Trauma
• Contact reactions	

Symptoms and signs

Well demarcated non-pitting oedema is the characteristic feature. Angioedema may affect many organ systems. Visible swelling is common in peripheral angioedema. It is often associated with local burning sensation and pain without pronounced itchiness or local erythema.

The most commonly involved areas:

Peripheral

Skin and urogenital area (e.g., eyelids or lips, tongue, hands, feet, scrotum, etc.).

Abdomen

Abdominal pain (sometimes it can be the only presenting symptom of angioedema).

Larynx

Throat tightness, voice changes, and breathing trouble (indicators of possible airway involvement), potentially life-threatening respiratory distress.

Diagnostic tests

Most mild cases of angioedema do not require laboratory testing [4]. The value of aeroallergen screening for patients with angioedema is limited. Suspected allergies to food, stinging insects, latex, and antibiotics can be screened and diagnosed. For angioedema without urticaria (especially those with recurrent episodes), diagnostic tests should include the following:

- C4 level
- C1 esterase inhibitor (C1INH) quantitative and functional measurements
- C1q level

For chronic or recurrent angioedema without a clear trigger, clinicians may consider the following tests: CBC with differential counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, urinalysis, comprehensive metabolic profile, antinuclear antibody (ANA) testing, thyroid studies, including levels of thyroid stimulating hormone, free T4, and thyroid autoantibodies (antimicrosomal and antithyroglobulin), particularly in women or in patients with a family history of thyroid disease or other autoimmune diseases.

If the history and physical examination findings suggest specific problems, other tests that may be helpful include the following [5]: stool analysis for ova and parasites, *Helicobacter pylori* workup, hepatitis B and C virus, toxocara antibodies, rheumatoid factor, cryoglobulin levels and imaging studies.

Management

The primary goal of management is to reduce swelling, discomfort and complications. Most medications used in treating urticaria and anaphylaxis are also used in the management of many types of angioedema. Adrenaline should be used when laryngeal angioedema is suspected. In addition, supportive care should be provided, regardless of the aetiology [6].

Panel 3

Medications used in the management of angioedema [7]

- Alpha and beta-adrenergic agonist agents (eg. adrenaline)
- Antihistamines
- Histamine H2 antagonists (eg. ranitidine, cimetidine)
- Leukotriene receptor antagonists (eg. montelukast, zafirlukast)
- Tricyclic antidepressants (eg. doxepin)
- Corticosteroids (eg. prednisone, methylprednisolone, prednisolone)
- Androgen derivatives (eg. danazol, oxandrolone)
- Progesterone based contraceptive pills.
- Antifibrinolytic agents (eg. aminocaproic acid, tranexamic acid)
- Immunomodulators (eg. cyclosporine, mycophenolate, methotrexate)
- Agents used in treating C1INHHAE: C1 INH concentrates, ecallantide, and icatibant.

Medication for acute attack and prevention of hereditary angioedema

Refer tables 1 and 2.

Table 1. Medications for acute attacks of hereditary angioedema

Drug	*Approved*	*Self-dosing*	*Dosage*	*Potential adverse effects*
Plasma-derived nanofiltered C1 inhibitor (Berinert)	United States: adolescents and adults Europe: all ages	Yes	20 U/kg intravenously	Rare: anaphylaxis Theoretical: blood-borne infection
Plasma-derived nanofiltered C1 inhibitor (Cinryze, Cetor	Europe: adolescents and adults	Yes	1,000 U intravenously, with possibility of second dose of 1,000 U after 60 minutes	Rare: anaphylaxis Theoretical: blood-borne infection
Ecallantide (Kalbitor)	United States: ≥ 16 years old	No	30 mg subcutaneously	Uncommon: antidrug antibodies, anaphylaxis
Icatibant (Firazyr)	United States and Europe: ≥ 18 years old	Yes	30 mg subcutaneously	Common: transient discomfort at injection site
Recombinant human C1 inhibitor (Rhucin)	Europe: adults United States: pending	No	50 U/kg or 4,200 U intravenously, whichever dose is higher	Uncommon: anaphylaxis in rabbit-sensitized patients

Table 2. Medication for prophylaxis of hereditary angioedema

Drug	*Approved*	*Self-dosing*	*Dosage*	*Potential adverse effects*
Plasma-derived nanofiltered C1 inhibitor (Cinryze)	United States and Europe: ≥ 12 years old	Yes	Short-term: 500 – 1,500 U intravenously 1 hour before event Long-term: 1,000 U every 3 – 4 days	Rare: anaphylaxis Theoretical: blood-borne infection
Danazol (Danocrine)	United States: adults Contraindicated during pregnancy and lactation, children untill growth is complete	Yes	Short-term: 200 mg by mouth 3 times a day for 5 – 10 days before event Long term, adult: ≤ 200 mg/day (100 mg every 3 days 600 mg/day Children: 50 mg/day (50 mg/week – 200 mg/day)	Common: weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, elevated liver enzymes, hypertension, alterations in lipid profile Uncommon: decreased growth rate in children, masculinization of female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma and carcinoma

