

**CEFOXITIN**



*The “Chancellorsville Portrait” of Thomas J. “Stonewall” Jackson, made near Fredericksburg, Virginia. One of only two known portraits taken of him during the time of the Civil War.*

*The battle of Chancellorsville was Robert E. Lee's greatest victory, indeed it was one of the greatest military victories in the history of warfare. Vastly outnumbered, five to one, Lee utterly out maneuvered Joseph Hooker's massive Union army of the Potomac, and in a surprise attack routed it and sent it reeling back across the Potomac. The stunning victory was due in large part to Lee's most daring and enigmatic commander General T.J "Stonewall" Jackson, second only to Lee himself as the idol of the South. The only real hitch at Chancellorsville was that the attack was staged so late in the day that the Confederates were not able to exploit their surprise flanking attack to the degree that Jackson had wanted. In consequence, he decided to continue the attack into the night, a very rare event in the Civil War.*

*In an age without any modern communications, and in densely forested wilderness, confusion rapidly became the order of the day, or rather of the night! A full moon gave some little light, casting an eerie silver glow amidst the trees. Musket shots flashed out from all directions monetarily lighting the night - yet neither side were really sure who was firing on who, or who was enemy and who was foe. Hideous rebel yells echoed in the dark unnerving Federal soldiers. Union commander General Alpheus S. Williams later recollected, "Human language can give no idea of such as scene, such an infernal and yet sublime combination of sound and flames and smoke, and the dreadful yells of rage, of pain, of triumph, or of defiance"*

*Eager to see for himself what was going on Jackson had personally ridden out into no man's land with his skirmishers to scout. Alexander "Sandie" Pendleton, an officer on Jackson's staff, became seriously alarmed at the danger Jackson was exposing himself to, and remonstrated with him, "General don't you think this is the wrong place for you"? But Jackson had always been fearless, utterly indifferent to the possibility of his own death. "The danger is over!", he shouted, "the enemy is routed! Go back and tell A.P Hill to press right on!" Pendleton then departed on his mission, that may well have saved his life. Later on returning back towards Confederate lines, during a seeming lull in the fighting the crack of a lone musket shot rang out from some somewhere in the direction of Union lines. This triggered an explosive volley of fire in response from nervous Confederate pickets of the 7th and 18th North Carolina - Jackson and his party were caught directly in the line of the crossfire. Four of the party were killed instantly. Ten of the group of nineteen were casualties. Jackson himself was knocked from his horse with a wound to his right hand, and two wounds to his left arm. "Cease firing!" Lieutenant Joe Morrison, screamed out, "You are firing into your own men!" When the firing stopped, the survivors, rushed to Jackson's aid. It was immediately apparent that his wounds were serious. The General was gently placed onto a wagon, all the while his officers trying to conceal from the troops the identity of the wounded man. They evacuated him to Dowdall's Tavern and urgently called for Jackson's most trusted surgeon, Hunter Holmes McGuire.*

*"I hope you are not much hurt General", an alarmed McGuire exclaimed. "I am badly injured Doctor", Jackson replied. "I fear I am dying. I am glad you have come, I think the wound in my shoulder is still bleeding". McGuire later reported, "I found his clothes saturated with blood, and blood still oozing from the wound. I put my finger upon the artery above the wound and held it till lights were procured by candles....and then I readjusted the handkerchief which had been applied as a tourniquet, but which had slipped a little. Without this (having) been done, he would probably have died in ten minutes".*

*By this time Jackson was suffering fearfully, but McGuire administered morphine and whiskey which eased his agony. Momentarily saved from death, Jackson was still too close to the fighting*

*and there was a real risk he could be captured by Union soldiers. It was decided to evacuate the General to McGuire's Second Corps Field Hospital, four miles away, safe from the immediate area of battle. An ambulance wagon was passing with two wounded soldiers. On hearing who the new casualty was, one of them, Major Arthur L Rogers, who had a gunshot wound to his arm immediately gave up his place for Jackson. The identity of the occupant of the ambulance was closely guarded from curious bystanders who wondered why such a large troop of cavalry were in train with it. But as the wagon passed by, suspecting troops took off their caps and lowered their eyes in tearful silence amidst the din of the titanic battle that raged around them.*

*At the Second Corp Hospital, were waiting three of the Confederate Army's most respected and experienced surgeons, Black, J William Walls and Robert T. Coleman. In order to properly examine the full nature of Jackson's wound chloroform would have to be administered. It was left to Maguire, who was a close friend of Jackson to inform him of the probable need for amputation, if his life was to be saved. "If we find the condition to warrant amputation", McGuire quietly asked, "may we proceed at once". "Yes certainly Dr McGuire, Jackson managed to say, "Do for me whatever you think right". Coleman then fashioned a crude cone into the shape of a funnel, and through this administered a half ounce of chloroform. Jackson's senses began to decline, as he mumbled, "What an infinite blessing....blessing....blessing....". When he awoke, his left arm was gone. Hunter McGuire had needed to perform the necessary surgery.*

