THE NORTHERN HOSPITAL

VANCOMYCIN

"The Red Studio", oil on canvas, 1911, Henri Matisse, Museum of Modern Art, New York City.

"I do not literally paint that table, but the emotion it produces upon me….It is only after years of preparation that the young artist should touch colour - not colour used descriptively, that is, but as a means of personal expression…Where I got the color red - to be sure, I just don't know, but I find that all these things . . . only become what they are to me when I see them together with the color red."

Henri Matisse.

In the Autumn of 1905 all of Paris was abuzz! The Salon d'Automne had just opened, and the people queued up to see the very latest in the world of the Arts. The traditionalists seemed to have grudgingly accepted, the new Art Nouveau, stunningly beautiful as it was, it was certainly hard not to! Even the Impressionists, by this time were relatively broadly accepted, and even appreciated, although the Post Impressionists were even now pushing the limits of this oeuvre. Amoung the excited throngs were the inevitable bevy of "art critics", always seemingly one step behind the game, ready to scoff and to frown, and generally "educate" the ignorant public in matters of "good taste". But 1905 was the modern world. Impressionism had changed everything forever, and Art Nouveau promised stunning new possibilities. There was certainly an air of anticipation, especially within the mind of one particular most eminent art critic by the name of Louis Vauxcelles. As Louis strolled from exhibition room to exhibition room, he frowned and tut tutted, but nothing would prepare him for the shock of what he was to encounter in one particular room. He walked in, stood uncomprehending for a moment, then gasped out loud, "Mon Diu - c'est Donatello au milieu des fauves!" Fauvism had ushered in the future shock of the Twentieth century!

What first caught Louis's eye lay in the very center of the room - a beautiful Renaissance style sculpture - a Donatello one assumes, but his does not appear to have been recorded for posterity - but then surrounding this masterpiece on all sides were works the like of which had not been seen before - brilliantly colorful abstractions! Louis simply blinked in uncomprehending bewilderment, he could make out what the paintings were of, but he couldn't understand the vivid non-life like way in which objects and people were being portrayed - Fauves - wild beasts he called these works! "My God - it's a Donatello - amoung wild beasts!" Many shared his bewilderment, and yet this only made the "Fauvist" room the most popular in the exhibition - everyone wanted to see what the fuss was about! Like the term "impressionism" a generation before, the term "Fauvism" - or "wild beasts" - was meant to be derogatory but like impressionism it captured the popular imagination, and the term firmly stuck. Later, after Louis had regained his composure, he would record his derisive appraisal of the "Fauvists"..."...A movement I consider dangerous (despite the great sympathy I have for its perpetrators) is taking shape among a small clan of youngsters. A chapel has been established, two haughty priests officiating. MM Derain and Matisse; a few dozen innocent catechumens have received their baptism. Their dogma amounts to a wavering schematicism that proscribes modeling and volumes in the name of I-don't-know-what pictorial abstraction. This new religion hardly appeals to me. I don't believe in this Renaissance... M. Matisse, fauve-in-chief; M. Derain, fauve deputy; MM. Othon Friesz and Dufy, fauves in attendance...and M. Delaunay (a fourteen- year-old-pupil of M. Metzinger...), infantile fauvelet".

Fauvism was a short lived genre, lasting around 1900 - 1920, but really its most prominent period was just a few years within the first decade of the new century. It was an extreme form of Post Impressionism, and although only short lived and never a formally organized or cohesive movement, it nonetheless holds an important part in the history of Art in the Twentieth century. It has been described as the very first of the of the major European avant-garde movements that would lead to an astonishing radiation of oeuvres never before seen in the long history of Art. After Fauvism anything was possible - and throughout the course of the Twentieth century, this is precisely what was seen. The first inclination of evolution and change came with the impressionists in the mid to late Nineteenth century. At the beginning of the Twentieth Fauvism announced that all "rules" had finally been dispensed with. The idea

behind fauvism was to present feelings, particularly in the form of vivid color which inspired inner emotions. Impressionism had begun this philosophy, Post Impressionism had taken things further, but a new movement, Neo Impressionism, with its rigid and exacting "rules" seemed to be destroying the original idea of throwing way the rule book. Impressionism had gone about as far as it could go, and indeed many saw that it had begun to revert Art back to the old ways of dogma and convention. Fauvism was, in part, a reaction against Neo Impressionism. In other words, Impressionism had lost its way - Fauvism should now show the way forward….and it did.