(continued)

Drug	*Approved*	*Self-dosing*	*Dosage*	*Potential adverse effects*
Aminocaproic acid (Amicar)	Not approved for hereditary angioedema	Yes	Adults: 1g by mouth 3 times daily Children: 0.05 g/k twice daily (0.025 g/kg twice daily – 0.1 g/kg twice daily)	Common: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with elevated muscle enzymes Uncommon: thrombosis
Tranexamic acid (Lysteda)	Not approved for hereditary angioedema	Yes	Adults: 1 g twice daily – (0.025 g/kg twice daily) 1.5 g 3 times daily) Children: 20 mg/kg twice daily (10 mg/kg twice daily – 25 mg/kg 3 times daily)	Same as with aminocaproic acid

Panel 4

Management of ACE induced angioedema [8]

- Stop drug and use other classes of anti-hypertensive agents
- All ACE inhibitors are to be avoided
- Management of angioedema depends on site of involvement – securing the airway by intubation may be necessary
- ARB receptor antagonists are generally considered safe
- Consider use of icatibant or ecallantide to treat symptoms

Prognosis [9]

The prognosis for patients with angioedema depends on the aetiology.

- Angioedema with identifiable causes. If the trigger(s) can be identified and avoided, angioedema can be prevented
- Angioedema without identifiable causes. There is a variable clinical course, ranging from mild to severe, and a few days to many years; the response to conventional treatment is less predictable
- HAE. Lifelong treatment is often required
- AAE. Outcome depends on the treatment of underlying lympho-proliferative or autoimmune disorders

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Bacterial skin and soft tissue infections

Summary

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

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

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

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

Keywords: antibiotics, cellulitis, impetigo, soft tissue infection

*(Aust Prescr 2016; **39**: 159-63)*

Introduction

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

Impetigo

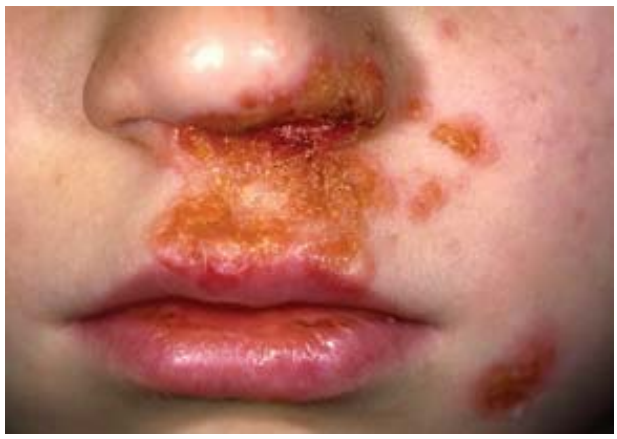
Impetigo is a superficial bacterial infection that can develop either through direct invasion of normal skin (primary) or infection at sites of damaged skin (secondary) (Fig. 1). It is common in children and is highly contagious. There are two forms:

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

Boils and carbuncles

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

Fig. 1 **Impetigo**



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Folliculitis

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

Cellulitis and erysipelas

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

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

Cellulitis extends further into the deep dermis and subcutaneous tissue. It commonly involves the lower limbs (Fig. 3) and in most cases is unilateral. Bilateral lower limb cellulitis is exceedingly rare and usually reflects stasis

