

LINCOMYCIN



Incredibly rare image of Confederate Troops on the march. Soldiers of the Army of Northern Virginia, passing through the Union Township of Frederick, Maryland during Robert E. Lee's first invasion of the North, September 1862.

".....The body of men moving along with no order, their guns carried in every fashion, no two dressed alike, their officers hardly distinguishable from the privates....They were profane beyond belief and talked incessantly...Many of them were from the far South and spoke in a dialect I could scarcely understand... They rode like circus riders ...were these the men that had driven back again and again our splendid legions?... They were the dirtiest men I ever saw, a most ragged, lean and hungry set of wolves....Yet, there was a dash about them that the Northern men lacked...."

(Unionist woman, eye witness to the advance of Lee's Army through Frederick, Maryland, September 1862).

With Europe poised to recognize the Confederacy, the unthinkable looked increasingly likely - the Union was going to lose the war.

"We must change our tactics or lose the game" Abraham Lincoln wrote in 1862. To Lincoln it was clear now that it was no longer possible to restore the old Union. A new one had to be embraced. By summer he knew what tactic was needed to win the war - emancipation - but doubted whether he would ever have the political or military opportunity to use it.

"I find it hard to maintain my lively faith in the triumph of the nation and the law", New York lawyer George Templeton Strong, confided to his diary. These are the darkest days we have seen since Bull Run" What no one knew was that the year would soon see the bloodiest day of the war, and then the brightest

"It could have been a very ugly, filthy war with no redeeming characteristics at all. And it was the battle for emancipation, and the people who pushed it forward - the slaves - the free black people - the abolitionists - and a lot of ordinary citizens - it was they who ennobled what otherwise would have been meaningless carnage into something higher. (Barbara Fields Civil War Historian).....

"There is no doubt that Jefferson Davis and other leaders of the South have made an army. They are making, it appears, a navy, and they have made what is more than either. They have made a nation. We may anticipate with certainty the success of the Southern states" (William E. Gladstone)

Confederate gospel held that Britain and France could not survive without Southern cotton. Before long one, or both, would surely intervene on behalf of the Confederacy to end the Union blockade. To put more pressure on Europe, the Confederates cut cotton production by 90 %. 2.5 million bales were burned or left to rot on Confederate wharves to keep it out of English hands. Now in addition to directing a war at home, Lincoln had to find a way to keep Europe from coming in on the side of the South. And increasingly, in the North, there was pressure for emancipation, and it came from unlikely people in unlikely places.....

"The slavery question perplexes the President almost as much as ever, and yet I think he is about to emerge from the obscurities where he has been groping into somewhat clearer light. So you see, the man moves" (Salmon P Chase)

"July 4, 1862. I would do it if I were not afraid that half the officers would fling down their arms and three more states would rise". (Abraham Lincoln)....

"My paramount object in this struggle is to save the Union and is not either to save or to destroy slavery. If I could save the Union without freeing any slave, I would do it. If I could save it by freeing all the slaves, I would do it and if I could save it by freeing only some, and leaving others alone I would also do that" (Abraham Lincoln, August 22, 1862)

“It seems to me the time is fast approaching when some joint offer of mediation by England, France and Russia might be made with some prospect of success to the combatants in North America. The proposal would naturally be made to both North and South. If both accepted, we should recommend an armistice and cessation of blockades, with a view to negotiation on the basis of separation”
(Prime Minister, Lord Palmerston).

Lincoln had to have a victory.

“September 3; 1862. The present seems to be the most propitious time since the commencement of the war for the Confederate army to enter Maryland”.
(Robert E. Lee)

The brilliant Southern victories of spring and summer had brought Lee’s army international renown. One more successful campaign, he wrote Jefferson Davis, would force Europe to recognize the Confederacy. Now for the first time, Lee led 40,000 soldiers across the Potomac and onto Union soil...On the morning of July 22, 1862, the President called a cabinet meeting. What he said took everyone by surprise. After long thought, he told them, he had decided to emancipate the slaves.

“It was a stunning moment. It was against everything Lincoln had promised the Republicans and indeed the country, that he would not become an abolitionist, he would not strike at slavery where it existed. Here, suddenly. He was changing the character of the war.

