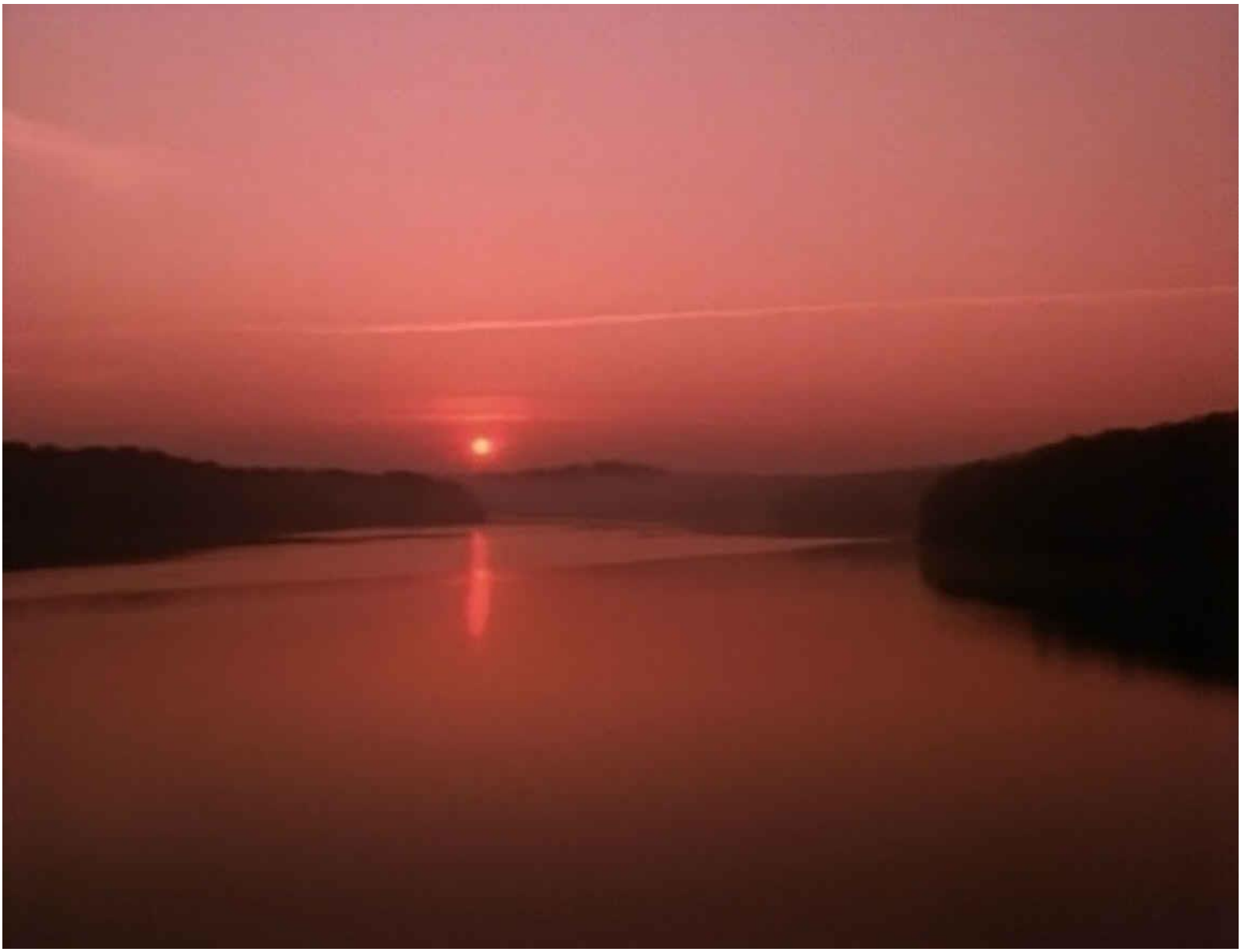
THE NORTHERN HOSPITAL

TEICOPLANIN



The Rebel Yell rent the night from a thousand campfires - (Still from Ken Burns', "The Civil War", 1990)

They both had a particular way of yelling. The Northern troops made a sort of hurrah. It was called by one soldier, "The deep generous manly shout" of the Northern soldier.

The Confederates of course, had what was called the Rebel Yell.

We don't really know what that sounded like. One Northerner described it….he said…he described it by describing the peculiar corkscrew sensation that goes up your backbone when you hear it, and he said "And if you claim you've heard it and weren't scared, that means you never heard it!"

It was…it was…basically I think, a sort of fox hunt yip, mixed up with a sort of banshee squall. And it was used on the attack.

