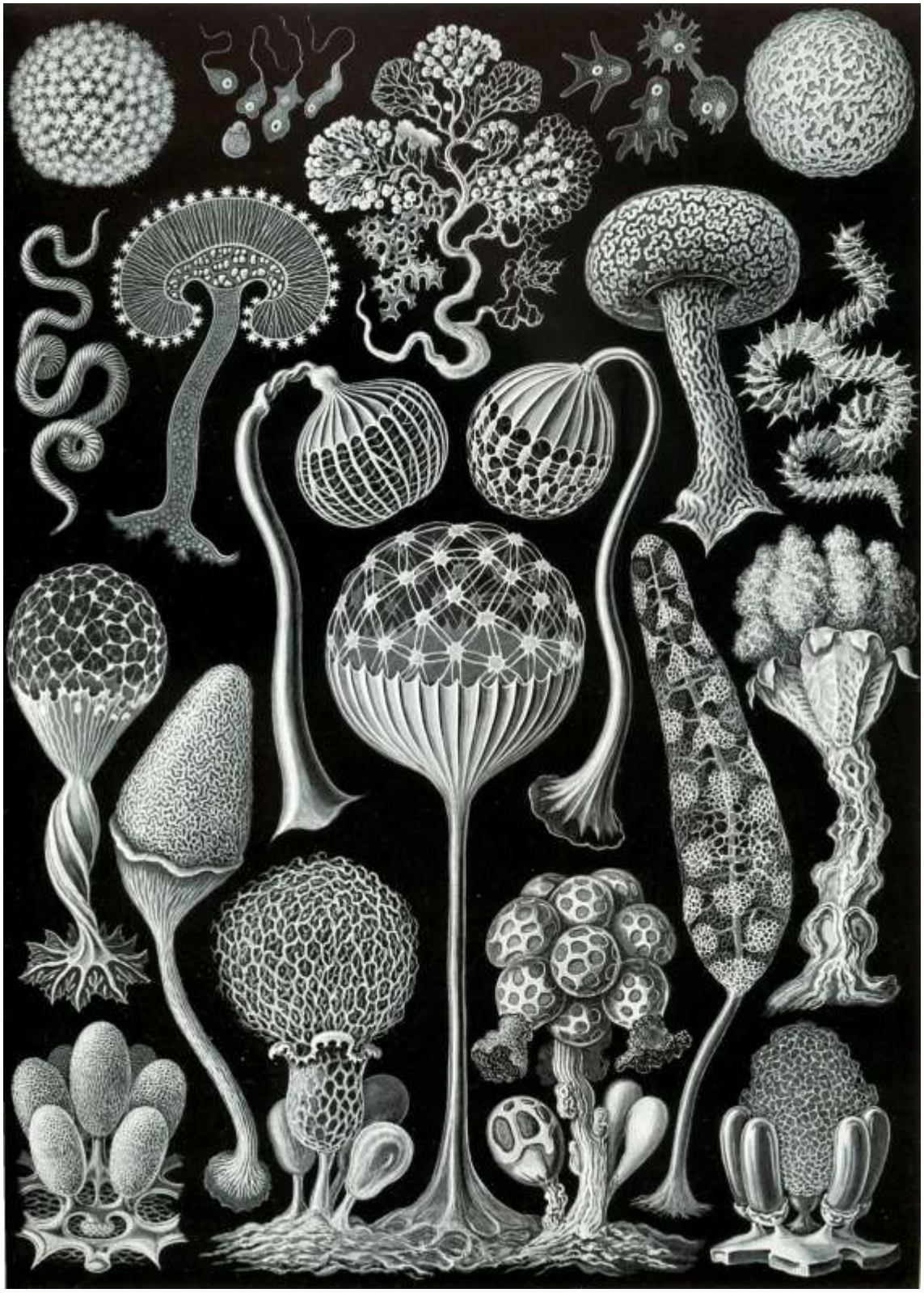
THE NORTHERN HOSPITAL

CEFTRIAXONE



The Mycetozoa (Fungi), Ernst Haeckel, 1904.