(William Safire, Journalist).

But secretary of state Seward worried that until the army had won a real victory, emancipation would seem like the last shriek on retreat.

Lincoln agreed to wait for a victory. It’s hard to separate one issue from another. Obviously, Lincoln had to win the war. He had to keep his respectability as President of a country that would not allow itself to be defeated by a group of rebels. That was always an issue, especially in 1862. He could not let himself be made a fool and the Union be made a fool by standing up for principles that could not be vindicated on the battlefield.

....

(Barbara Fields, Civil War Historian).....

Lincoln as a result of Antietam, converted the war to a higher plane, again the master politician. He announces a preliminary emancipation proclamation. Of course it doesn’t free a single slave in revolt, frees only as a war measure and only frees slaves in states where the Confederacy is in control, and it will take effect on the first day of January
(Ed Bearss, Civil War Historian).

“On the first day of January, in the year of our Lord 1863, all persons held as slaves within any state or designated part of a state, the people whereof shall then be in rebellion against the United States, shall be then, thenceforth, and forever free”
(Abraham Lincoln).

On September 22nd, just five days after the battle of Antietam, the President issued his emancipation proclamation. "If my name ever goes into history", Lincoln said, "it will be for this act".

The South was outraged. Jefferson Davis called it the "most execrable measure recorded in the history of guilty man". At a Washington dinner John Hay, the President's 23 year old secretary noted, that "Everyone seemed to feel a new sort of exhilarating life. The President's proclamation freed them as well as the slaves. It was no longer a question of the Union as it was, that was to be reestablished. It was the Union as it should be - that is to say washed clean from its original sin. We were no longer merely the soldiers of a political controversy. We were now the missionaries of a great work of redemption, the armed liberators of millions. The war was ennobled. The object was higher". Abroad the proclamation had the effect Lincoln had hoped for. Neither England nor France was willing openly to oppose a United States pledged to end slavery.

"The triumph of the Confederacy would be a victory of the powers of evil, which would give courage to the enemies of progress and damp the spirits of friends all over the civilized world. The American Civil War is destined to be a turning point, for good or evil, of the course of human affairs"
(John Stuart Mill)

"Put not your trust in princes, and rest not your hopes on foreign nations. This war is ours. We must fight it out ourselves".
(Jefferson Davis)

That December Lincoln spoke to Congress. "The dogmas of the quiet past are inadequate to the stormy present. As our case is new, so we must think anew, and act anew. We must disenthrall ourselves, and then we shall save our country. Fellow citizens, we cannot escape history. The fiery trial through which we pass will light us down, in honor of dishonor, to the latest generation. We say we are for Union. The world will not forget that we say this. In giving freedom to the slave, we assure freedom to the free - honorable alike in what we give and what we preserve. We shall nobly save or meanly lose the last best hope of Earth.

"December 31. Well the year 1862 is drawing to a close, and as I look back, I am bewildered when I think of the hundreds of miles I have tramped, the thousands of dead and wounded that I have seen. But we hope for the best and feel sure that the Union will be restored. Goodbye 1862.
(Elisha Hunt Rhodes).

'We shout for joy that we live to record this righteous decree - free forever! Oh, ye millions of free and loyal men who have earnestly sought to free your bleeding country from the dreadful ravages of revolution and anarchy, lift up now your voice in joy and thanksgiving. With freedom to the slave will come peace and safety to your country"
(Frederick Douglas)

On December 31st a large crowd of abolitionists including Harriet Tubman and Wendell Phillips, gathered together at the music hall in Boston.

At midnight the emancipation proclamation would take effect. On the stage, William Lloyd Garrison wept with joy beside Frederick Douglass. The cheering crowd called for Harriet Beecher Stowe. She stood in the balcony, tears in her eyes. At a Washington D.C. contraband camp former slaves testified. One remembered the sale of his daughter. "Now no more of that", he said, "They can't sell my wife and children anymore. Bless the Lord"

On the sea islands off South Carolina, Federal agents read the proclamation aloud to former slaves under the spreading boughs of a huge oak tree. As the commander of a new all-black regiment unfurled an American flag, his men broke into song. "It seemed the choked voice of a race at last unloosed" he wrote.