*By this time news had got out that General Stonewall Jackson had been seriously wounded. This roused Confederate troops to an ungoverned frenzy. Led by Jackson's own "Stonewall Brigade", they finally broke the Union lines amidst the thunderous banshee squalls of tens of thousands of rebel yells and screams of "remember Jackson". May 3 would be the second bloodiest day of the entire Civil War, ranking second only to Antietam, but unlike the indecisive result of that battle at Chancellorsville, victory for the Confederacy was total. Robert E. Lee's elation however was suddenly tempered with the news that his best commander had been very seriously wounded. He sent a courier to Jackson with a brief but emotional dispatch, "General I have just received your note informing me that you were wounded. I cannot express my regret at the occurrence. Could I have directed events, I should have chosen for the good of the country to have been disabled in your stead....I congratulate you upon the victory, which is due to your skill and energy". When the courier had finished reading the message, Jackson responded true to his deep religious convictions, "General Lee is very kind, but he should give the praise to God".*

*Lee made excuse not to rush to Jackson's side as he could not leave his troops at such a critical moment - but in truth he was so overcome with grief that he did not trust that he could control his emotions in front of the attending troops if he did so. Later on after Jackson had been transferred to the Chandler house, Lee would send his famous message to Jackson, via Chaplain Lacy, "Give General Jackson my affectionate regards, and say to him he lost his left arm, but I my right arm. Tell him to get well and come back to me as soon as he can".*

*In the days following the operation, Jackson seemed to be recovering well, until one night he awoke feverish and complaining of pain in his side. Hunter McGuire was called. Initially he assumed that Jackson had an injury that had resulted from a fall when his stretcher bearers had stumbled in the dark, yet he could find no real clear evidence of a traumatic cause for this new symptom. "I could not discover by examination any evidence of injury", he wrote, "The skin was not bruised or broken, and the lung performed, as far as I could tell, its proper function. I recommended some simple application & rub, telling him it would probably pass off soon". The*

*pain did seem to settle with the treatment but on May 7, at around 1.00 am Jackson again complained of pain, this time intense in his left side and accompanied by nausea and a high fever. He called for McGuire, who rushed into his room to find Jackson's bed sheets soaked through with perspiration, and Jackson himself panting for breath. Following further discussions within the ever increasing team of medical specialists a diagnosis of pneumonia was finally made. In a pre-antibiotic age this was a fearful diagnosis. Over the ensuing three days Jackson's breathing became increasingly laboured and he became delirious, barking out orders to his divisional commanders. By the 10th of May McGuire knew that Jackson was not going to survive. Anna his wife was called for and given the news. She approached her husband with tears in her eyes. Jackson weakly said, "Anna, none of that, none of that" . Anna felt she had to tell her husband that the doctors now believed he would die, and so she told him, then buried her head in the blankets to hide her sobbing. He said "Oh no my child. It's not that serious", and then finally she said, "You'll be with the Lord this day" He called for surgeon McGuire who had been standing outside in the anteroom. He said "Anna informs me that you have told her I am to die today. Is it so?' McGuire replied as gently as he could that there was nothing more he or any of the other surgeons could do. He turned his face away and replied, "Good. Very Good... It's alright...I always wanted to die on a Sunday".*

*McGuire offered him brandy and morphine but he said, "No. I want to keep my mind as clear as I can till the last". But his mind began to wander. He was calling on A.P Hill, "Prepare for action!". And then all of a sudden, he went very quiet and in a clear distant voice, spoke his last words.. "Let us cross over the river and rest under the shade of the trees". Jackson had come home to his long ago childhood. As a child he was a loner and after backbreaking days of work at the Mill in the boiling sun, he would swim across the river and sit by himself under the shade of some trees.*

*The death of Stonewall Jackson rocked the entire Confederacy. The scenes of unbridled joy in Richmond upon hearing of the great victory at Chancellorsville, were suddenly replaced by a unbelieving and shocked silence. Confederate flags flew at half mast. All eyes now turned to Robert E. Lee. Lee turned his eyes to the North. The time would be now or never to strike into the very heartland of the Union and win the war. Could Jackson have taken Little Round Top at Gettysburg? History up until and, especially including, the time of Chancellorsville would suggest that he very well could have. Jackson was victorious in every battle he ever fought bar two, and one of those was a relatively minor battle fought at Kernstown, the other Antietam was indecisive. Robert E. Lee spoke no truer words, when he said, to Stonewall Jackson, "You have lost your left arm, but I have lost my right".*