Humanity today is like a waking dreamer, caught between the fantasies of sleep and the chaos of the real world. The mind seeks but cannot find the precise place and hour. We have created a Star Wars civilization, with Stone Age emotions, medieval institutions, and godlike technology. We thrash about. We are terribly confused by the mere fact of our existence, and a danger to ourselves and to the rest of life…

Humanity is a biological species, living in a biological environment, because like all species, we are exquisitely adapted in everything: from our behavior, to our genetics, to our physiology, to that particular environment in which we live. The earth is our home. Unless we preserve the rest of life, as a sacred duty, we will be endangering ourselves by destroying the home in which we evolved, and on which we completely depend…

Edward O. Wilson

There are three great multicellular kingdoms of life on Earth. The first two are well known, the plants and the animals. The third is perhaps not quite as well known to most non-biologists, and it is the fungi. It may seem surprising that molecular evidence shows that the fungi, so plant-like in appearance are actually more closely related to animals than they are to plants! The magisterial Richard Dawkins in his book, "The Ancestor's Tale", shows that animals and fungi had a common ancestor back in deep geological time; possibly around 1.5 billion years ago. This "rendezvous" point is actually more recent (though of course "recent" is a purely relative term here when considering the immense and staggeringly incomprehensible time scales of geological time) than that of the animals and plants, possibly around 3 billion years ago. It may also be surprising that it is thought that fungi colonized the land from the sea, before the plants did, (and of course both these kingdoms colonized the land well before the first animals did so). It is not surprising therefore that the fungi have a very very ancient affiliation and integration with the terrestrial world, that even today, is only incompletely understood.

About 69,000 different species of fungi have been scientifically described, however, this is inconsequential, given the fact that by some estimates there are around 1.5 million species of fungus on Earth! When most people are asked the question "What is the largest living thing on the planet", they will say the Blue Whale, and while this is true in the sense of the largest living animal, it is not the largest living organism on the planet. This distinction possibly belongs to a certain species of fungus, the Armillaria solidipes - a single specimen found in Malheur National Forest in Oregon covers an area of 3.4 square miles and has been estimated at possibly, 2,400 years old! Richard Dawkins points out that what see easily see in the form of mushrooms and toadstools really give the wrong impression of the true extent of some fungal organisms. He writes, " …these conspicuous plant-like structures are the spore producing tips of the iceberg. Most of the business part of the organism that made the mushroom is under the ground" . This "business end" takes the form of an immense underground complex network of hyphae that course through the ground soil, and that ultimately belong to just one organism. The network of hyphae are known as the mycelium of an individual fungus and these can spread through the soil up to a kilometer or more! The mushrooms and toadstools are merely the above ground fruiting bodies of the organism that produce its reproductive spores. Hyphae are interesting structures. They can be divided into cells by cross-walls, but sometimes these cross walls are not present and nuclei containing the DNA of the

fungus are merely dotted throughout the hyphae in a syncytial network. Not all fungi form mycelia though, some like yeasts are merely single celled organisms. The hyphae extend through the soil, digesting dead and decaying organic material, and so provide an important means of cleansing the soil of dead organic matter. The good health of the plant kingdom on Earth is vital to the survival of all animals, including humans. If all humans disappeared from the face of the Earth, the plant kingdom would still happily thrive, but if all plants disappeared, then the human species would be driven to extinction in short time. Some fungi have important symbiotic relationships with plants, and so indirectly are also vital to human existence. Their mycelia networks act as root hairs to plants' roots, that help increase the roots' surface area that is available to absorb water to the mutual benefit of both organisms. Some fungi form colonies with algae or cyanobacteria to create symbiotic life forms, know as lichens, (and which are not therefore true plants). Richard Dawkins writes, "In my vision of life….such a collaboration is not in principle different from the collaboration of an organisms, "own" genes. We are all symbiotic colonies of genes - genes cooperating to weave phenotypes about them" - such as lichens - or more directly relevant to humans the very mitochondria of our eukaryotic cells!

