THE NORTHERN HOSPITAL

AMPICILLIN

"Figure on a Moonlit Lane", oil on canvas, 1874, John Atkinson Grimshaw.

1940: May 25, 11.55 PM

One mouse got up and staggered about for a few seconds, then fell down, twitched once or twice and was dead. Other (controls) - very seedy +

1940: May 26, 1.30 A.M

+ +

1940: May 26, 3.28 A.M

(Last control) - moved about drunkenly. With each inspiration lifted its head and opened its mouth widely. Respiration became slower, animal twitched and died. +

Four others, all healthy!

Laboratory notebook entries of Norman Heatley May 1940.

On May 26th 1940, at 3.45 AM in the morning a brilliant young biochemist by the name of Norman Heatley, was furiously riding his bicycle home from the Dunn School laboratories at Oxford University. As he cycled down the dark moonlit lanes his head was positively spinning and his heart was pounding, not because of exertion, but because of a feeling of unbounded exhilaration! He had just been witness to one of the most astonishing medical breakthroughs in history. The exhilaration was heightened, as unlike the situations of the first flight of the Wright brothers, or the explosion of the atomic bomb, or Neil Armstrong walking on the Moon, he was the sole witness to the event. As he sped past a few lonely figures scattered along the moonlit lane he was suddenly halted by an aged Home Guardsman aiming a rifle straight at him. "Halt - who goes there!?", he screamed out. Heatley made no mention that he had just witnessed history being made, there would have no point trying to explain to an uncomprehending and agitated Guardsman, on the lookout for suspicious persons who could be German spies. He demanded an explanation as to where Heatley was going in such a rush, in the middle of the night. He simply explained that he had been working on important secret business at the Dunn school and was just wanting to get home, which seemed to satisfy the Guardsman who let him continue on his way.

What Heatley had witnessed, and recorded in the Dunn school laboratory notebooks, was no less than the discovery antibiotics in the form of Penicillin could indeed be used as a therapeutic agent.. The night before Howard Florey had injected four of eight mice with penicillin, an agent, accidently discovered by Alexander Fleming some twelve years previously, and which Heatley had managed to extract from crude mould broths, to see what the effect would be. All eight mice had previously been injected with a lethal dose of highly virulent streptococcal bacteria. It was known by Florey's team from Flemings' earlier serendipitous discovery that the mysterious substance, produced by the common mould, penicillium notatum could kill virulent disease causing bacteria....in a petri dish. But Fleming had not pursued the matter any further, nor particularly did he promote it. It would be left to Florey and his brilliant Oxford team, including Ernst Chain, to extract it, purify it, characterise its exact nature, produce it in quantities that could be worked with and to fully understand its miraculous potential implications for medicine. After countless

hours of difficult and painstaking research, May 25th 1940, marked the day that Florey's team was finally able to test penicillin - in vivo. The results were nothing short of world changing. The streptococcus bacteria was one of the greatest scourges to humanity. Along with the even more virulent staphylococcus, these had been responsible for hundreds of thousands of deaths from horrifically contaminated wounds during the First World War. And now Britain and her empire were locked in a second war, which in 1940 looked very much lost. Hundreds of British soldiers were dying daily of infected wounds sustained in the Battle for France. Nothing, not even the new sulpha chemicals, could combat infections caused by these bacteria. A badly contaminated wound meant death just as certain as a bullet wound to the heart.

The next morning, Sunday May 26th, at 11.00 A.M Florey, Chain and Heatley met at the lab as prearranged. Heatley showed them the dead mice who had not received any penicillin, and the live mice - all perfectly well who had received it. Chain could barely suppress his surprise and excitement. Florey, ever careful and unlike Chain, little prone to emotional outbursts simply exclaimed, "It looks quite promising!" When his long time lab assistant (and mistress) was told of the results she put things rather more succinctly, "This looks like a miracle!".