*David McCullough, Barbara Fields and Shelby Foote
in Ken Burns', "The Civil War", 1990.*

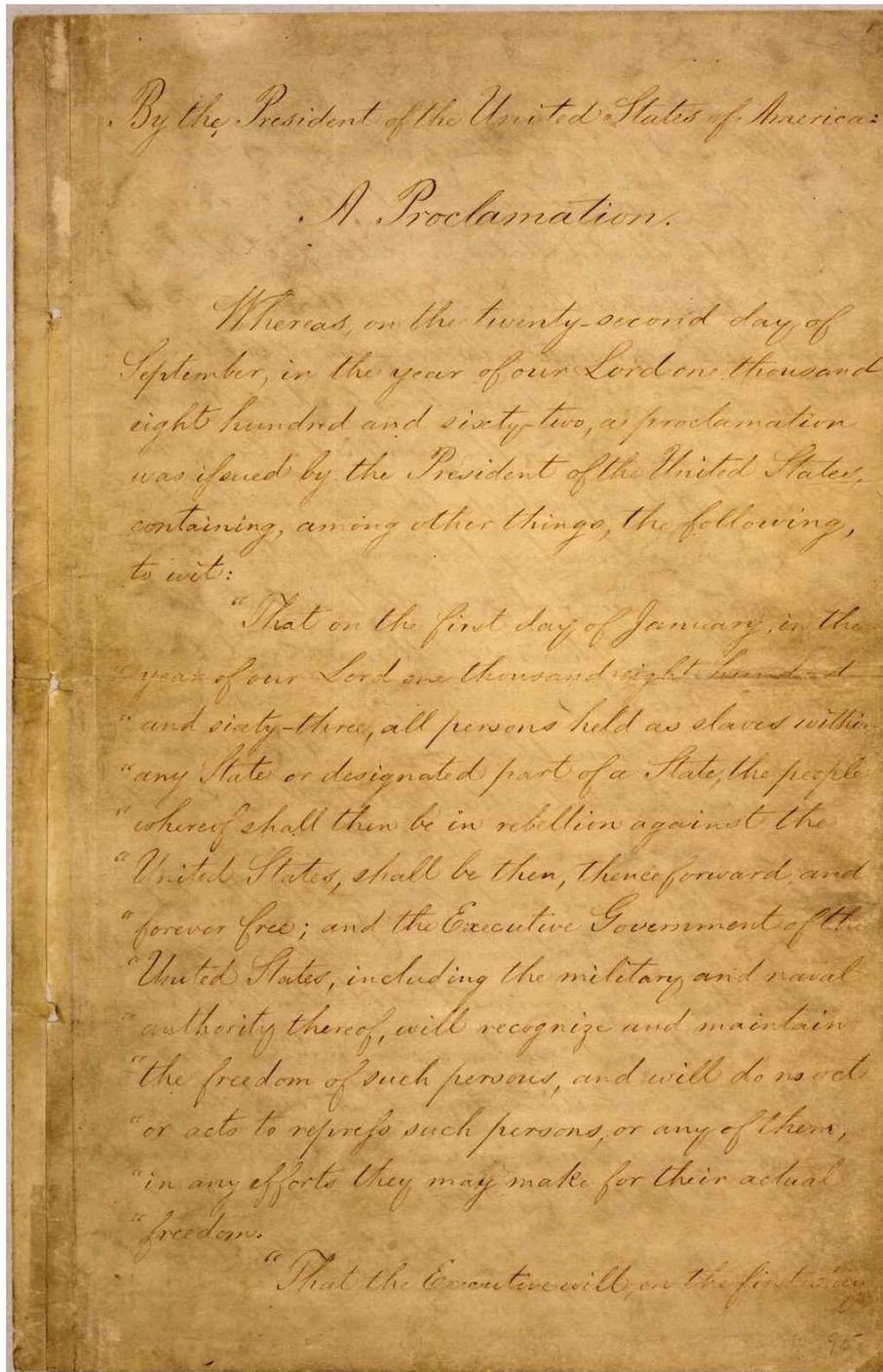
On the morning of July 22, 1862, Abraham Lincoln called an urgent cabinet meeting. Despite having been elected on a platform of allowing slavery in states where it already existed, he announced to a stunned room that now he believed the time had come for the emancipation of all slaves. The war had been going badly. Robert E. Lee had defeated the biggest army the Union could muster at the Battle of the Seven Days. Another setback like that could see European recognition of the Confederacy, or even worse - active intervention on the side of the South. Lincoln believed that by announcing emancipation, it would put the north in the moral right in the war, hitherto, the conflict had been simply about Union versus State's rights. The aim of the war had to change, Lincoln told his cabinet - no power in Europe would dare openly support the South, if Lincoln declared for emancipation. The North was divided on the issue, and Lincoln knew he had to tread extremely carefully. "I would do it", he said "if I were not afraid that half the officers would fling down their arms and three more states would rise". Then came the shocking news of General Pope's crushing defeat at the Battle of Second Bull Run. If the news of that were not shocking enough, reports then came in that Robert E. Lee had crossed the Potomac. The North was on its knees. Announcing emancipation at this time would now amount to political suicide. Lincoln had to have a victory. Then it came...of sorts. In the bloodiest battle of the war to date, Lee had been stopped at Antietam. Though McClellan had claimed the battle a "great victory", Lee had managed to escape with most of his army. McClellan, shaken by the ferocity and the scale of the battle however had lost his nerve and refused to pursue Lee back across the Potomac. "I am tired of the sickening sight of the battlefield, with its mangled corpses and poor suffering wounded", he declared, "Victory has no charms for me when purchased at such cost".