Of more directly tangible interest to many humans of course is the epicurean benefits of certain fungi, for example, the action of some yeast fungi, such as the species that like curdled milk and produce cheeses or those that like grapes and produce wine! The fruiting bodies, that is - mushrooms - of some species of course are a culinary delight. To counterbalance all these happy relationships though sadly are also groups of fungi such as rusts that cause deadly disease in plants or other species that cause bothersome skin and nail infections in humans, or certain other mushrooms that are hallucinogenic or even deadly poisonous.

Perhaps the most medically well known and famous and of the fungi are the penicillin producing species. Somewhat less well known is the fact that other fungi also produce different antibiotics, notably the prototype cephalosporins, which were discovered just a few years after the end of the Second World War. One of the great Edward O. Wilson's most impassioned pleas, is the preservation of life's diversity on planet Earth, but not only its preservation for its own sake but for the potential key roles each play in the overall ecosystems of life on Earth, systems we do not always understand and with which we interfere with at our own peril. We only understand a very small fraction of the fungal species on Earth. The untapped potential of an estimated 1.5, million species of which we know virtually nothing could bring us unimagined future benefits.

"…I will argue that every scrap of biological diversity is priceless, to be learned and cherished, and never to be surrendered without a struggle….We should preserve every scrap ….while we learn to use it and come to understand what it means to humanity".

Edward O Wilson.

CEFTRIAXONE

Introduction

Ceftriaxone is a very useful third generation broad spectrum cephalosporin antibiotic.

It is commonly used for the empiric treatment of serious and life threatening gram positive and gram negative infections.

It is are *inactive* against MRSA

One important difference between ceftriaxone and cefotaxime is that ceftriaxone is contraindicated in neonates (i.e < 2 months of age)[4] due to bilirubin displacement and kernicterus risk. Cefotaxime can be used in neonates instead.

History

The cephalosporin antibiotics were first isolated from the fungus ***Cephalosporium acremonium.***

They were discovered by **Giuseppe Brotzu** (1895 - 1976) an Italian pharmacologist (and politician) in 1948 in Sardinia.

Cephalothin was the first cephalosporin antibiotic introduced into clinical practice in 1964.

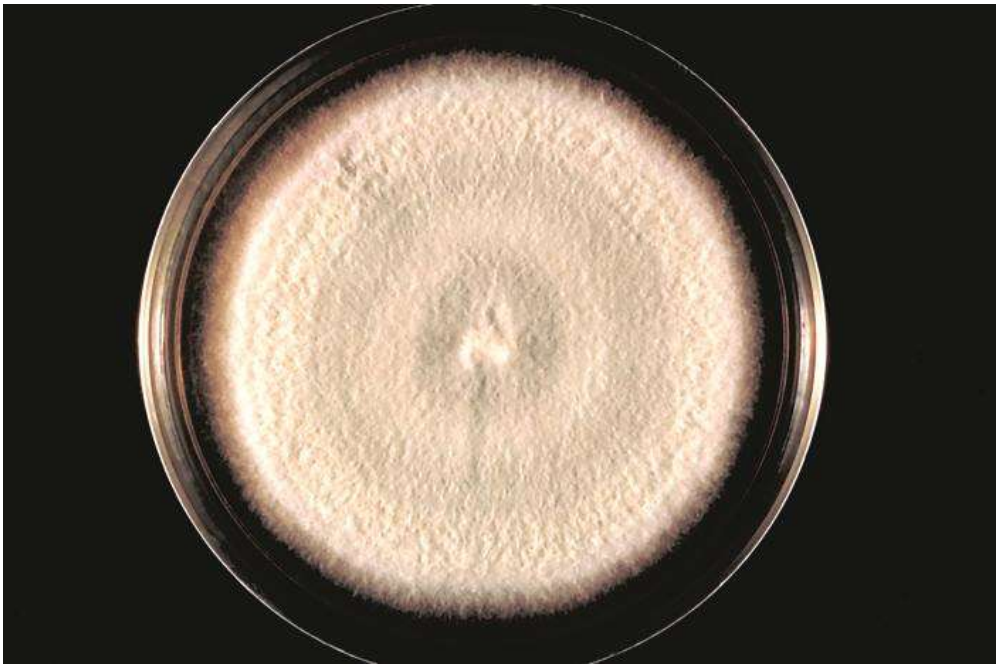


Plate culture of the fungus Acremonium falciforme. The cephalosporin class of antibiotics were developed from the acremonium (formerly known as cephalosporin) genus of fungi.