By general consensus most Art historians would admit that the greatest exponent of Fauvism, was Henri Matisse. Perhaps the most illustrative examples of Fauvism is Matisse's series of "red paintings" - one superb example being his "Red Studio" of 1911. Here we see all the essential features of Fauvism. Matisse realized that the human brain is symbolic in its thinking - its sees patterns everywhere - a few simple lines can suggest a form or an object - the mind simply reconstructs what is missing or reinterprets what it is really seeing. Matisse sought to project emotion - not concrete objects. In the Red Studio we his considered efforts to ***deliberately*** *break all the rules. We see his studio - the vivid red positively vibrates intense sensation - perhaps it shows the warmth of his studio on a cold Parisian day - or perhaps it shows the heat and passion of his own inner psyche - either way the emotion is in the eye of the beholder - and no two people have exactly the same emotions! In the Red Studio our mind immediately tries to reconstruct a three dimensional stereotyped image of the real world. Matisse says No! - feel only the emotion of my studio!. He tries to deconstruct our distracting vision of a concrete outer world. He does this in a number of ways. The intense red colors disguise the normal contours and boundaries we see in real life. A certain flatness is obtained, beginning to diminish the illusion of a three dimensional space. The clock face in the background has no hands on it - taking us away even from the illusion of time. The large pink painting in the left hand corner defines the corner of the room, and yet when we follow the line of its right border upwards we see the there is no continuing line to define this corner - only a flat universal redness. Lines of convergence to the vanishing point is a key trick of the perception of visual depth - we see this to a degree with the table on the left - but on the right we see these lines reversed in the figure of the chair! Most intriguing of all however, is the faint outlines of the table, chairs, dresser and other solid objects. The true nature of these cannot be appreciated unless one examines the actual work very closely. They are not lines at all - but gaps left in the paint showing the underlying blank white canvas. This is to reverse the normal Figure-Ground Relationship. The background, in red, essentially lies on top or projected outwards when compared to the lines of the supposedly solid objects - an opposite situation to normal. The solid objects appear to be almost dissolving into the background. The background dominates over the solid foreground objects - normal perspective is reversed! Matisse has attempted to take away all the virtual cues the mind uses to construct the three dimensional physical world - all be are left with is the raw inner emotions of the room - a pulsating, warm, aggressive, passionate, - dimensionless and timeless "Red Studio". We see his Art works displayed - but the room itself is irrelevant.*

When we treat our patients with Vancomycin we may encounter a most unusual Fauvism! - a patient all in red! We must however not let our mind deceive us by the artificial construction of something familiar - anaphylaxis. A rather different situation will be far more likely - the much more benign anaphylactoid reaction - known as the "Red Man Syndrome".

VANCOMYCIN

Introduction

Vancomycin is an amphoteric **glycopeptide** antimicrobial substance produced by the growth of certain strains of *Amycolatopsis orientalis* (formerly *Nocardia orientalis)*.

It is a narrow - range bactericidal agent against many **gram positive** organisms.

It is *not* effective against gram negative organisms.

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

It is essential that vancomycin is used appropriately to minimize the emergence of multiply resistant organisms, such as **vancomycin resistant enterococcus (VRE)** and **Glycopeptide Intermediate Staphylococcus aureus (GISA),** as well as to minimize its potentially serious side effects.

Close monitoring (of creatinine and trough levels of vancomycin) is an important aspect of vancomycin therapy.

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 developed in the early 1990s.

Chemistry

Vancomycin is an amphoteric **glycopeptide** antimicrobial substance produced by the growth of certain strains of *Amycolatopsis orientalis* (formerly *Nocardia orientalis)*.

Vancomycin is not *chemically* related to any of the other currently used antimicrobial groups.

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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Preparations include:

Tablets, (capsules):

- **125 mg, 250 mg.**

Ampoules:

- **500 mg** vial powder, **1 gram** vial powder (for reconstitution).