And an old Confederate veteran after the war was asked at a UDC meeting in Tennessee somewhere to give the Rebel Yell. The ladies had never heard it. And he said, "It can't be done, except at a run, and I couldn't do it anyhow with a mouth full of false teeth and a stomach full of food"…. So they never got to hear what it sounded like.

Shelby Foote in Ken Burns' "The Civil War", 1990

Antietam had been the bloodiest battle in American history until that time. Though the Confederates had been stopped in their invasion of the North, they had not been destroyed, the whole encounter ending in a stalemate. Robert E. Lee had reformed his lines waiting for the expected final assault. It never came. George B. McClellan, appalled at the scale and ferocity of the battle had hesitated. Lee saw his chance. Realizing he could not sustain the attrition in the way that the Northern army could, he withdrew from Maryland, back across the Potamic into Virginia. A half hearted chase across the river by units of McClellan's army was bloodily repulsed by Stonewall Jackson. This gave Lee time to withdraw more deeply into Virginia, where he would rebuild his battered army in anticipation of the next Union invasion of the South. Still McClellan hesitated unwilling to take Lee on, on his home soil. Stonewall Jackson, always eager to go onto the offensive, finally agreed with Lee that on this occasion discretion would be the better part of valour. He withdrew his corps back into his beloved Shenandoah Valley.

There Jackson realized his 25,000 men were in no shape for another campaign, and that Lee had been right in withdrawing from Maryland. An officer in Brigadier-General Maxcy Gregg's brigade commented, "It is difficult to describe the condition of the troops at this time. They were sun-burnt, gaunt, ragged scarcely at all shod, spectres and caricatures of their former selves. The brigade as a whole was an emaciated, limping ragged, filthy mass, whom no stranger to their valiant exploits could have believed capable of anything the least worthy".

But Jackson while recuperating in the Valley at least did so knowing that he had the undying love of his troops. A Georgian sergeant in one of Longstreet's regiments noted, "One day while near Winchester, I heard cheering down the road in front. Some of the boys thought it was Stonewall Jackson, or a rabbit....Everyone made for the road, and sure enough it was General Jackson, galloping along the road with his escort. He passed us with his cap off (in acknowledgement) and the cheering continued on down the line as far as we could hear. The boys claim that he is getting tired of the army because Longstreet's men keep him bareheaded so much....He certainly creates more excitement than all of the rest of the officers put together". "If Jesus Christ were to ride along the ranks on the foal of an ass", one Alabama private in Rode's division said, "there would not be half the cheering and huzzaing than there is when General Jupiter Stonewall

Jackson rides along our ranks! The soldiers cheer him as if they think him to possess some supernatural power, and indeed I expect he is a great man. There is one thing about it, he seems to be a great deal keener to get into a fight than I am!"

Despite the personal adulation however Jackson fretted about the state of morale in his army in the months following the horrific attrition at Antietam. Though he rarely showed emotion of any sort to his troops his affection for them matched their own for him.

On one stifling night in his tent, unable to sleep, he could hear an occasional rebel yell, being given off in the distance by one particular sector of the encampment. The yell, caught on, one unit picking it up after the other. Jackson got out of bed and strolled over to a nearby fence, resting his elbows on it trying to discern the direction the yelling was coming from, listening intently. As he listened the Rebel Yell grew and rose like a great tsunami, culminating in a deafening crescendo echoing out into the night and across the valley.

After it had run its course, Jackson turned back towards his tent, no longer concerned about the morale of his men. "That was the sweetest music I ever heard", he exclaimed, a sentiment, despite hearing the Rebel Yell a hundred times, he would repeat but once in his life.....at Chancellorsville.

Old Union veterans of the American Civil War all agreed that one of the most chilling recurring nightmares they retained of that conflict was the massed Rebel Yell. There was of course no electronic recording technology during the time of the Civil War, and so we really have no inkling today of what it sounded like, apart from a few seconds of scratchy old footage of several feeble octogenarians attempting it in the 1930s. But this of course gives no sense of the reality of what it must have been like - the massed chorus of tens of thousands of young soldiers in the full vigour of youth, in tandem with the deafening roar of cannon and musket fire. The magisterial Civil War historian, Shelby Foote, considered the closest we can understand it, was that it was a kind of hybrid "fox-hunt yip and banshee squall"

The Rebel Yell was usually given on the attack, but it could also be given on sudden ambush, as at Chancellorsville, were it would have its most terrifying effect. "And if you claim you've heard it and weren't scared", an old Union veteran once, explained, "that means you never heard it!"