Chemistry

Ceftriaxone is a semisynthetic cephalosporin.

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

Classification

The cephalosporins can be classified into **5** principle groups or "generations": [1]

1. **First Generation**:

   Moderate-spectrum cephalosporins

   Principally gram positive activity, but with some limited gram negative activity.

   - Cephalothin
   - Cephalexin
   - Cephazolin.

2. **Second Generation**

   Slightly less gram positive cover than first generation agents, but extended activity against gram negatives and anaerobes.

   Moderate-spectrum cephalosporins with **anti-Haemophilus** activity:

   - Cefaclor
   - Cefuroxime

   Moderate-spectrum cephalosporins with **anti-anaerobic** activity:

   - Cefoxitin

4. **Third Generation**

Reasonable gram positive cover, and further extended activity against gram negative agents.

Broad-spectrum cephalosporins:

- Ceftriaxone
- Cefotaxime

5. **Fourth Generation**

Good gram positive cover and good gram negative cover

Broad-spectrum cephalosporins with **antipseudomonal** activity:

- Cefepime
- Ceftazidime

6. **Fifth Generation**

Newer very broad spectrum agents.

Broad-spectrum cephalosporins with **anti-MRSA** activity:

- Ceftaroline

Preparations

Ampoules:

- 500mg, 1 gram, 2 gram (as powder for reconstitution).

Mechanism of Action

The cephalosporins are **bactericidal** agents.

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

Bacterial resistance factors:

Beta lactamases:

The cephalosporins have *variable* resistance to bacterial beta-lactamases. [1]

Plasmid mediated **extended-spectrum beta-lactamase enzymes (ESBLs)** are produced by some organisms (e.g. E. coli, Klebsiella pneumoniae, Enterobacter species). These may inactivate broad spectrum cephalosporins such as ceftriaxone (and cefotaxime).

Extended spectrum beta-lactamases (ESBLs), confer resistance to all cephalosporins, penicillins (unless given with a beta-lactamase inhibitor) and aztreonam.

Cephalosporinases:

Some organisms (e.g. *Serratia*, *Citrobacter* and *Enterobacter* species) have chromosomal resistance in the form of **cephalosporinase** enzymes.

Resistance can develop during the course of treatment. [1]

In general however ceftriaxone has a high degree of stability in the presence of beta-lactamases, types I, II & III, penicillinases and cephalosporinases, of gram negative and gram positive bacteria. [3]

It is susceptible to type IV beta-lactamases [3]

Pharmacodynamics

Cefotaxime and **ceftriaxone** have a broad spectrum of activity that includes:

1. Gram positives:
    - However they are *less* active against staphylococci than the older cephalosporins, and are *inactive* against MRSA.
2. Gram negatives:
    - They are active again the majority of community-associated enteric Gram-negative rods.

Although cefotaxime has better intrinsic activity against staphylococci than ceftriaxone, the antistaphylococcal activity of both drugs is **dose dependant**; at lower doses, co-administration with flucloxacillin for empirical therapy of staphylococcal infections may be recommended.

Cefotaxime and ceftriaxone do *not* have clinically useful activity against enterococci.

Pharmacokinetics

Absorption:

- Ceftriaxone is **poorly** absorbed from the gastrointestinal tract

It is administered parenterally, i.e **intramuscularly** or **intravenously.**

Intravenous administration is the preferred route.

Distribution

- Protein binding varies from 85 - 95 % depending on blood concentrations.
- Apparent volume of distribution from 5.78 to 13.5 liters
- When meninges are inflamed, ceftriaxone and cefotaxime display significant diffusion into the cerebrospinal fluid
- Ceftriaxone crosses the placenta
- Ceftriaxone appears in breast milk in low concentrations.

Metabolism and excretion:

- Up to around 65% of ceftriaxone is excreted in the urine as unchanged drug.
- The rest is metabolized in the liver and predominantly excreted in the bile.
- Renal excretion of ceftriaxone is **not** affected by prior administration of probenecid.