  Vancomycin hydrochloride for intravenous infusion is a lyophilized powder for reconstitution.

  When reconstituted in water, it is a clear solution with a pH of 2.8 to 4.5.

  Intravenous administration should be slow and in dilute solutions.

Mechanism of Action

Vancomycin 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 vancomycin is *not* classed as a "beta - lactam" drug).

It produces immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.

Pharmacokinetics

Absorption:

- Vancomycin is given **IV (slow infusion)** or **orally** (although it is not well absorbed orally, and is only given orally for cases of clostridium difficile).

  It **cannot** be given IM.

Distribution:

- The Vd is around 0.3 to 0.69 L/kg

- Protein binding is approximately 55 %

- Excreted into breast milk in small amounts.

Metabolism and excretion:

- **There is no apparent metabolism of the drug**
- **Excretion appears to be entirely renal**

The mean elimination half life of vancomycin from plasma is 4 - 6 hours in subjects with normal renal function.

Renal dysfunction *significantly* slows excretion. **Serum levels will rise in patients with renal impairment, and toxicity may result.**

In anephric patients, the average half life of elimination is 7.5 days.

Vancomycin is not effectively removed by either haemodialysis or peritoneal dialysis; there have been no reports of vancomycin clearance with haemoperfusion.

Pharmacodynamics

In general terms vancomycin is bactericidal against many **gram positive** organisms, including MRSA.

Note however that methicillin-susceptible *Staphylococcus aureus* (MSSA) may in fact be more resistant to vancomycin, compared to other beta-lactams (such as flucloxacillin or cephazolin).

It is not effective against gram negative organisms, mycobacteria or fungi.

Indications

Vancomycin (and Teicoplanin) are active against a wide range of Gram-positive organisms.

Gram-negative organisms are **not** susceptible.

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

Particular situations include:

1. MRSA:

   Treatment (and in special situations, prophylaxis) of serious infections with methicillin-resistant organisms:

   - Staphylococcus aureus (**MRSA**)

Or

- Multi-resistant Staphylococcus epidermidis.

2. Severe penicillin allergy:

   - Treating severe infection with susceptible organisms in patients who are **hypersensitive to penicillin**

3. Meningitis due to highly penicillin-resistant *Streptococcus pneumoniae*.

4. Endocarditis:

   - Vancomycin (or teicoplanin) may be used for prophylaxis of endocarditis in patients hypersensitive to penicillin.

5. Clostridium difficile:

   - Vancomycin has been given orally to treat antimicrobial-associated diarrhoea caused by ***Clostridium difficile*** not responsive to metronidazole.

     The emergence of resistance in enterococci makes it essential to reserve it for severe cases unresponsive to metronidazole.

     In severe cases associated with ileus, vancomycin can be given as a retention enema.

6. Serious sight - threatening eye infections:

   - Endophthalmitis

7. Certain situations of surgical prophylaxis, (given as a single dose).

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.

Contraindications/ Precautions

These include:

1. Renal impairment (requires dose adjustment and careful monitoring).

2. Allergy to vancomycin, (note that cross reactivity with *teicoplanin* can also occur).

- A history of previous "Red Man Syndrome", does **not** contraindicate future use of vancomycin, however infusion rates should be **slowed.**

3. Elderly, (increased risk of toxicity).

4. Administration with other *nephrotoxic* drugs such as aminoglycosides which increase the risk of renal toxicity.

5. Vancomycin should be avoided (if possible) in patients with previous hearing loss.

Pregnancy

Vancomycin is considered safe to use in pregnancy.

It is classified as a class B2 drug with respect to pregnancy.

Class B2 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 are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Breast feeding

Safe to use; may cause loose bowel actions in the baby.

Adverse Effects

These include:

1. Hypotension:

   - This can occur with excessively rapid bolus administration (over several minutes).

     Vancomycin should be *infused slowly* over **at least 60 minutes.**

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

2. Nephrotoxicity:

   - Nephrotoxicity is more likely in **renal impairment.**

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

   - It appears to be directly related to vancomycin serum concentration.

- Teicoplanin is less nephrotoxic than vancomycin.

