THE NORTHERN HOSPITAL

FLUCLOXACILLIN

"Chloris", oil on canvas, 1902, John William Godward.

....But he that dares not grasp the thorn, Should never crave the rose...

Anne Bronte, "The Narrow Way", 1848

There used to be a greying tower alone on the sea
You became the light on the dark side of me
Love remained a drug that's the high and not the pill
But did you know that when it snows
My eyes become large and the light that you shine can be seen?

Baby, I compare you to a kiss from a rose on the grey
Ooh, the more I get of you, the stranger it feels, yeah
Now that your rose is in bloom
A light hits the gloom on the grey

There is so much a man can tell you, so much he can say
You remain my power, my pleasure, my pain
Baby, to me, you're like a growing addiction that I can't deny
Won't you tell me, is that healthy, baby?
But did you know that when it snows
My eyes become large and the light that you shine can be seen?

Baby, I compare you to a kiss from a rose on the grey
Ooh, the more I get of you, the stranger it feels, yeah
Now that your rose is in bloom
A light hits the gloom on the grey

I've been kissed by a rose on the grey
I've been kissed by a rose on the grey
And if I should fall, will it all go away?
I've been kissed by a rose on the grey

There is so much a man can tell you, so much he can say
You remain my power, my pleasure, my pain
To me, you're like a growing, addiction that I can't deny
Won't you tell me, is that healthy, baby?
But did you know that when it snows
My eyes become large, and the light that you shine can be seen

Baby, I compare you to a kiss from a rose on the grey
Ooh, the more I get of you, the stranger it feels, yeah
Now that your rose is in bloom
A light hits the gloom on the grey

Yes I compare you to a kiss from a rose on the grey
Ooh, the more I get of you stranger it feels, yeah
And now that your rose is in bloom
A light hits the gloom on the grey

Now that your rose is in bloom
A light hits the gloom on the grey

"Kiss From a Rose", Henry Olusegun Adeola Samuel (Seal) - 1995

The rose holds ancient and powerful symbolism for many different cultures. This symbolism - across cultures - is two faced - both good and bad. In the Persian tradition the first rose emerged from the ground by the life giving rays of the rising sun. From Persia it spread its seeds to all the lands of the earth. It was revered as a symbol of beauty, vitality, fertility and purity. When the first white rose bloomed a nightingale was so entranced it burst into song, but overcome by its perfume it lost its senses and fell to the Earth and stained some of the white roses with its blood. Red roses were a sad reminder of the nightingale lured to its doom by the intoxicating scent of the white rose. The rose was sacred to Islam, whilst being associated with pleasures it was also linked with pain in view of its thorns. Nowhere however was the two-edged symbolism of the rose more powerful than in the West. In classical Greece, it was said that the first rose was given to the world by Chloris, the beautiful goddess of flowers. The Romans called her Flora. Its visual appeal and alluring perfume caught not only the attention of mortals - but of also the gods of Olympus themselves. Aphrodite, the goddess of love, claimed it as her own sacred flower, a fitting symbol of the Greek gods in general - all too human in their natures. On the one hand the rose symbolized love, the velvety red petals, being likened by the poets of the age to the soft ruby lips of a woman. But on the other hand - there was also danger in the form of its thorns - dark symbolism of doom or even love that is forbidden. The medieval mind of course expounded the sins of the flesh - and the thorn of the rose was the price to be paid for those forbidden pleasures. The modern age continued the ambiguous tradition. Anne Bronte's claim that "he that dares not grasp the thorn, Should never crave the rose", reflects the modern adages - "a faint heart never gained the love of a woman" or "better to have loved and lost - than never loved at all", - or perhaps in the more generic sense "there be no gain, without some pain".

The symbolism of the rose also held a dichotomous place in medical history. It was the prize object of beautiful gardens, but in an age before antibiotics, a scratch from a rose thorn, was not the triviality that we see this injury to be today. On most occasions of course, there was no harm done but in some cases infection set in - took over - consumed - and killed. Once infection became established there was nothing medicine could do. Nature would take its course, the fight between the body's immune system and the organism was fought without regard to anything human medicine could bring to that struggle. In the days before antibiotics, there were wards known as the "septic wards" - filled with patients with severe infections, many arising from such trivial incidents as the scratch of a rose thorn. Occasionally the patient's natural immunity would triumph, sometimes the surgeon's knife could drain a large purulent mass and save the patient's life - but overall - the fact remained that over fifty percent of those admitted to the septic ward would die despite all the ingenuity the medical profession could muster against the infection. Then in 1940 all this changed with the miraculous war time work of Howard Flory and his team at Oxford, England. They achieved one of the greatest medical breakthroughs in the history of medicine - the first patient ever saved from an overwhelming bacterial infection, by the use of a miraculous new agent that went by the name of penicillin.