Lincoln was furious, though McClellan could claim a tactical victory, he could have won the war. Antietam nonetheless, was victory enough, to give Lincoln the political mantle he needed, as "savior" of the Union. On September 22nd, just five days after the battle of Antietam, he issued his emancipation proclamation:

"On the first day of January, in the year of our Lord 1863, all persons held as slaves within any state or designated part of a state, the people whereof shall then be in rebellion against the United States, shall be then, thenceforth, and forever free"

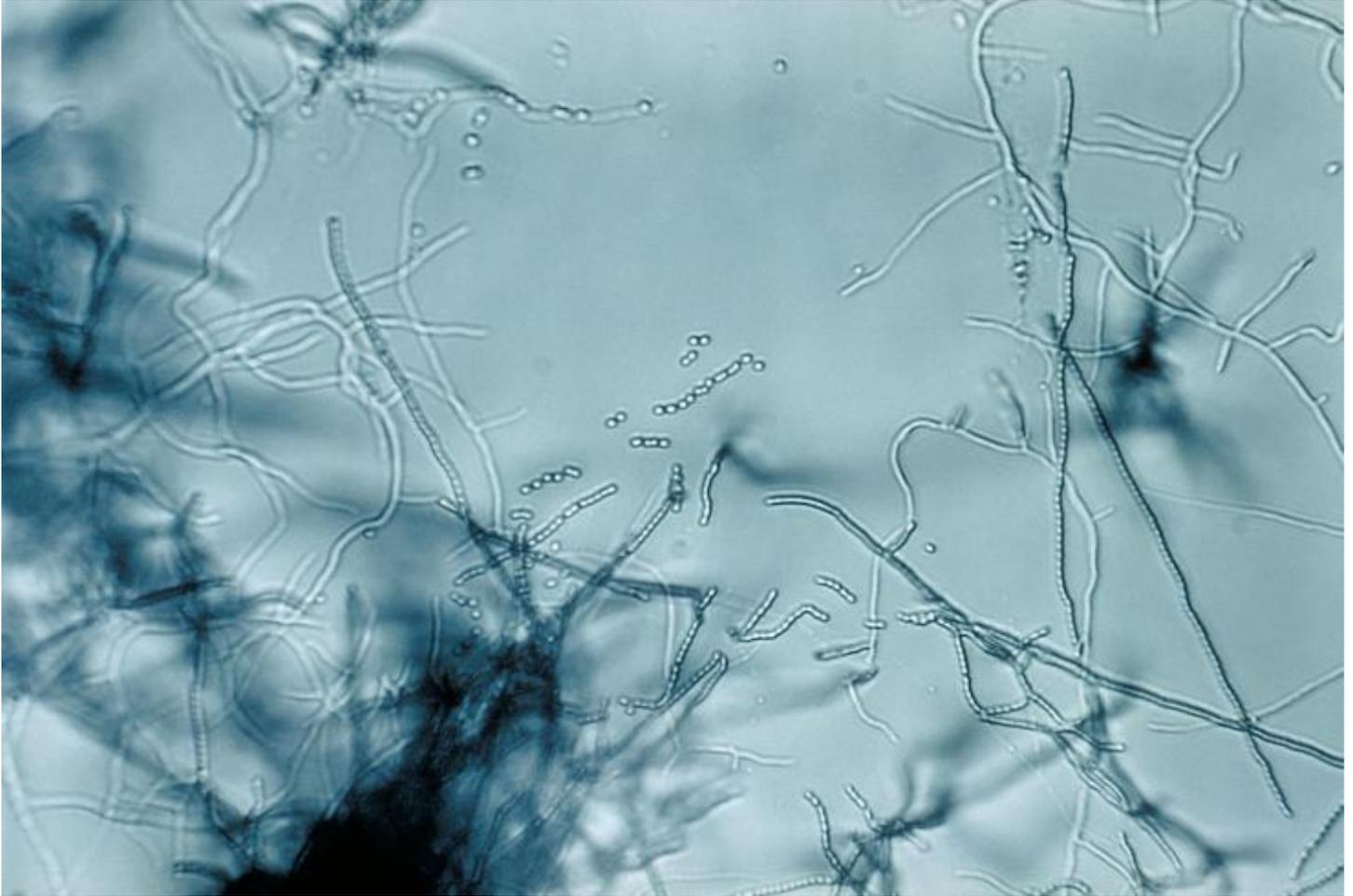
"If my name ever goes into history", Lincoln said, "it will be for this act".