*Traditionally it was thought by many that Stonewall Jackson died from wounds he received from "friendly" fire at the Battle of Chancellorsville. Though his wounds were very serious, examinations of contemporary sources, suggest that he more likely died of pneumonia. This could have possibly been brought on by his weakened state and brutal surgery, however there are reports that in the early hours of the morning of May 2, a Colonel on Lee's staff, A.L Long was serving cups of coffee to Jackson as he was shivering wildly. Could in fact this "shivering" have been rigors, in which case the pneumonia that would eventually kill him had already taken hold, well before he suffered his battle wounds. In any case it is an arresting thought that a simple and cheap Twentieth century beta-lactam antibiotic such as cefoxitin could have saved the life of one of histories' greatest generals and altered the course of history.*

# CEFOXITIN

## Introduction

**Cefoxitin** is a second generation semisynthetic cephalosporin beta lactam antibiotic, for **IV use**.

The cephalosporins are moderate to extended range antibiotics.

**They have variable resistance to bacterial beta-lactamases.**

The widespread use of cephalosporins across the world has been linked with the increasing prevalence of infections caused by multiresistant organisms including: <sup>1</sup>

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant enterococci (VRE)
- Other multiresistant Gram-negative organisms
- Clostridium difficile.

**Cefoxitin** is a moderate spectrum second generation cephalosporin that also has **anti-anaerobic activity**.

## 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.

## Chemistry

Cefoxitin is a semisynthetic cephalosporin 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

## Classification

The cephalosporins can be classified into 5 principle groups or “generations”: <sup>1</sup>

### 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**

### 3. **Third Generation**

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

Broad-spectrum cephalosporins:

- Ceftriaxone
- Cefotaxime

### 4. **Fourth Generation**

Good gram positive cover and good gram negative cover

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

- Cefepime
- Ceftazidime

## 5. **Fifth Generation**

Newer very broad spectrum agents.

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

- Ceftaroline
- Ceftolozane (& Tazobactam)

### Preparations

Cefoxitin as:

Ampoules:

- 1 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.

**The cephalosporins have variable resistance to bacterial beta-lactamases.** <sup>1</sup>

Some organisms (e.g. *Serratia*, *Citrobacter* and *Enterobacter* species) have chromosomal resistance in the form of **cephalosporinase** enzymes, and resistance can develop during treatment. <sup>1</sup>

### Pharmacodynamics

Cefoxitin is a moderate-spectrum cephalosporin with **anti-anaerobic** activity:

Cefoxitin is not active against *Pseudomonas* species, most strains of enterococci and many strains of *Enterobacter cloacae*. <sup>3</sup>

Methicillin resistant staphylococci are almost uniformly resistant to cefoxitin. <sup>3</sup>

### Pharmacokinetics

Absorption:

- Cefoxitin is given **IV**.

It can be given IM but this is painful, and IV is the preferred route of administration.

### Distribution

- Although cefoxitin will penetrate into the cerebrospinal fluid, concentrations are considerably lower than in the plasma.
- Cefoxitin crosses the human placenta
- Cefoxitin is excreted in human breast milk in small amounts.

### Metabolism and excretion:

- Cefoxitin is excreted virtually unchanged by the kidneys

### Indications

Indications include: <sup>2</sup>

Infections due to susceptible / likely susceptible bacterial organisms as:

1. An Alternative to other antibacterial combinations for surgical prophylaxis for some GI procedures
2. An alternative to other antibacterial combinations for mixed anaerobic infections, e.g. peritonitis

**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 cefoxitin.
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.

### Pregnancy

Cefoxitin is a category B1 drug with regard 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 cefoxitin has not been associated with an increased risk of birth defects or adverse pregnancy outcomes.

Cefoxitin is safe to use during pregnancy.

### Breast feeding

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

Cefoxitin 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.

### 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. 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. Rapid IV administration of large doses may result in seizures, especially when inappropriately high doses are used in renal impairment. <sup>2</sup>

### 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: <sup>2</sup>

#### Adult:

- Cefoxitin IV 1 - 2 grams every 8 hours. Maximum 12 grams daily.
- For severe infections:** IV 2–3 grams every 6 - 8 hours; or 2 grams every 4 hours.

#### Child:

- Cefoxitin IV 20 - 40 mg/kg (maximum 2 grams) every 6 - 8 hours.
- For severe infections:** IV 40 mg/kg every 6 hours.

Up to 200 mg/kg (maximum 12 grams) daily has been used.

### Surgical prophylaxis <sup>2</sup>

#### Adult:

- IV 2 grams to be completed before skin incision.

#### Child:

- IV 30 - 40 mg/kg (maximum 2 grams) to be completed before skin incision.

## References

1. eTG Complete - July 2018.
2. Cefoxitin in Australian Medicines Handbook, Accessed August 2018.
3. Cefoxitin in MIMs 1 September 2013.
4. Cefoxitin in RWH Pregnancy & Breast feeding guidelines, 17 January 2017

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Reviewed August 2018.