3. Ototoxicity :

- Vertigo and tinnitus are seen in milder reactions
- Deafness can occur and may be may transient or permanent.
- Ototoxicity has been reported predominantly in patients who:
  - ♥ Have been given excessive doses
  - ♥ Have **renal impairment.**
  - ♥ Have an underlying hearing loss
  - ♥ Are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside.
- Ototoxicity is very rare with *teicoplanin.*

3. **Red man syndrome:**

This is **not** a true allergic reaction.

Symptoms are *partly* due to histamine release and include:

- Fever
- Chills
- Erythema, facial and upper torso rash (or flushing)

If this reaction occurs:

- Treat with antihistamines (e.g. promethazine).
- Slow the infusion rate (to at least **> 60 minutes**).

In more severe reactions:

- Hypotension, angioedema and itch can occur.

Cease the infusion and treat as for anaphylaxis. Re-challenge is not recommended in this situation.

These reactions occur far less often with *teicoplanin* than with vancomycin, and if vancomycin reactions become severe, then *teicoplanin* will usually be a suitable alternative.

Red man syndrome is uncommon, providing that the vancomycin infusion is being given at appropriate rates.

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. GIT Upset:

   - Oral vancomycin may cause indigestion, nausea, vomiting, diarrhoea.

7. Thrombophlebitis:

   - IV administration may cause local pain/ thrombophlebitis.

8. Extravasation may cause local tissue necrosis.

Dosing

Oral therapy for Clostridium difficile-associated disease: [2]

- Adult, **oral,** dosing is usually 125 mg every 6 hours for 10 days (500 mg/dose may be used in severe disease).
- Child >1 month, oral 5 mg/kg (maximum 125 mg) every 6 hours for 10 days. In severe disease, 10 mg/kg (maximum 500 mg) every 6 hours has been used.

Note that vancomycin is not effective by the oral route for other types of infections.

IV regimes:

Local recommendations for optimal dosing can vary.

Higher vancomycin doses than were used previously are now recommended by some authorities in an effort to ensure that concentrations are adequate and to minimize resistance development. These however are often based on theoretical considerations or opinion and have little clinical evidence to support them. [2]

Precise dosing regimens will depend on:

- **Patient actual weight**
- **Renal function**
- **The condition that is being treated**

If given by intermittent administration, 12 hourly vancomycin dosing is now recommended for all indications in patients with normal renal function. [1]

Use local recommendations for dosing - where these exist

As a **generic *guide***, to achieve adequate trough levels:

Dosing can be thought of as occurring in **3 stages**:

1. The loading dose.
2. The first maintenance dose
3. The second and subsequent maintenance doses.

Loading dose:

The recommended **loading dose** is **25 - 30 mg/kg** (*actual body weight*) generally to a maximum of **1.5 0 2.0 grams IV.**

This first dose does not require reduction in the presence of renal impairment.

A loading dose of vancomycin may be considered to help achieve a therapeutic concentration more quickly, particularly in patients with serious infections who are critically ill.

Weight-based dosing is recommended for the loading dose, since both volume of distribution and clearance of vancomycin are correlated with *actual* body weight.

Actual Body Weight	**Loading Dose IV**
< 50 kg	**25 mg/kg (to maximum 1.25 grams)**
50-59 kg	**1.5 grams (to maximum 1.5 grams)**

≥ 60 kg	**2 grams**

First Maintenance Dose:

The first maintenance dose and its timing will be based on the **creatinine clearance.**

Note that the creatinine clearance should be calculated using the **Crockcroft-Gault equation**, in preference to the eGFR that is reported in laboratory results.

A medical calculator for the Crockcroft-Gault equation can be found on:

- www.mdcalc.com/
- Via the Australian Medicine's Handbook.

Creatinine clearance	**Initial maintenance dose (IV)**	**Timing of trough-level**
> 90 mL/min	1.5 grams 12-hourly	Immediately before the 4th dose
60 - 90 mL/min	1 gram 12-hourly	Immediately before the 4th dose
20 - 59 mL/min	1 gram 24-hourly	Immediately before the 3rd dose
< 20 mL/min or hemodialysis or peritoneal-dialysis	1 gram STAT only when levels less than 20 mg/L	Take a spot-level 48 hours after the first dose
Haemodiafiltration (CVVHDF)	1 gram 12-hourly	Immediately before the 3rd or 4th dose

Note that a **trough level** refers to a level that is taken immediately before the scheduled dose, (or at most 30 minutes before the scheduled dose).