In our fight against the microbial pathogenic world, by the agency of acquired resistance, we may, suffer terrible defeats. At these times it will be necessary to change our tactics, and try a different approach. The antibiotic lincomycin gives us such an opportunity. Though not a primary strategy for most infections, when the battle goes against us in the form of bacterial resistance or beta lactam allergy, lincomycin gives us an alternative weapon. Indeed lincomycin was named for the town of Lincoln, which in turn was named for President Abraham Lincoln - the greatest President in American history, and one who had a particular genius for the pragmatic!



Emancipation Proclamation, Abraham Lincoln, 22nd September 1862,
United States Department of State.

LINCOMYCIN



A slide culture of a Streptomyces species

“...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 scrapwhile we learn to use it and come to understand what it means to humanity”.

Edward O Wilson.

Introduction

Lincomycin is a **lincosamide** antibiotic that comes from the actinomycetes bacteria *Streptomyces lincolnensis*.

Lincomycin (and clindamycin) and are active against Gram-positive aerobes and most anaerobes.

They are used as second-line therapy in those intolerant to conventional therapy or where resistance is of concern.

Lincomycin is less potent than clindamycin, but will have equipotent effects if used in higher doses (and is considerably cheaper than clindamycin).

History

Lincomycin, was the first **lincosamide antibiotic** to be developed.

It was isolated from *Streptomyces lincolnensis* in soil samples from **Lincoln, Nebraska** (hence the name).

Clindamycin, was then developed which exhibits greater antibacterial activity.

Streptomyces is the type genus of the family Streptomycetaceae. This genus has over 550 known species with more being discovered each year.

It is a critically important microorganism to medical science as it is the largest known antibiotic producing genus of bacteria, producing antibacterial, antifungal, antiparasitic and immunosuppressant substances, from which multiple lifesaving antimicrobial drugs have been developed

Chemistry

Lincomycin hydrochloride is the monohydrated salt of lincomycin, a substance produced by the organism *Streptomyces lincolnensis*

Clindamycin is derived from lincomycin

Clindamycin and lincomycin are often discussed along with the macrolides, but they are **not** chemically related to the macrolides.