May 26th 1940 marked a poignant day in history. In the despair of total defeat, the British began their dramatic evacuation of the beaches of Dunkirk - on the very same day that penicillin was proved to be an effective and safe drug - in vivo. In 1943 Florey himself a medical doctor, would be saving the lives of severely wounded Allied soldiers in North Africa, who the surgeons' knife in isolation was powerless to save. For the first time in history military casualties were being saved from severely infected wounds. By 1944, the might of American industry, following a medical "Manhattan Project", was producing a staggering 10 billion units of penicillin a month, enough to treat every Allied soldier fighting in both Europe and the Pacific.

Alexander Fleming and Howard Florey were knighted in 1944. In 1945 Fleming, Florey and Chain jointly received the Nobel Prize for Medicine or Physiology. The Nobel committee, by its own rules, does not jointly award prizes to any more than three people. Norman Heatley, though instrumental in the initial extraction of penicillin from crude mould broth, and about whom, Sir Henry Harris recorded in 1998 "Without Fleming, no Chain or Florey; without Florey, no Heatley; without Heatley, no penicillin", received no awards (at the time) at all, and even today remains virtually unknown. Posterity will remember him however, as his three simple notes recorded in the lab books of the Dunn laboratories, recording the deaths with little red crosses of the mice not treated with penicillin mark a shining moment in medical history - it is no less than the birth certificate of the antibiotics.

The penicillins are still widely used antibiotics today. Infectious disease caused by staphylococci and streptococci however remain problematic due to the ongoing evolution of bacterial resistance. Newer penicillins with greater spectrums of activity were developed in the years following Florey's team's work and continue to be developed. Ampicillin is one such example.

AMPICILLIN

Introduction

Ampicillin is a semisynthetic aminopenicillin antibiotic, very similar to amoxycillin, though it is generally for parental use rather than oral use. (Amoxycillin is better absorbed orally than ampicillin).

It is a **moderate spectrum** penicillin that has somewhat less activity against gram positive organisms when compared to the narrow spectrum penicillins; however it has some extended activity against some gram negative organisms

Ampicillin is *not* effective against **beta lactamase producing** organisms.

It is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system

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

Ampicillin is derived from the penicillin nucleus, 6-aminopenicillanic 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

Available preparations include:

Ampoules: 500 mg (as powder for reconstitution).

1 gram (as 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.

Pharmacodynamics

Ampicillin is active against some strains of gram positives:

- Alpha-haemolytic and beta-haemolytic streptococci.
- Diplococcus pneumoniae
- Non-penicillinase producing staphylococci
- Streptococcus faecalis

Ampicillin is active against some strains of gram negatives:

- It is active against most strains of *Haemophilus influenza*

Resistant strains:

- **Escherichia coli** isolates are **increasingly resistant** to Ampicillin *in vitro* due to the presence of penicillinase producing strains
- All strains of Pseudomonas species, Klebsiella species, Enterobacter species, indole positive Proteus species, *Serratia marcescens*, Citrobacter species, penicillinase producing *N. gonorrhoeae* and penicillinase producing *H. influenzae* are resistant.

Pharmacokinetics

Absorption:

- Ampicillin is given **intravenously.**

  It may be given by the intramuscular route, but the IV route is preferred.

Distribution:

- Ampicillin sodium diffuses readily into most body tissues and fluids with the exception of brain and spinal fluid.

Metabolism and excretion:

- Ampicillin is excreted mainly via the urine

Probenecid can inhibit the tubular secretory mechanisms.

- There is some metabolism to penicilloic acid derivative which is then excreted in the urine.

Indications

Ampicillin is commonly used for:

1. Uncomplicated lower respiratory tract infections:
    - Bronchitis (acute and acute on chronic)
    - Community-acquired pneumonia
2. Acute cholecystitis (with gentamycin)
3. Peritonitis (with metronidazole and gentamycin)

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:

- 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.
- 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.

Pregnancy

Ampicillin is a category A drug with respect to pregnancy.

Category A drugs are those drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of

malformations or other direct or indirect harmful effects on the fetus having been observed.

