

**IMIPENEM AND CILASTATIN**



*“The Beheading of St. John the Baptist”, oil on canvas, 1608.  
Michelangelo Merisi da Caravaggio. St. John’s Cathedral, Valletta, Malta.*

*Wanted for murder, Caravaggio goes on the run.*

*In his absence he is sentenced to abande capitale.*

*There’s a price on his head. Literally.*

*Show up with his head in a basket and you get the reward.*

*Once again his network of patrons and admirers rallies round to keep him afloat.*

*Throughout the summer of 1606 they help him hide out, and in return, sick and sober by what he's done, Caravaggio makes paintings.*

*Paintings that help him on his way far beyond the jurisdiction of the papal state.*

*Somewhere the police and bounty hunters won't find him.*

*Naples.*

*Here, in a city where cutting your throat is nothing to get worked up about, Caravaggio is a celebrity.*

*But his paintings are full of pity, tenderness, and mercy.*

*Hardly surprising, since as a murderer he knows his immortal soul is in grave danger.*

*A year goes by since the murder and escape from Rome.*

*The Neapolitans can't get enough of him.*

*Caravaggio is doing great work, and guess what?*

*No fights.*

*So why does he suddenly leave, and end up in Malta, of all places? Not to be a crusader against the Turks, that's for sure.*

*But there was one thing that Malta, the Christian island in the Muslim Mediterranean, could give him which Naples couldn't -*

*Status. Respect. A knighthood.*

*One of his patrons makes the right noises, and introduces Caravaggio to the Holy Order of the Knights of St. John. One of most rich and powerful organizations in Europe.*

*Becoming a knight would mean not only honor and respect, but also a chance to wipe the bloody slate of his past clean.*

*Now, normally being a convicted murderer would be an insurmountable obstacle to admission.*

*Not for Caravaggio.*

*On 14 July 1608 the robe with the Maltese Cross is put around the fugitive's shoulders, and he is officially proclaimed one of the greatest of painters, living or dead.*

*In exchange for all this, Caravaggio undertook a painting for the knights' cathedral.*

*You have to imagine this place filled with robes and incense, and echoing with deep, dark anthems.*

*The beheading of John the Baptist is the biggest thing Caravaggio had ever done.*

*Seventeen feet long, filling the entire eastern wall of the oratory.*

*It's movie screen-sized.*

*He wanted the knights to feel it not as a painting, but as a living drama going on right in front of them.*

*No wonder it sends a shiver through us...this...thing. This infamous butchery.*

*Taking place in a grim prison yard, where the body of John the Baptist has been dragged to have his head hacked off.*

*It's a scene of remorseless cruelty that tears your insides out and turns art upside down.*

*Art is supposed to bring us beauty, but just look at that semicircle of figures, and you'll see something has gone terribly wrong.*

*That perfect lily-white arm carries the golden bowl into which the Baptist's head will drop.*

*The solemn soldier, the embodiment of authority, is giving the order for an atrocity.*

*That perfect nude is a cold-blooded hit man with a knife.*

*The action seems to go on forever. Until, like that anguished old woman, all you can do is scream. Caravaggio gives us death, twice over.*

*The death of John the Baptist, and the death of our most cherished illusion about art, that it can make us finer, more humane.*

*"Dream on", says Caravaggio.*

*In the face of this barbaric power, all we can ever be are impotent spectators, just like those prisoners in the grim darkness, screwing their necks to get a look.*

*It's this ruthless honesty that makes this such a modern work.*

*Art without any vision of consolation or redemption.*

*It's a chilling scene.*

*For me, it's about the most powerful statement an artist could possibly make about the human condition.*

*About the brutality of state murder. But it's also autobiography.*

*Caravaggio has signed this picture, writing his name in the blood of John the Baptist.*

*Only a guilt-stricken killer could possibly feel this desperately about wanting the violence to stop. Only Caravaggio could want so badly for the blood of the martyr to wash away his crime.*