Our battle against the gram positive microbial pathogenic world seems, like Antietam, a horrible attrition on both sides. No matter how much we attack with our latest weaponry, resistance is always lurking, and so we never quite gain final victory. One of our last defences remains teicoplanin this agent being effective even against vancomycin resistant organisms. Yet even then these rebel organisms are not broken, but remain defiant - just when we least expect it they give their rebel yell of defiance that spreads quickly from one organism to another, till building to a crescendo we are ambushed once again - now in the form of VanA-strains. And so the battle continues.....

TEICOPLANIN

Introduction

Teicoplanin, (trade name in Australia, "**Targocid**") like vancomycin is a **glycopeptide** antibiotic.

Like vancomycin, **teicoplanin** is a narrow - range bactericidal agent against many **gram positive** organisms.

It is effective against MRSA but its main use is for patients with proven or suspected infections caused by **VanB-strains of VRE** (**Vancomycin Resistant Enterococci**).

Teicoplanin is usually inactive against VanA-strains.

Teicoplanin is *not* effective against gram negative organisms.

Teicoplanin has a longer half-life than vancomycin, and so can be given **once daily**.

It can also be given by IM or IV injection (vancomycin is given by IV infusion but not IM).

It is indicated for potentially life threatening infections which cannot be treated with another effective, less toxic antimicrobial drug.

Compared with vancomycin, teicoplanin:

- **Has much less toxicity**
- **Less requirement for monitoring blood levels**

History

Vancomycin was first isolated in 1953.

It was first used clinically in 1955.

It was approved by the FDA in 1958 to treat penicillin resistant staphylococci. (MRSA was first seen in 1961).

Teicoplanin was first described in 1978 but was not introduced into clinical practice until 1988.

Chemistry

Teicoplanin is a glycopeptide antibiotic produced by *Actinoplanes teichomyceticus*

Classification

The **glycopeptide antibiotics** are a class of antibiotics of microbial origin that are composed of glycosylated cyclic or polycyclic nonribosomal peptides.

The glycopeptide antibiotics include:

1. **Vancomycin**

2. **Teicoplanin**

Preparation

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Teicoplanin as:

Ampoules:

- 400 mg (as powder for reconstitution).

Mechanism of Action

Teicoplanin is **bactericidal.**

It inhibits bacterial cell wall synthesis by preventing formation of peptidoglycan polymers.

This effect occurs at a site that is **different from that affected by penicillins** (and so is teicoplanin *not* classed as a "beta - lactam" drug).

Pharmacodynamics

Teicoplanin is a glycopeptide antibiotic with similarities to vancomycin.

The drug acts by inhibiting cell wall synthesis in dividing organisms. As this mechanism is different to the action of beta-lactam antibiotics, teicoplanin has no cross resistance with these drugs.

Only Gram positive organisms are susceptible

Teicoplanin may be as effective as vancomycin for most indications.

Some vancomycin-resistant enterococci are susceptible to teicoplanin.

It is effective against **VanB-strains of VRE** (**Vancomycin Resistant Enterococci**). It is usually **inactive** against VanA-strains.

Like vancomycin, there is evidence for a **significant post-antibiotic effect** for glycopeptides against a range of Gram-positive organisms.[5]

All Gram negative organisms are resistant.

Pharmacokinetics

Absorption:

- Teicoplanin is given IV by **slow injection over 5 minutes** or **infused over 30 minutes**.

  It can be given IM (maximum dose at one site, 400 mg), hover the IV route is preferred.

- Peak levels are reached at the end of infusion (IV); and 3 to 4 hours following IM administration

Distribution:

- The apparent volume of distribution at steady state is similar to total body water, i.e. 0.6 L/kg.
- Protein binding is high at 90 - 95 %
- Teicoplanin can cross the human placenta
- It is unknown if teicoplanin is excreted into human breast milk.

Metabolism and excretion:

- Teicoplanin undergoes very little metabolism. Most of the administered drug is excreted unchanged in the urine.
- Elimination half - life is long at 70 - 100 hours

Indications

Teicoplanin is indicated for severe / life -threatening infections caused by susceptible organisms including:

1. **MRSA**
2. **MRSE**
3. **VRE (Van B phenotypes)**
4. Clostridium difficile-associated disease (relapse or unresponsive to metronidazole treatment)

5. Antibacterial prophylaxis:

   - For **endocarditis** before certain procedures in penicillin-hypersensitive people at high risk.

   - For major surgical procedures involving implantation of prostheses (e.g. cardiac and vascular procedures) in institutions with a high rate of MRSA or MRSE

Contraindications/ Precautions

These include:

1. Known allergy to teicoplanin

2. Thrombocytopenia

   - This may occur during vancomycin or teicoplanin treatment

     It may also recur if due to been immune-mediated mechanisms.