Breast feeding

Ampicillin is safe in breast feeding.

Adverse Effects

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

The principle adverse effects of Ampicillin include:

1. GIT upset (oral administration)

2. Allergic reactions:

    - Including serious and *fatal* **anaphylactic** reactions.

      Anaphylaxis is more frequent following **parenteral** therapy, but it has also occurred in patients on oral therapy.

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 reactions.

    - Hypersensitivity reactions:

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

    - **Amoxycillin (or ampicillin) rash:**

      This is a widespread, erythematous maculopapular rash.

      It is relatively common.

      The exact mechanism is uncertain, but it is not considered to be a true immune mediated reaction.

      It often occurs after > 7 days treatment and resolves within 1 - 7 days after treatment is stopped, (or after 6 - 14 days if it continues).

      It is more frequently seen in those with:

- ♥ Infectious mononucleosis.
- ♥ HIV infection
- ♥ Acute lymphoblastic leukaemia
- ♥ Chronic lymphocytic leukaemia

See appendix 1 below.

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.

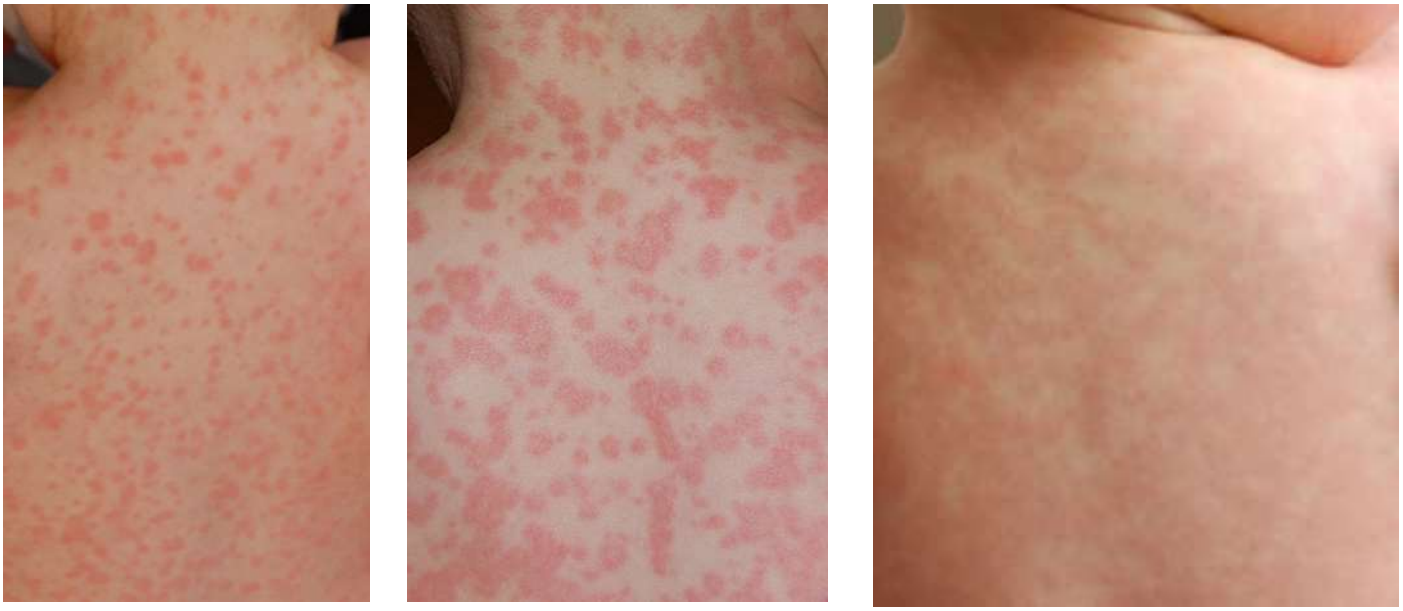
In *general* terms:

IV:

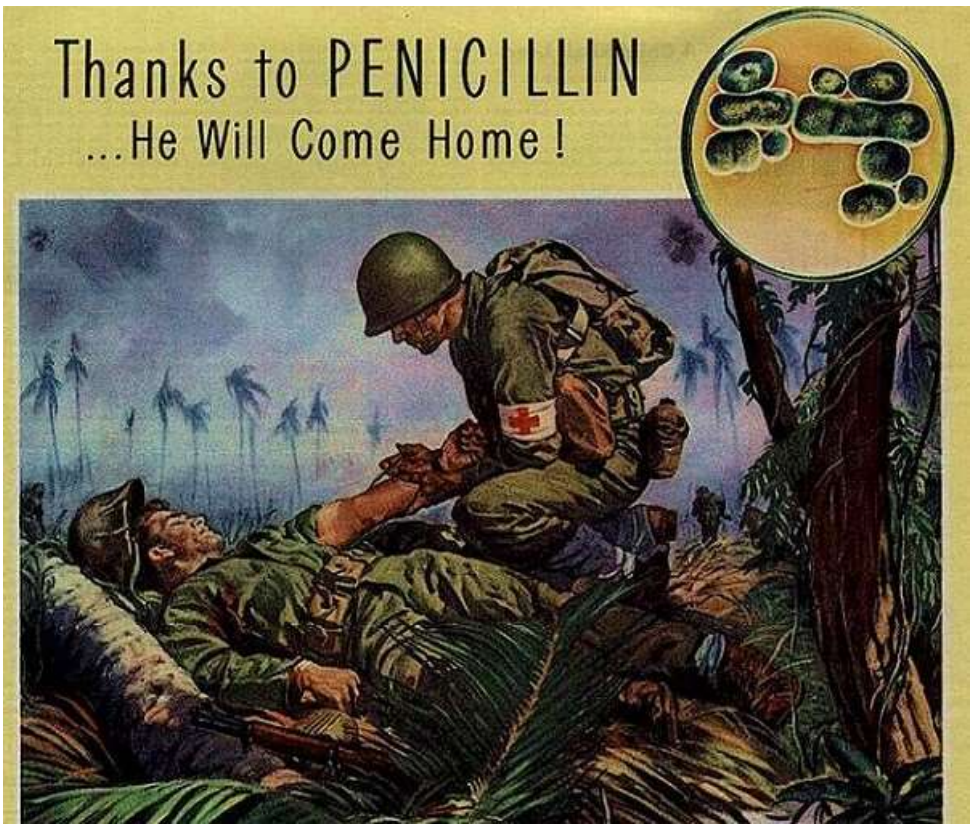
- Ampicillin **1- 2 grams IV 4 - 6 hourly**

Appendix 1

Non-allergic amoxicillin rash:



Left: Eight days after first dose. This photo was taken 24 hours after the rash had begun. Middle: Eight hours after the first photo, individual spots have grown and begun to merge. Right: At 23 hours after the first photo, the colour appears to be fading, and much of rash has spread to confluence. (*Wikimedia Commons*).



Left: The work on penicillin was carried out under the most difficult of war time conditions. Money and materials of every kind were in very short supply. Here Norman Heatley, shovel in hand, is seen in his spare time away from the laboratory - furiously digging air raid shelters adjacent the Dunn laboratories. Although Florey's team feared they could be a target for German air raids - Oxford itself, fortunately for medical science, was never attacked.

Right: Penicillin Poster Advertisement of August 1944 from Schenley Laboratories, (Time-Life). By 1944, the might of American industry, was producing a staggering 10 billion units of penicillin a month. Enough to treat every Allied soldier fighting in both Europe and the Pacific.

References

1. eTG Complete - November 2014.

    - Antibiotic Therapeutic Guidelines, 15th ed 2014.

2. Ampicillin in Australian Medicines Handbook, accessed February 2015.

3. Ampicillin in MIMs 1 May 2011

Dr J. Hayes
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