Indications

Infections due to susceptible / likely susceptible bacterial organisms.

Ceftriaxone is used in the treatment of a wide range of serious and life threatening infections, including: [2]

1. Empirical treatment of severe pneumonia (with other agents)
2. Empirical treatment of bacterial meningitis (with other agents):
    - Unlike older cephalosporins, ceftriaxone and cefotaxime are effective for meningitis because in the presence of **meningeal inflammation** they achieve therapeutic concentrations in the cerebrospinal fluid. [1]
3. Empirical treatment of septicaemia (with other agents).
4. Empirical treatment of orbital cellulitis (sometimes with other agents)
5. Serious intraabdominal infections:
    - Acute cholecystitis (alternative to ampicillin with gentamicin)

- Acute peritonitis (with metronidazole)
- Severe *Salmonella* enteritis (if other antibacterials unsuitable)
- Typhoid, paratyphoid (enteric fever)

6. Some STDs:
   - Gonococcal infection
   - PID
   - Sexually acquired epididymo-orchitis (with doxycycline)
7. Epiglottitis
8. Some prophylactic treatments:
   - Prevention of meningococcal disease (if rifampicin or ciprofloxacin contraindicated)
   - Prevention of *H. influenzae* type b disease (if rifampicin is contraindicated)

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 ceftriaxone
2. Caution in those with a history of an allergic reactions to other beta lactam antibiotics:
   - As cross-reactivity between penicillins, cephalosporins and carbapenems can occur.
3. Caution in significant renal impairment (Cr Cl < 20 mL/minute).
   - As a **class** the cephalosporins can occasionally cause neurotoxicity in patients with significant renal impairment; usually when administered too rapidly IV and in high doses

Neurotoxicity may manifest as confusion, seizures, encephalopathy.

4. Neonates (**contraindicated**):

There are two problems relating to use in neonates: [2]

- **Ceftriaxone is contraindicated in neonates (i.e < 2 months of age)[4] due to bilirubin displacement and kernicterus risk. Cefotaxime can be used in neonates instead.**

- **Calcium and ceftriaxone are incompatible; calcium-ceftriaxone precipitates in the lungs and kidneys of neonates have caused death.**

Pregnancy

Maternal use of ceftriaxone has not been associated with an increased risk of birth defects or adverse pregnancy outcomes. Ceftriaxone is safe to use during pregnancy.[5]

Ceftriaxone is a class B1 drug with respect to pregnancy.

Class 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.

Breast feeding

Ceftriaxone is safe in breast feeding.

Small amounts of ceftriaxone are excreted into the breast milk but these amounts are unlikely to pose harm in the breastfed infant. Ceftriaxone 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 as infant gut flora may be impacted. [5]

Adverse Effects

All the beta lactams including the cephalosporins have a **wide therapeutic index** and are not associated with significant adverse effects, apart from hypersensitivity reactions..

Adverse reactions include:

1. Allergic reactions:

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

3. Dermatological:

- Occasionally severe reactions such as Stevens-Johnson syndrome.

4. Pseudomembranous colitis:

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

     Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

5. **Bilirubin displacement and kernicterus risk in neonates.**

Dosing

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

In *general* terms:

Adult: 1 - 2 grams IV (or IM) once daily (or in 2 divided doses).

Child: 50 - 75 mg/kg (maximum 2 grams) IV (or IM) once daily (or in 2 divided doses).

For life threatening infections, such as **meningitis 12 hourly** dosing should be used.

See latest edition of Antibiotic Therapeutic Guidelines for full prescribing details.

References

1. eTG Complete - November 2014.

    - Antibiotic Therapeutic Guidelines, 15th ed 2014.

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

3. Ceftriaxone in MIMs 1 August 2013

4. Meningitis-Encephalitis in RCH Guidelines Website Accessed June 2016.

5. RWH Drugs in Pregnancy & Breastfeeding Guidelines, Accessed June 2016.

Further reading:

Richard Dawkins, "The Ancestor's Tale. A Pilgrimage to the Dawn of Life", Weidenfeld and Nicolson, 2004.

Dr J. Hayes

Reviewed June 2016.