The first maintenance dose can be given as soon as the trough level have been taken, you do not have to wait for the result unless the creatinine clearance is **< 20 mL/min – in which case the dose should be withheld pending the result of the trough level.**

The terminology **spot level** is generally used when the next dose is *withheld, pending the result.*

Trough Levels:

A level of **15 - 20 mg/L** is generally aimed for unless treating a case of CNS infection (e.g. meningitis).

When treating a CNS infection a trough level of **20 - 25 mg/L** is aimed for.

Vancomycin trough-levels predict efficacy. Low trough-levels (< 10 mg/L) have been associated with treatment failure and emergence of resistance.

The second and subsequent maintenance doses:

These doses are based on the **trough** (or **spot levels)** as well as the current dosing regimen.

For patients with Cr Cl > 60 mL/min (or on dialysis):

Trough-level	Current dose		
	1 g 12-hourly	1.5 g 12-hourly	2 g 12-hourly
< 10 mg/L	increase to 1.5 g 12-hourly	increase to 2 g 12-hourly	therapeutic levels may be difficult to achieve, consult ID for further advice
10 – 14 mg/L	increase to 1.25 g 12-hourly	increase to 1.75 g 12-hourly	therapeutic levels may be difficult to achieve, consult ID for further advice
15 – 20 mg/L*	dose change not required	dose change not required	dose change not required
21 – 30 mg/L*	decrease to 1 g 24-hourly	decrease to 1.25 g 12-hourly	decrease to 1.5 or 1.75 g 12-hourly
> 30 mg/L	withhold dose until level < 20 mg/L. Consult ID for further advice	withhold dose until level < 20 mg/L. Consult ID for further advice	withhold dose until level < 20 mg/L. Restart at 1 g 12-hourly if indicated.

Patients with Cr Cl 20 - 59 mL/min:

Trough-level	Current dose		
	1 g 24-hourly	1 g 12-hourly	1.5 g 12-hourly
< 10 mg/L	increase to 1 g 12-hourly	increase to 1.5 g 12-hourly	increase to 2 g 12-hourly
10 – 14 mg/L	increase to 750 mg 12-hourly	increase to 1.25 g 12-hourly	increase to 1.75 g 12-hourly
15 – 20 mg/L	dose change not required	dose change not required	dose change not required
21 – 25 mg/L	extend dosing interval, 1 g 48-hourly	extend dosing interval, 1 g 24-hourly	decrease to 1.25 or 1.5 g 12-hourly
> 25 mg/L	withhold dose until level <	withhold dose until	withhold dose until level <

	20 mg/L, and extend dosing interval according to the time taken to fall below 20 mg/L[#]	level < 20 mg/L, and extend dosing interval according to the time taken to fall below 20 mg/L[#]	20 mg/L. If vancomycin is still indicated, restart at 1g 12- or 24-hourly. Consult ID if dosing advice required.

dosing intervals should be in multiples of 12-hours (i.e. 12-, 24-, 36-, 48-hourly)

Patients with Cr Cl < 20 mL/min including those on dialysis:

Patients with severe renal impairment (Cr Cl < 20mL/min) who are not on CVVHDF will require spot-levels after the first STAT dose of vancomycin with the dose withheld until the level is available.

The time it takes for the level to fall below 20 mg/L determines when to give the next dose and frequency of spot-level monitoring.