*Now it would be nice, wouldn't it, if that was the end of the story?*

*Outlaw painter redeemed by knockout masterpiece.*

*Art changed forever. Sinner saved.*

*But in Caravaggio's case, salvation doesn't come that easily.*

*The painter who wants violence to stop can't even control his own.*

*Barely a month after he's been admitted to the Order of St. John, Caravaggio is imprisoned for assaulting a brother knight.*

*Simon Schama, "The Power of Art", BBC Television, 2010.*

*Caravaggio had become comfortable in his exile in Naples - but he craved the one thing that Naples could not give him. Respectability. Then like a bolt out of the blue; unexpected salvation comes to him. Powerful figures behind the scenes have been working feverishly to rehabilitate the name of the great painter. The right strings are pulled and all of a sudden Caravaggio receives an invitation from the most powerful and respected institution in all of Christendom - second only to the Papacy itself - the Knights of St. John of Malta. "Join us Michelangelo, work for us!" Caravaggio doesn't hesitate. For while he is content. He even produces one of the greatest works of the early Baroque age "The Beheading of St. John the Baptist", a work that would dominate any gallery in the Louvre, but today stands in the grand Cathedral of St. John's in Valletta instead; a perpetual symbol of gratitude to the Knights who gave him a safe haven in his hour of greatest need. Even so, he still struggled to suppress the rage that he always carried deep within himself.*

*Imipenem was the first of the heavy artillery used in the battle against the ESBL bacteria. Board of spectrum and a powerful weapon, it seemed like it had the battle won. But soon it concealed a hidden flaw; its vulnerability to inactivation by a certain renal dipeptidase enzyme and so it lost its prestigious commission to a rival antibiotic by the name of meropenem. What it needed was a powerful ally to once more restore its respectability. As the Knights of St John of Malta came to the rescue of Caravaggio, so cilastatin came to the rescue of imipenem. All again seemed well, until, as for Caravaggio, underlying flaws again remerged - its relatively higher propensity to cause neurological complications compared to its upstart competitor!*

## IMPENEM AND CILASTATIN

### Introduction

**Imipenem** is a **carbapenem** antibiotic. It is combined with the *dipeptidase inhibitor*, **cilastatin**

Carbapenems have the **broadest spectrum** of all the antibacterial classes, with good activity Gram-positive organisms and Gram-negative organisms (including extended activity against many resistant strains of Gram-negative organisms) and anaerobes.

The widespread use of carbapenems has been linked with increasing prevalence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multiresistant Gram-negative organisms and *Clostridium difficile*.

Their use therefore is usually reserved for **serious / life threatening infections**.

**Imipenem may be inactivated by a renal dipeptidase enzyme. It is therefore usually formulated in combination with a dipeptidase inhibitor, cilastatin.**

**Imipenem has several disadvantages compared to meropenem including:**

- **It does not achieve as high levels in the CSF**
- **It has a higher incidence of seizure complications**

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

### History

When the first bacterial beta - lactamases emerged in the late 1960s, and reduced the efficacy of the penicillins, an intensive search for both beta - lactamase inhibitors and beta - lactamase resistant antibiotics was launched.

The carbapenem antibiotics were originally developed from the carbapenem thienamycin, a natural substance derived from the gram positive bacterium, *Streptomyces cattleya*.

Imipenem/cilastatin was introduced in 1985.

Meropenem was introduced in 1996.

Ertapenem was introduced in 2001.

### Chemistry

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

The carbapenems have a particular chemical structure that renders them highly resistant to most beta-lactamases

### Classification

The carbapenem antibiotics include:

- Imipenem
- Meropenem
- Ertapenem

### Preparations

Ampoules:

- Imipenem 500 mg, and cilastatin 500 mg (as powder for reconstitution).

### Mechanism of Action

The carbapenem antibiotics are **bactericidal** agents.

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

Carbapenems have the broadest spectrum of all the antibacterial classes, with good activity against Gram-negative and Gram-positive organisms and anaerobes.

They are resistant to hydrolysis by most beta-lactamases including extended-spectrum beta-lactamases (ESBLs)

However, Gram-negative organisms with acquired ability to produce metallo-beta-lactamases (carbapenemases) often inactivate all beta-lactams except aztreonam.

Cilastatin sodium, is an *inhibitor* of the renal dipeptidase, **dehydropeptidase I** enzyme which can deactivate imipenem.