In September 1940, a police officer in Oxford by the name of Albert Alexander was happily working in his beloved rose garden when he was scratched on the face by a rose thorn. Initially he did not think much of it, but over the ensuing days a suppurating infection set in which rapidly became very much worse. He was admitted to the Radcliffe Hospital in October and sent to the septic ward in a terrible state. He was diagnosed with

a staphylococcal infection and from the medical records of the day it is possible to surmise that he had in fact developed a bacterial cavernous sinus infection. He rapidly lost his left eye and was in danger of losing his right. The sulpha chemicals used to treat infection in those days were completely ineffective. The doctors knew he was certain to die. Charles Fletcher, a medical officer working in the septic ward recalled, "He was in great pain, he was oozing pus everywhere, he was desperately and pathetically ill". But news had reached the Radcliff Hospital that a miraculous new drug known as penicillin had newly been developed by Howard Florey and his team at the Dunn School Laboratories of Oxford. Animal studies had been stupendously successful in treating lethal streptococcal infections and even a few human cases had been cured of minor bacterial infections. Howard Florey was urgently called to treat Alexander. Penicillin would be tested for the first time on a patient certain to die. On February 12th Alexander was given 200 mg of penicillin intravenously, the largest dose ever given to a human subject up until that time. Within 24 hours he showed astonishing improvement. Over the next few days - receiving 100 mg every three hours, his temperature normalized, his purulent discharge dried up and he began to feel better and to eat. It looked as if Alexander would survive. Fletcher and Florey were ecstatic. Fletcher recalled Florey's remark on his life's work, "this sort of thing only happens to you once in a life-time". But as Alexander became better, there was another desperate call to treat a 15 year old by the name of Arthur Jones who had developed a serious infection in his leg. As Alexander appeared to be recovering, the last remaining doses on penicillin available in England were given to Jones. When this ran out Alexanders urine was used to re-extract penicillin to give to Jones. In the meantime Alexander's condition suddenly worsened once again - the doctors this time were powerless - there was no penicillin left in the whole of England. To Fletcher and Flory's immense distress Alexander died of a recurrence of overwhelming infection. Florey was certain that penicillin could cure severe staphylococcal and streptococcal infections - if only enough of it could be produced. Just over a year later Florey finally had enough penicillin to treat a life threatening infection. In March 1942, Anne Miller who was dying of puerperal sepsis was given large doses of intravenous penicillin - and became the first person in history to be saved from certain death from streptococcal septicaemia.

The symbolism of the light and the dark side of the rose persisted into the late Twentieth century. Is "Kiss from a Rose" - a heartfelt love song? - or is it about something sinister - cocaine addiction? In the 21st century the rose symbol, in the medical field at least, is no longer quite so ambiguous. Albert Alexander would have been well pleased to know that he played a crucial role in helping medical science ensure that in the future no one need die again from the simple scratch of a rose thorn. In the history of medical science the story of Albert Alexander and his beloved rose garden is a story of hope amidst the greatest despair - and the rose now, like the Valentine's Day floral dedication, is an unambiguously beautiful symbol.

".....Just remember in the winter, far beneath the bitter snow
Lies the seed, that with the sun's love in the spring becomes the rose".

FLUCLOXACILLIN

Introduction

Flucloxacillin is narrow spectrum penicillin with good cover against **gram-positive organisms** including **staphylococci**.

It is a member of the **beta-lactamase stable** group of penicillins.

It is not active against MRSA or gram negative organisms.

Like all beta lactam antibiotics, flucloxacillin may cause significant / life threatening allergic reactions, but it also has the additional potential for significant hepatic toxicity.