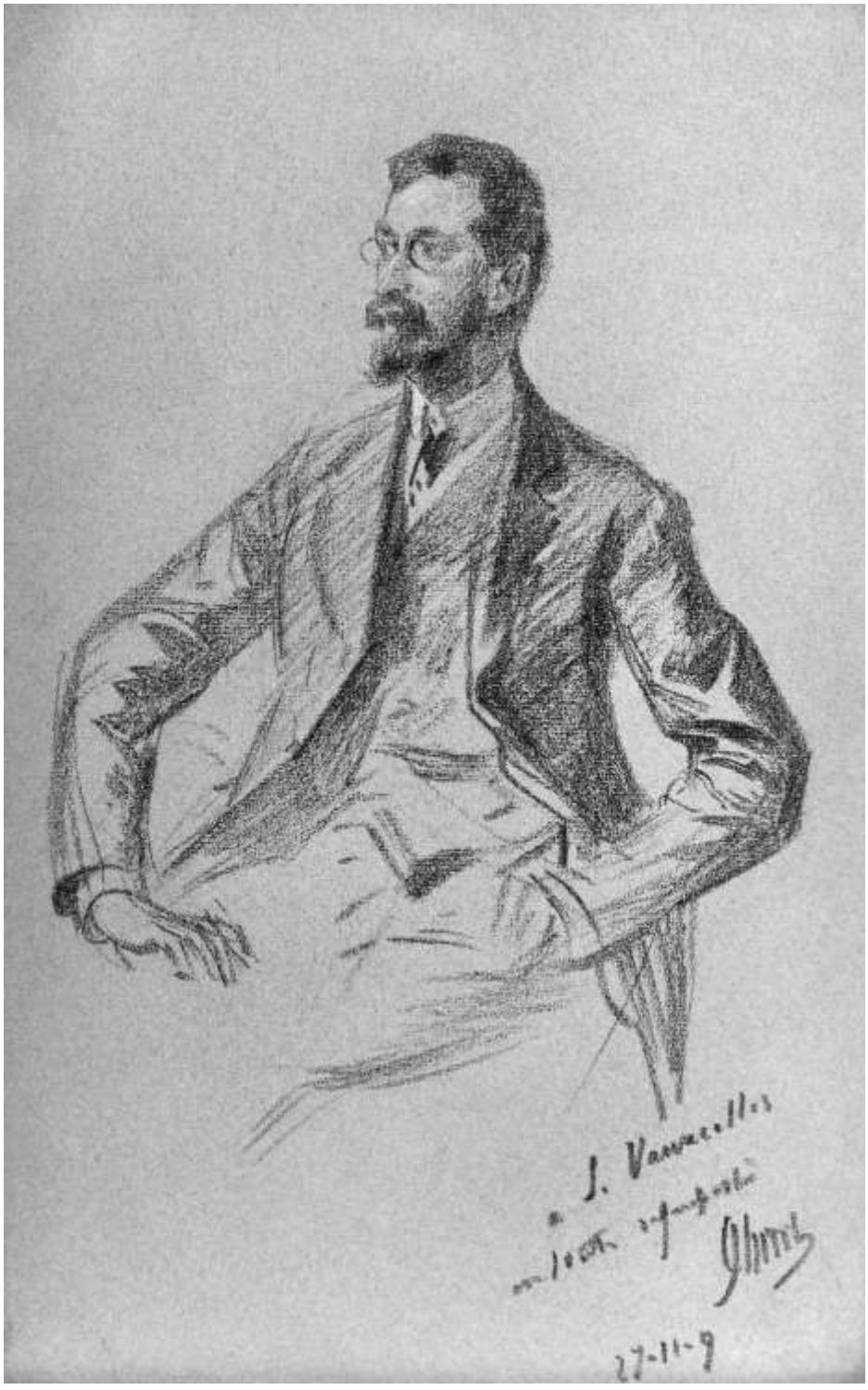
Infusion rates:

Vancomycin should be given slowly over **at least 60 minutes** (at a rate **not > 10 mg/minute** for doses > 500 mg) in dilute solutions, to help avoid its principle adverse reactions.

For example: For a dose of 1.5 grams = 1500 mg = dose to be given over 150 minutes.

It should be given via a large peripheral vein (or centrally) to minimize the chances of extravasation.

In patients with renal impairment the dose interval must be increased or the dose reduced, or both.



"Mon Diu - c'est Donatello au milieu des fauves!"

Louis Vauxcelles, charcoal on paper, Jules Chéret 1919

References

1. eTG - July 2015.

    - Antibiotic Guidelines 15th ed 2015.

2. Vancomycin in Australian Medicines Handbook Website, Accessed August 2014.

3. Vancomycin in MIMs Website 1 June 2013

4. Critical Care Drug Manual, Dr Paul Young Wellington Hospital Intensive Care Unit, NZ 2010.

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