

CEFEPIME



“The Annunciation”, Tempera on wood, 1433 - 34. Fra Angelico, Museo Diocesano, Cortona, Italy.

*“Oh”, I said to him, “are you not Oderisi,
the honour of Gubbio and of that art
which they in Paris call illumination?”*

*“Brother”, he said, “the pages smile brighter
From the brush of Franco of Bologna.
The honour is all his now - and only mine in part.*

*“Indeed, I hardly would have been so courteous
while I still lived - an overwhelming need
to excel at any cost held fast my heart.*

*“For such pride here we pray our debt.
I would not be here yet, except, while living,
and with the means to sin, I turned to God.*

*“O vanity of human powers,
how briefly lasts the crowning green of glory,
unless an age of darkness follows!*

*“In painting Cimabue thought he held the field
but now its Giotto has the cry,
so that the other’s fame in dimmed.*

*“Thus has one Guido taken from another
the glory of our tongue, and he, perhaps, is born
who will drive one and then the other from the nest.*

*“Worldly fame is nothing but a gust of wind,
first blowing from one quarter, then another,
changing name with every new direction.*

Dante Alighieri, Purgatorio; Canto XI, 79 - 102 (1306-1317)

According to some literary historians Dante Alighieri’s monumental poem “The Divine Comedy” is the greatest work of literature ever produced in the Western lexicon, and, by some definitions, perhaps it is. Of course the term “great” can be defined in many different ways, with different types of greatness having different weighting with different scholars. The work is at the least intensely fascinating from many different points of view. From that of the historian of the Renaissance it gives an unparalleled insight into the medieval mind, in particular in regard to the intense and titanic intellectual battles that were being fought during this period, not only in academic circles, but increasingly in the collective consciousness of the wider population. The battle was that of the newly emerging humanism, that evolved from the “relearning” of classical knowledge lost to the West for almost a millennium, but preserved in the Islamic world. Humanism essentially was the recognition of the logical science and beauty of the natural world as opposed to an age long obsessed with death and the afterlife - an obsession so fossilized into the early medieval mind that no other vision of life appeared remotely possible. Life was merely a short brutal transit to either heaven or hell after death. But with the great relearning this dismal view slowly began to change. Perhaps the true miracle was life itself - not what happened after death.

It is intensely fascinating to follow the evolution of this change in mindset through the visual arts of the Fourteenth and Fifteenth centuries. Up until the late Thirteenth century the purpose of all Art was to portray religious or moral messages, to prepare people for the afterlife to come. The message was the most important issue - the artwork of itself was completely irrelevant. If it was beautiful this was merely to inspire religious feeling in the people. The images are flat, dimensionless, and stereotyped, with barely a difference in style over many centuries. So irrelevant were the Artists that produced these works we do not even know their names. But then by the late Thirteenth century we do begin to learn of some of them. In the work of Cimabue we see the usual religious motifs - but on closer inspection we see subtle changes occurring - slight individual changes in appearance are seen in the standard images! People were being depicted more as individuals rather than standard icons - where previously an emperor of the Sixth century had been depicted exactly the same as one of the Ninth - the only change being in the name inscribed over it. Cimabue broke the mold by individualizing the figures with their own personalities. For the first time the Artist him or herself gained recognition for their work. The pupil of Cimabue, Giotto, then took things to a completely new level again. He created a sensation by depicting figures of real people with real emotions and distinct personalities in realistic scenes. Difficult as it is for us to imagine today this was a novel and revolutionary step. Scandalously the artists themselves were becoming famous for their works, Giotto immensely so.

This personal fame did not sit well with many of the religious or even secular authorities. The purpose of Art was to convey dogma to the people - and its purpose was certainly not to celebrate earthly existence. Dante himself struggled mightily with this dilemma. In the Divine Comedy he spoke of his journey through Heaven and Hell but he created a third kingdom of the afterlife - purgatory - things were not quite so black and white! Surely many people did not deserve the eternal fires of hell for pride - and yet perhaps they did not exactly deserve heaven either! Dante of course in his day was considered a great writer, but it was socially unacceptable to take even the slightest credit for any earthly achievement, unless you happened to be a king or great prince. All achievement was for the greater glory of God and God only! Dante struggled with this concept. He writes of the souls in Purgatory doing time for the sin of Pride. This sin hits a raw nerve for Dante. Of all the mortal sins it was pride in his own literary abilities that he feared would be his greatest need for atonement in the afterlife. Poignantly he questions a famous illuminator Oderisi. The shades of the Proud on the First Terrace of Purgatory are now laid low by being crushed under great stones - "For such pride here we pray our debt". He praises Odeseri for his beautiful works, but Odeseri responds that another illuminator, Franco of Bologna, was greater than he, showing that he has learnt humility. Dante reflects that the painter Cimabue was quickly eclipsed by his own pupil Giotto, who was a contemporary of Dante and indeed who painted Dante's portrait into one of his works. He also talks of a writer by the name of Guido being eclipsed by another writer of the same name. The whole point of these observations is to show that the new humanism is really fostering the sin of Pride and thus an offense to God. Then unable to help himself Dante mentions that perhaps an even greater writer than Guido has already been born - "he, perhaps, is born who will drive one and then the other from the nest". This comment has been the source of intense intellectual debate over the centuries - was Dante actually referring to himself as the writer who will eclipse all others?