History

In **1897** the French physician, **Ernest Duchesne** (1874 - 1912) at the École du Service de Santé Militaire in Lyons, published a medical thesis entitled *Contribution à l'étude de la concurrence vitale chez les micro-organismes : antagonisme entre les moisissures et les microbes* (Contribution to the study in vital competition in microorganisms: antagonism between molds and microbes). In this work he noted the ability of *Penicillium glaucum*, a fungus, used in the making of some types of blue cheeses, to inhibit the growth of some bacteria. The stunning implications of his thesis were completely unappreciated and it was largely ignored.

The Scottish biologist, pharmacologist and botanist, **Alexander Fleming**, (1881 - 1955) is credited with the discovery (or rediscovery) of penicillin in **1928**, when he noticed that the fungus, ***Penicillium notatum*** which had accidently contaminated a plate culture of staphylococcus, appeared to be inhibiting the growth of the staphylococcus. From this observation he isolated the fungal substance penicillin in the form of a crude culture "broth" - essentially the discovery of the world's first antibiotic. However, somewhat astonishingly, he then did virtually nothing with his discovery.

It would be left to the brilliant **Australian** scientist **Howard Florey** (1898 - 1968) and his research team, (most notably Ernst Boris Chain and Norman Heatley) at Oxford University, to isolate pure penicillin, demonstrate the miraculous "in-vivo" ability of penicillin to kill pathogenic bacteria, demonstrate its safety in vivo, and to then actually produce it in large enough quantities to be used as an effective therapeutic agent in humans in the early 1940s. Penicillin would be responsible for saving not only many civilian lives, but also countless lives of soldiers then fighting in the Second World War, lives that in the conflicts of previous ages would most certainly have been lost from infectious complications of their wounds and their surgery.

Howard Florey, Alexander Fleming and Ernst Boris Chain shared the 1945 Nobel Prize for Physiology or Medicine.

Chemistry

Penicillin is the archetype beta-lactam antibiotic.

The **beta-lactam antibiotics** are structurally related via their central **beta lactam** moiety. Side chains determine antibacterial, pharmacological and pharmacokinetic properties.

The beta-lactam antibiotics include:

1. Penicillins
2. Cephalosporins
3. Carbapenems
4. Monobactams

Flucloxacillin is derived from the penicillin nucleus, (6-amino-penicillanic acid).

Classification

The penicillins are classified into 5 principle groups:

1. Narrow-spectrum penicillins:

   These are **narrow spectrum** antibiotics with cover against **gram positive bacteria.**

   Examples include:

   - **Phenoxymethyl-penicillin, (Penicillin V)**
   - **Benzyl-penicillin, (penicillin G)**

2. Narrow-spectrum penicillins with antistaphylococcal activity:

   These are stable to beta-lactamase enzymes produced by some bacteria such as staphylococci.

   Examples include:

   - **Dicloxacillin**
   - **Flucloxacillin**

3. Moderate spectrum penicillins:

   These have better activity than benzylpenicillin against *some* Gram-negative organisms (e.g. *Escherichia coli*, *Haemophilus influenzae*),

They are however inactivated by strains that produce beta-lactamase enzymes.

Examples include the aminopenicillins:

- **Amoxycillin**
- **Ampicillin**

4. Broad-spectrum penicillins (beta-lactamase inhibitor combinations):

   The beta-lactamase enzyme inhibitors **clavulanate** and **tazobactam** have little inherent antibacterial activity.

   They inhibit the enzymes produced by *Staphylococcus aureus*, *Bacteroides fragilis* and *H. influenzae*, and also some of the beta-lactamase enzymes produced by *E. coli* and *Klebsiella* species and so can *significantly* extend the spectrum of activity of penicillin antibiotics when used in combination.

   Examples include:

   - **Amoxycillin and clavulanate**
   - **Ticarcillin and clavulanate**
   - **Piperacillin and tazobactam**

5. Broad-spectrum penicillins with antipseudomonal activity:

   These penicillins have extended activity against *Pseudomonas aeruginosa*, though high doses are required.

   These drugs are only available in combination with a beta-lactamase enzyme inhibitor

   Examples include:

   - **Piperacillin**
   - **Ticarcillin**

Preparations

Flucloxacillin as:

Capsules:

- 250 mg, 500 mg

Oral liquid:

- 25 mg/mL (powder), 100 mL, 50 mg/mL (powder), 100 mL.

Ampoules:

- 500 mg, 1 gram (powder for reconstitution).