Classification

The lincosamide antibiotics include:

1. **Lincomycin**
2. **Clindamycin**

Clindamycin is generally preferred to lincomycin as it is generally *more potent*; (however, lincomycin is less expensive).

Preparation

Lincomycin hydrochloride as:

Ampoules:

- 300 mg/mL, 2 mL

Mechanism of Action

Lincosamide is a **bacteriostatic** antibiotic which inhibits bacterial protein synthesis by binding to the bacterial **50s** ribosomal subunit.

Lincosamides do not interfere with protein synthesis in human cells (or those of other eukaryotes) because human ribosomes are structurally different from bacterial ribosomes.

The macrolides such as erythromycin, clarithromycin, and azithromycin also act at the bacterial 50s ribosomal subunit and may compete for binding at this site.

Pharmacodynamics

Lincomycin (and clindamycin) are active against:

1. Gram-positive aerobes (including MRSA)
2. Most anaerobes.

It is *not* active against gram negative organisms.

Lincomycin is less potent than clindamycin.

Pharmacokinetics

Absorption:

- Lincomycin can be given **orally** or **intravenously**.

It is rapidly absorbed after an oral dose.

Distribution:

- Protein binding is variable at around 30 to 85%
- Lincomycin distributes well to most body tissues, apart from the CSF
- Lincomycin can cross the human placenta
- Lincomycin is excreted into human breast milk.

Metabolism and excretion:

- The metabolism of lincomycin is not well characterized, but it is both metabolized in the liver and excreted unchanged in the urine.

Indications

Lincomycin (as well as clindamycin) are used as second line therapy in patients who are intolerant of first line therapy to conventional therapy or where resistance is of concern.

It may be used as an alternative in patients with severe allergy to penicillins and cephalosporins including: ²

1. Skin, soft tissue infections
2. Bone infections
3. Dental infections
4. Anaerobic infections
5. Endocarditis prophylaxis

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. Known hypersensitivity to lincomycin or clindamycin.
2. Cross resistance: ²
 - There is complete cross-resistance between clindamycin and lincomycin
 - Cross-resistance often exists between lincosamides and macrolides for staphylococci and streptococci
3. Severe renal failure:
 - Reduce dose
4. Severe hepatic failure:
 - Reduce dose

Pregnancy

Lincomycin is a class A drug with respect to pregnancy

Class A drug 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

Maternal use of lincomycin has not been associated with an increased risk of birth defects or adverse pregnancy outcomes. Lincomycin is safe to use during pregnancy.

Breast feeding:

Small amounts of lincomycin are excreted into breast milk, but these amounts are unlikely to cause harmful effects in the breastfed infant.

Lincomycin is safe to use during breastfeeding, but observe the breastfed infant for potential adverse effects such as diarrhoea, vomiting, skin rash or thrush.

Adverse Effects

These include:

1. GIT upset:

- Nausea, vomiting, **diarrhea.**
- **Clostridium difficile** associated disease
 - ♥ Symptoms may occur up to several weeks after cessation of antibiotic therapy.
 - ♥ **Because *clindamycin* therapy has been associated with severe colitis which may be lethal, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate.**

2. Dermatological:

Can range from non-specific rashes to life threatening conditions.

- Erythema multiforme
- DRESS
- Toxic epidermal necrolysis.
- Contact dermatitis (with topical use)

3. Allergic reactions:

- Including serious anaphylactic reactions.

Dosing

The recommended dosing of lincomycin for adults is:

- **600 mg IV, 8 hourly.**

Dilute 600 mg in at least 100 mL of glucose 5%, glucose/sodium chloride or sodium chloride 0.9% and infuse slowly over at least **1 hour** to reduce the risk of hypotension.

Note that clindamycin is more potent than lincomycin and so some clinicians use higher than the recommended doses of IV lincomycin for **serious** infections; at these doses, lincomycin has *equal efficacy to clindamycin* (and is considerably cheaper).²

References

1. eTG - March 2017.
2. Lincomycin in Australian Medicines Handbook, Website Accessed June 2015.
3. Lincomycin in MIMs 1 May 2014.
4. Lincomycin in RWH Pregnancy & Breast feeding Guidelines, 17 January 2017.

Dr J.Hayes
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