3. Hearing impairment:

   - May increase the risk of ototoxicity from glycopeptides (especially vancomycin).

4. Treatment with ototoxic drugs, e.g. aminoglycosides

   - May increase the risk of ototoxicity, particularly with vancomycin.

Pregnancy

Teicoplanin 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.

Published reports describing the use of teicoplanin during pregnancy have not been located.

Consider an alternative medicine during pregnancy if possible.

However, if teicoplanin is the medicine of choice, it should not be withheld during pregnancy, but consultation with an Infectious Diseases Specialist or Clinical Microbiologist for further advice is recommended.

Breast feeding

Published reports describing the use of teicoplanin during breastfeeding have not been located.

Although teicoplanin is poorly absorbed when taken orally, consider an alternative medicine during breastfeeding where possible.

In circumstances where teicoplanin is the medicine of choice, teicoplanin therapy should not be a reason to discontinue breastfeeding.

However, observe the breastfed infant for potential adverse effects such as diarrhoea, vomiting, skin rashes or thrush.

Adverse Effects

Teicoplanin being a **glycopeptide** antibiotic share similar adverse effects with vancomycin, although the incidence and severity of these are much less.

They may include:

1. Hypotension:

    - This can occur with excessively rapid bolus administration

      If hypotension occurs, the infusion should be slowed or temporarily stopped.

2. Nephrotoxicity:

    - Nephrotoxicity is more common when glycopeptides are used with aminoglycosides and in renal impairment.

      It appears to be related in particular to vancomycin serum concentration.

      Teicoplanin is **less nephrotoxic** than vancomycin.

3. Ototoxicity :

    - Ototoxicity is occasionally seen with vancomycin. It is **very rare** with **teicoplanin**

3. Red man syndrome:

    Usually due to infusion being given too quickly.

It is **not** an allergic reaction although symptoms are partly due to histamine release; they include fever, chills, erythema, facial and upper torso rash, which may be followed by hypotension, angioedema and itch.

Symptoms may be treated with antihistamines (e.g. promethazine)

The risk is reduced by increasing the infusion time to > 60 minutes.

These reactions occur far less often with teicoplanin compared to vancomycin.

4. Allergic reactions:

   - True anaphylaxis (not to be confused with "red man syndrome") is rare.
   - Note also that allergic cross-reactivity between *teicoplanin* and vancomycin can occur.

5. Serious skin reactions can occasionally occur:

   - Stevens-Johnson syndrome/ toxic epidermal necrolysis.

6. Blood dyscracias:

   - Thrombocytopenia (may be immune-mediated)
   - Neutropenia

7. Thrombophlebitis:

   - This occurs more common than with vancomycin.

Dosing

Teicoplanin is given IV by **slow injection over 5 minutes** or **infused over 30 minutes**.

Adults:

To avoid under-dosing, consider using the fixed doses for patients <70 kg, and the weight-based doses for those >70 kg.

For severe infections, e.g. septicaemia:

- Teicoplanin IV, initially 6 - 12 mg/kg (or 400 - 800 mg) every 12 hours for 3 doses,

Then

- 6 mg/kg (or 400 mg) IV once daily.

For septic arthritis:

- Teicoplanin IV, initially 12 mg/kg (or 800 mg) every 12 hours for 3 doses,

Then,

- 12 mg/kg (or 800 mg) once daily.

Renal impairment:

CrCl 40 - 60 mL/minute:

- Give usual doses for the first 3 days, then usual dose every 2 days (or half usual dose once daily)

CrCl <40 mL/minute:

- Give usual doses for the first 3 days, then usual dose every 3 days.

Child:

- >1 month, Teicoplanin IV 10 mg/kg (maximum 800 mg) every 12 hours for 3 doses,

Then,

- 10 mg/kg (up to 400 mg) once daily.

IM Administration:

Teicoplanin can be given IM (maximum 400 mg at a single site)

Monitoring:

Laboratories that perform teicoplanin assays are limited

Measure trough concentration when treating **serious infections**: it should be >10 mg/L (>20 mg/L for infections such as septic arthritis, S. aureus endocarditis). [2]

There is however little evidence to support a direct relationship between high trough or peak serum teicoplanin concentrations and most of the known toxicities (*Australian Society for Antimicrobials, Newsletter No.11 December 2002*).

Monitor renal function and complete blood count at least once a week; more frequently during prolonged and/or high-dose treatment and in people with impaired renal function including the elderly

Consider monitoring hearing during long courses

References

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