Mechanism of Action

The penicillins are **bactericidal** agents.

They interfere with **bacterial cell wall peptidoglycan** synthesis during the stage of active multiplication, thereby leading to cell lysis and death.

Flucloxacillin is a member of the **beta-lactamase stable** group of penicillins.

Pharmacodynamics

Flucloxacillin is a narrow spectrum penicillin but with considerable activity against Gram positive organisms including:

- Beta-lactamase producing *Staphylococcus aureus.*
- Beta-haemolytic Streptococci *(Streptococcus pyogenes)*
- *Streptococcus pneumoniae.*

It is **not** active against:

- Gram negative bacilli
- Methicillin resistant *Staphylococcus aureus,* (i.e. MRSA)
- *Streptococcus faecalis.*

Pharmacokinetics

Absorption:

- Flucloxacillin can be given **orally** or **intravenously.**

  It is also well absorbed following intramuscular administration.

Distribution:

- Flucloxacillin is highly bound to serum proteins, at 92 - 95 %.
- Flucloxacillin crosses the human placenta.

- Flucloxacillin is excreted into human breast milk in small amounts.

Metabolism and excretion:

- Flucloxacillin is predominantly excreted by the kidneys, (by both glomerular filtration and tubular secretion) and high levels of active antibiotic are produced in the urine.

- The concurrent administration of probenecid delays the excretion of flucloxacillin.

- Elimination half life is short at 0.75 - 1.5 hours.

Indications

Infections due to susceptible / likely susceptible bacterial organisms, including:

1. Staphylococcal skin/ soft tissue infections

Other indications:

2. Pneumonia (often in combination with other agents).

3. Osteomyelitis, septic arthritis (often in combination with other agents).

4. Septicaemia, (often in combination with other agents).

5. Empirical treatment for endocarditis (often in combination with other agents).

Note that, as for all antibiotics, the prevalence of bacterial resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Contra-indications/precautions

These include:

1. Contraindicated with a history of severe or immediate allergic reaction to penicillin.

    - Including urticaria, anaphylaxis, interstitial nephritis to a penicillin (seek specialist advice if using a penicillin is critical).

    - Although anaphylaxis is more frequent following parenteral therapy, it may also occur in patients on oral therapy.

2. Caution in those with a history of an allergic reactions to *other* beta lactam antibiotics such as a carbapenem or a cephalosporin:

- As cross-reactivity between penicillins, cephalosporins and carbapenems can occur.

3. Patients with a previous history of flucloxacillin associated jaundice or hepatic dysfunction.

4. Renal impairment:

   - As flucloxacillin is excreted to a large extent by the kidney, the dose or dose interval may need modification in patients with renal failure, as the half-life in these patients is increased.

     Dosage recommendations for various plasma creatinine levels for patients with impaired renal function however are not available.

Pregnancy

Flucloxacillin is a category B1 drug with respect to pregnancy.

Category B1 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Maternal use of flucloxacillin has not been associated with an increased risk of birth defects or adverse pregnancy outcomes.

Flucloxacillin is safe to use during pregnancy.

Breast feeding

Small amounts of flucloxacillin are excreted into breast milk, but these amounts are unlikely to pose harm in the breastfed infant.

Flucloxacillin is safe to use at the recommended doses during breastfeeding. However, observe the breastfed infant for potential adverse effects such as diarrhoea, vomiting, skin rash or thrush.

Adverse Effects

All the beta lactams including the penicillins have a **wide therapeutic index**

The principle adverse effects of flucloxacillin include:

1. Allergic reactions

2. Liver toxicity.

- Flucloxacillin can cause **severe hepatitis** and **cholestatic jaundice,** which may be protracted.

  This reaction is more frequent in older patients (> 55) and those who take the drug for prolonged periods (> 2 weeks).

  Estimated incidence is around 1 in 15, 000 exposures.

3. Pseudomembranous colitis:

   - Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening.

4. Dermatological hypersensitivity reactions.

   - Usually mild, but occasionally can be severe e.g. exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Dosing

Exact dosing and the duration of dosing depends on the condition being treated as well as the severity of the condition and illness.

See latest Antibiotic Therapeutic Guidelines for full prescribing details.