Dante wrote his immortal work during a period of great intellectual transition, and his own internal struggle with this clearly comes through in the Divine Comedy over and over again. In the visual Arts we can trace this momentous cultural shift in the works of Cimabue and Giotto, and follow it through to those of the humble Dominican friar, Fra Angelico over a century after Dante's death. Though his motif was still intensely religious, Fra Angelico used modern depictions of dimensional perspective and space, based on the mathematically precise principles of Leon Battista Alberti. Once Giotto made the final break with flat templated religious iconism, there was no turning back.

In 21st century medicine we see constant evolution in our antibiotics as a matter of course. Cefepime represents no less than the fourth generation in its particular class. Big Pharma drives our progress in the antibiotics unhindered by outmoded medieval concepts of pride...though one suspects that the mortal sin of greed remains very much alive and well!



Left: The Virgin Orans 1037-61 Artist unknown, Mosaic, Byzantine, St Sophia Cathedral Kiev.

Middle: Madonna in Majesty, Cimabue, 1285-86, Tempera on Panel Uffizi, Late Byzantine - Early Renaissance, Galleria Degli, Florence

Right: The Lamentation, Tempera on Panel, Giotto di Bondone, 1304 - 06 Fresco Early Renaissance, Arena Chapel Giotto Padua Italy

CEFEPIME

Introduction

Cefepime is a fourth generation cephalosporin antibiotic with broad-spectrum activity including good **antipseudomonal** activity.

Because of its **wide therapeutic index** and its **very wide spectrum of activity**, cefepime is one of the current agents of choice for the **empiric** treatment of **serious/ life threatening** infections.

Cefepime is highly resistant to hydrolysis by most beta-lactamases

Cefepime may be used in cases of **febrile neutropenia**, when Tazocin has previously caused an allergic or other adverse reaction (of a non-life threatening nature).

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.

Cefepime was developed in 1994.

Chemistry

Cefepime 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:

- 1 gram (as powder for reconstitution).
- 2 grams (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.

Pharmacodynamics

Cefepime has a broad spectrum of *in vitro* activity that encompasses a wide range of Gram positive and Gram negative bacteria.

- Gram positives including:
 - ♥ *Staphylococcus aureus* (methicillin susceptible strains only)
 - ♥ *Streptococcus pneumoniae*
 - ♥ *Streptococcus pyogenes*
- Gram negatives including:
 - ♥ Enterobacter
 - ♥ *Escherichia coli*
 - ♥ *Klebsiella pneumoniae*

♥ *Proteus mirabilis*

♥ *Pseudomonas aeruginosa*.

Cefepime is **inactive** against most strains of *Clostridium difficile*.

Cefepime is highly resistant to hydrolysis by most beta-lactamases

Pharmacokinetics

Absorption:

- Cefepime is given **intravenously**.

It may also be given **intramuscularly**, however the intravenous route is preferred.

Distribution

- The average volume of distribution of cefepime is 0.3 L/kg.
- Protein binding is approximately 15 %.

Metabolism and excretion:

- Approximately 85 % of cefepime is excreted unchanged in the urine.

Approximately 15 % of Cefepime is metabolized in the liver

Indications

These include:

1. Infections caused by multi-resistant organisms, e.g. *P. aeruginosa*,
2. Serious infections in the immunocompromised
 - Including GIT, Respiratory, Skin/ Soft tissue/ Urinary tract.
3. Second line agent (after Tazocin) for empirical treatment of febrile neutropenia

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 cefepime
2. Caution in those with a history of allergic reactions to other beta lactam antibiotics:
 - As cross-reactivity between penicillins, cephalosporins and carbapenems can occur.

Pregnancy

Cefepime is a category B1 drug with respect to pregnancy.

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

Safe in breast feeding.

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.

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:

- **Cefepime 1 - 2 grams IV 8 – 12 hourly**

Child: give 50 mg/kg up to 2 grams IV

For febrile neutropenia:

- **Cefepime 2 grams IV 8 hourly**



Dante and Virgil on the Terrace of the Proud, woodcut print, 1865, Gustave Dore.

References

1. eTG Complete - March 2015
 - Antibiotic Therapeutic Guidelines, 15th ed 2014.
2. Cefepime in Australian Medicines Handbook, accessed August 2015.
3. Cefepime in MIMs 1 November 2012

Dr J. Hayes
Reviewed August 2015.