### Pharmacodynamics

**Meropenem** and **imipenem** have very broad activity including:

1. Many Gram-positive organisms
  - Including *Nocardia* species
  - However inactive against MRSA
2. Gram-negative organisms:
  - Including isolates producing extended-spectrum beta-lactamase enzymes (ESBLs)
  - *Pseudomonas aeruginosa* (comparable to that of aminoglycosides).
  - Imipenem has useful clinical activity against *Enterococcus faecalis*, which meropenem lacks.
3. Anaerobic organisms:
  - There is excellent activity against these including *Bacteroides fragilis*.

Carbapenem resistance is emerging worldwide, often due to the production of various **carbapenemase** enzymes, which also confer resistance to other antibiotics.

### Pharmacokinetics

#### Absorption:

- Imipenem - cilastatin is given **IV**.

#### Distribution

- Imipenem protein binding is approximately 20%.  
Cilastatin protein binding is approximately 40%.
- Imipenem distributes to the CSF to a lesser degree than meropenem

#### Metabolism and excretion:

- Imipenem, when administered alone, is metabolised in the kidneys by dehydropeptidase I resulting in relatively low levels in urine.

Cilastatin sodium, an inhibitor of this enzyme, effectively prevents renal metabolism of imipenem so that, when imipenem and cilastatin sodium are given concomitantly, fully adequate antibacterial levels of imipenem are achieved in the urine.

- The plasma half-life in adults of each component is approximately 1 hour.

### Indications

Imipenem may be used in serious / life-threatening infections including:

1. UTIs
2. Intra-abdominal infections
3. Lower respiratory tract infections.
4. Febrile neutropenia
5. Necrotizing soft tissue infection / gangrene, (often in combination with other agents):
  - Severe mixed aerobic and anaerobic infections, particularly when combinations with an aminoglycoside are contraindicated
6. Melioidosis, (usually in combination with other agents)
7. Septicaemia.

Imipenem is not used in meningitis due to its epileptogenic potential; meropenem is preferred.

**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 imipenem or cilastatin
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. Precluded in situations where neurotoxicity may occur:
- Meningitis
  - History of seizures.
  - If possible avoid combining with other drugs that can reduce the seizure threshold.
4. Renal impairment:
- Reduce the dose in renal impairment and use with caution (there is an increased risk of neurotoxicity in patients with renal impairment).

### Pregnancy

Imipenem and cilastatin is a category B3 drug with respect to pregnancy.

Category B3 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 shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

### Breast feeding

Compatible but may cause diarrhoea in the infant

### Adverse Effects

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

Adverse reactions include:

1. GIT upset, (as with most antibiotics).
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. 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. Neurotoxicity:
- Imipenem is associated with neurotoxicity (myoclonic activity, confusion and seizures), especially when excessive doses are used in people with CNS disorders (e.g. history of seizures) or renal impairment.
- Ertapenem is also associated with seizures, especially in those with CNS disorders or renal impairment.
- Meropenem** has the least neurotoxicity of the carbapenems.

### Dosing

Exact dosing 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:

- Imipenem 500 mg ( up 1 gram in severe infections) IV, 6 hourly

Child:

- 15 mg/kg up to 500 mg IV, 6 hourly

Infuse 250 - 500 mg doses over **20-30 minutes** and 1 gram doses over **40 - 60 minutes** (more slowly if nausea or vomiting occurs).

**Note that Imipenem is only available in combination with cilastatin. Doses are expressed as the imipenem component only.**

Maximum dosage is **4 grams daily** or **50 mg/kg daily**, whichever is lower.

**Doses are reduced in renal impairment, (see latest Antibiotic Therapeutic Guidelines).**



*“The Beheading of St. John the Baptist”, (Detail) oil on canvas, 1608. Michelangelo Caravaggio signed his name in the blood of the Baptist.*

### References

1. eTG - November 2015.
  - Antibiotic Therapeutic Guidelines, 15th ed 2014.
2. Imipenem in Australian Medicines Handbook Website Accessed June 2015.
3. Imipenem in MIMs 1 March 2014.

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