In *general* terms:

Oral:

- **Flucloxacillin 500 mg - 1 gram orally 6 hourly**

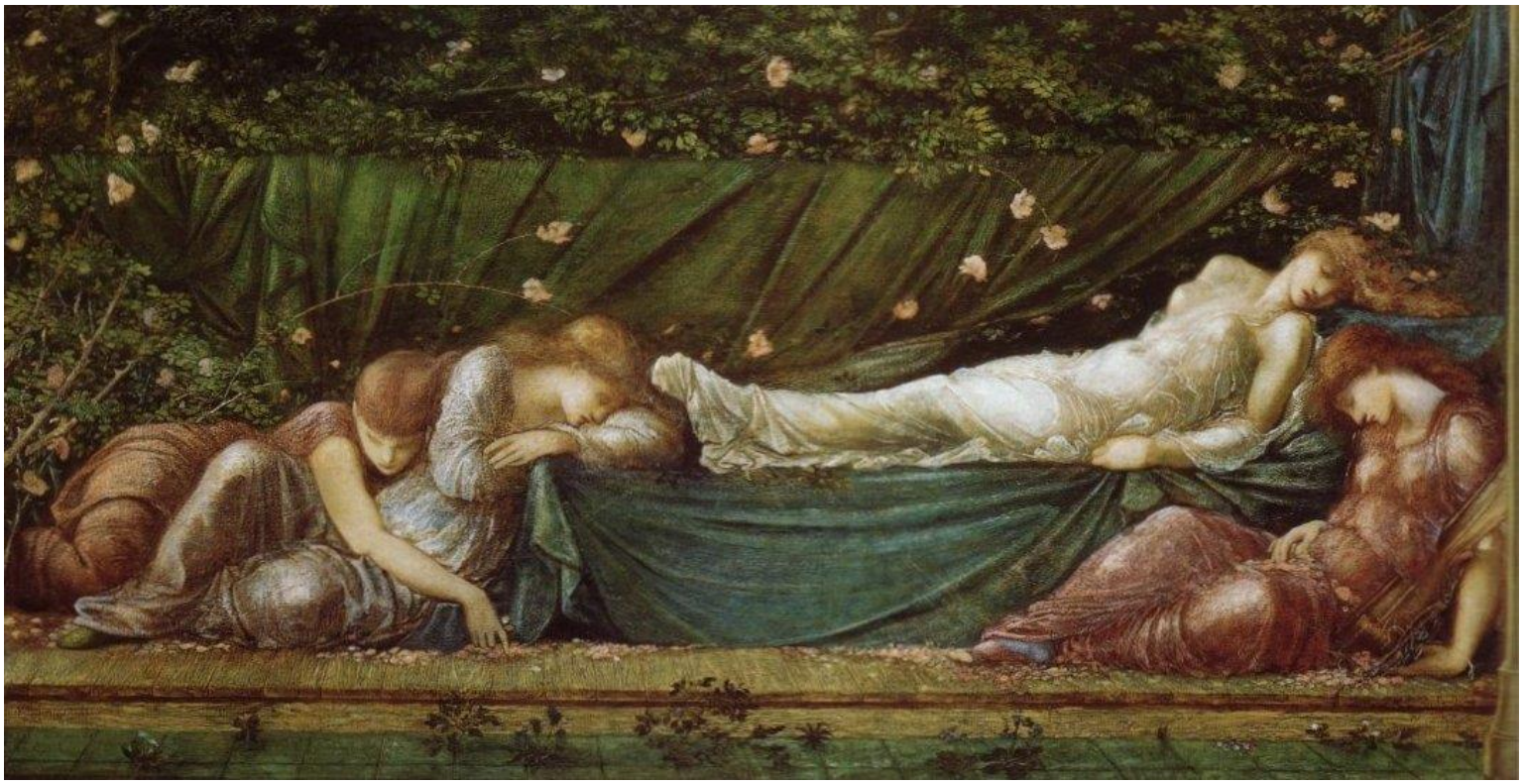
  Children: 12.5 mg/kg up to 500 mg.

IV:

- **Flucloxacillin 1 - 2 gram IV 6 hourly.**

  Children: 50 mg/kg up to 2 grams IV 6 hourly.

Anne Miller, 1942, The first person in history whose life was saved by antibiotics.



"The Rose Bower", oil on canvas, 1871 Edward Burne-Jones.

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Reviewed 1 August 2018.