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

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

MRSA methicillin-resistant Staphylococcus aureus

Fig. 2 **Erysipelas**

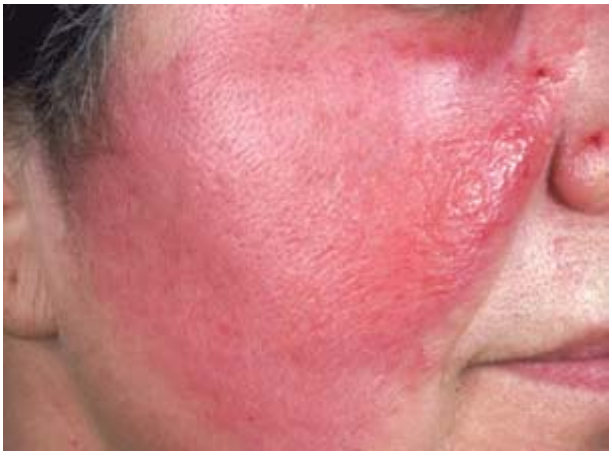

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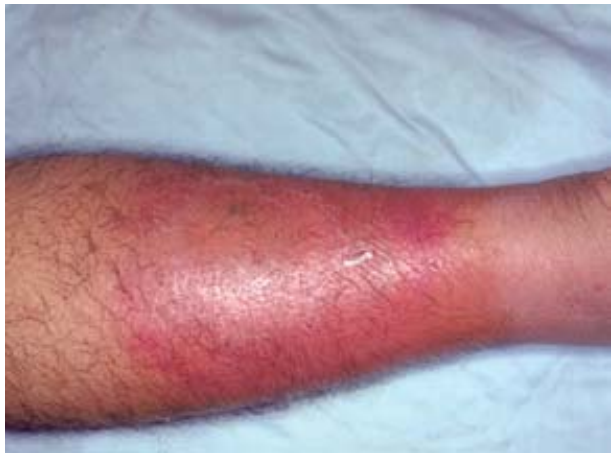
Fig. 3 **Cellulitis**



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dermatitis and does not require antibiotic treatment. Other areas of the body such as the eye and the abdominal wall can also be affected. Periorbital cellulitis involves the eyelids and does not extend into the bony orbit. Orbital cellulitis is a much more serious infection with deeper extension and impairment of vision and extraocular eye movements, often with pain.

Cellulitis is usually caused by either S. aureus or beta-haemolytic streptococci (groups A, B, C or G). Differentiating between these two organisms can help guide therapy. Streptococcal infection is usually characterised by acute onset of rapidly spreading erythema, lymphangitis and lymphadenopathy.

Staphylococcal cellulitis is usually associated with purulent lesions with erythema. Cultures from wounds or blood can further help delineate the causative organism. In the absence of positive cultures however, it can be difficult to discriminate between the two and antibiotic therapy to cover both organisms (for example flucloxacillin, dicloxacillin, cephalexin, clindamycin) is often used.

Diagnostic approach to cellulitis

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

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

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

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

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

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

Necrotising skin infections

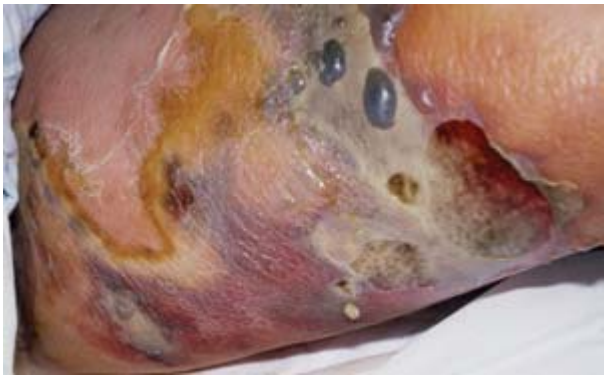
Necrotising skin infections, the best known of which is necrotising fasciitis, are a medical and surgical emergency that require prompt debridement and appropriate intravenous antibiotics. Infections can be caused by single or multiple pathogens (e.g. S. pyogenes, Gram negatives, Clostridium).

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

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

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

Fig. 4 **Necrotising fasciitis**



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

Methicillin-resistant Staphylococcus aureus (MRSA)

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

When to use topical antibiotics

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

When to use oral antibiotics

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

When to consider hospital referral and intravenous antibiotics

Patients with severe disease who are systemically unwell will require assessment in hospital for monitoring and intravenous antibiotics. Parenteral antibiotics can either be administered as an inpatient or through an Outpatient Parenteral Antibiotic Treatment or Hospital in the Home program.

Factors that would favour hospital management of cellulitis include:[5]

- comorbid conditions (renal impairment, diabetes, congestive cardiac failure, splenectomy) or immunosuppression
- rapidly progressive infection

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

How to manage recurrent skin infections

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

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

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

Conclusion

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

Conflict of interest: none declared.

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

Treat acute lesions.

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

Once active skin lesions resolve, eradicate staphylococcal carriage with

mupirocin nasal ointment for 5 days

PLUS EITHER

chlorhexidine 2% or triclosan 1% wash for 5 days in showers

OR

sodium hypochlorite solution (60 mL of 6% solution per bathtub) or triclosan 2% bath oil for 5 days in baths

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

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

If decolonisation measures fail, repeat topical regimen together with

oral rifampicin for 7 days

PLUS

oral dicloxacillin, fusidate sodium or trimethoprim plus sulfamethoxazole depending on susceptibility of the organism.

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