THE NORTHERN HOSPITAL

VANCOMYCIN RESISTANT ENTEROCOCCUS (VRE)

"Triton and Nereid", plaster, 1893, Auguste Rodin, Musee Rodin, Paris, (author's photograph)

While my master spoke the centaur had run past,
Below where we were standing, three new souls
had neared, although we did not see them
until we heard their shouts…

If, reader your are slow to credit
what I am about to tell you, it's no wonder;
I saw it, and I myself can scarce believe it

While I stood staring with raised brows,
a reptile with six legs propelled itself
at one of them, and fastened itself to him

It grabbed his belly with its middle claws,
Then with its forepaws held his arms
And bit him on both cheeks

It stretched its hind feet down the other's thighs,
thrusting its tail between them
and curled it up behind, above the buttocks.

Never did clinging ivy fix itself
so tight up a tree as did that fearsome beast
entwine itself around the other's limbs.

Then they fused together, as if made
of molten wax, mixing their colours
so that neither seemed what it had been before,

as over the surface of a scrap of parchment,
before the flame, a brownish colour comes
that is not black, yet makes the white die out…

Already the two heads had been united,
two sets of features blending
both lost in a single face.

Four separate limbs combined to form two arms,
The thighs and calves, the stomach and the chest
turned into members never seen before.

All trace of their first aspect was erased
and the unnatural figure seemed both two
and none; and off it went, at its slow pace.

As the green lizard beneath the scorching lash
of a dog-day heat, between one hedge and the
next, seems lightning as it streaks across the road,

just so appeared - darting toward the bellies
of the other two - a little fiery reptile,
black and livid as peppercorn…

Let Lucan now fall silent where he tells
of poor Sabellus and Nasidius,
and let him wait to hear what comes forth now!

Let Ovid not speak of Cadmus or Arethusa,
for if his poem turns him into a serpent
and her into a fountain, I grudge it not,

for never did he change two natures, face to face,
in such a way that both their forms
were quite so quick exchanging substance.

Their corresponding changes went like this:
the reptile split its tail into a fork
and he that was wounded drew his feet together.

First his calves and then his thighs began
To knit so that in but a moment
no sign of a division could be seen.

The cloven tail assumed the shapes
the other one was losing, and his skin
was turning soft while the other's hardened.

I saw the man's arms shrinking towards the armpits
and the brute's forepaws, which had been short,
lengthen, precisely as the other's dwindled.

Then the hind paws, twisting together,
became the member that a man conceals,

and from his own the wretch has grown two paws.

While the smoke veils one and now the other
with new colour and grows hair here
and elsewhere strips it off,

one of them rose to his feet, the other fell,
but neither turned aside his baleful glare
under each muzzle changed its shape.

In the one erect it shrank in to the temples,
and from the excess flesh absorbed,
two ears extruded from smooth cheeks.

Whatever did not recede, left over
from that excess, made a nose for the face
and gave the lips a proper thickness,

The one prone on the ground shoves out his snout
and draws his ears into his head
as a snail draws in its horns,

and his tongue, till now a single thing
and fit for speech divides, and the other's
forked tongue joins and the smoke stops.

The soul just now become a brute takes flight.
hissing through the hollow, and the other,
by way of speaking, spits after him.

Thus I saw the seventh rabble change
and change again, and let the newness of it
be my excuse if my pen has gone astray.

Dante Alighieri, The Inferno,
Canto XXV 36-138 (1306-1317)

A fierce centaur dashes past. Virgil and Dante have now reached the Seventh ditch of Malebolge in the Eighth Circle of Hell. In Malebolge the sins of fraud are punished. The Seventh ditch is reserved for the souls of those who in life were thieves on the grand scale. As Dante progresses into the deeper levels of Malebolge, the sights that greet his eyes become not only more horrific but more bizarre. He begins to fear that no one will believe what he is about to tell; "If, reader you are slow to credit what I am about to tell you, it's no wonder; I saw it, and I myself can scarce believe it….."

At first he cannot see the three damned souls but only hear their shouts. Suddenly a hideous six legged reptile streaks past him and latches itself onto the shade of one of the souls. It bites deeply into its face and digs its claws into its ghostly "flesh". Then it thrusts its tail between the shades legs in a hideous parody of a sexual act. The reptile is now so firmly attached to the shade, that it seemed, "Never did clinging ivy fix itself so tight up a tree as did that fearsome beast entwine itself around the other's limbs…."

Then incredibly the two figures appear to fuse together; "as if made of molten wax….". The colours of the reptile and the shade begin to blend, "mixing their colours so that neither seemed what it had been before". The changes sweep across the "body" of the shade, "as over the surface of a scrap of parchment, before the flame, a brownish colour comes that is not black, yet makes the white die out…" The monstrous hybrid then moves off slowly; "All trace of their first aspect was erased and the unnatural figure seemed both two and none; and off it went, at its slow pace…"

Just at this point a second reptile attacks another shade. What Dante witnesses surpasses anything that ancient mythology can come up with - not even Ovid in his Metamorphoses or Lucan in his tale of poor Sabellus and Nasidius, come close to this next horror! The reptile and the shade appear to blend into another hybrid figure, but this time all the while they seem to be exchanging their very substance! As the shade loses its arms and legs, so the reptile gains the shade's arms and legs. Dante follows the whole process with sickening revulsion - the lizard's tail becomes legs, its front paws become arms, its rear legs become a penis, its hide becomes skin, its posture changes from prone to erect, its snout becomes a face its serpentine hiss becomes a voice. The shade at the same time transforms into a reptile, the two have exchanged their very essence - "The soul just now become a brute takes flight, hissing through the hollow, and the other, by way of speaking, spits after him"

Dante is so repulsed by what he is seeing that he struggles to write down his experiences. Because he has seen terrible sights no mortal has ever seen he begs his readers to excuse the ink blots on his parchment, his hand trembles and he can scarce keep pace with the rapidly metamorphosing abominations that afflict his eyes; "let the newness of it be my excuse if my pen has gone astray".

The Seventh ditch of Malebolge is reserved for those who in life were unrepentant thieves on the grand scale. Always lusting after one another's processions, never satisfied with what they had, and never sharing anything at all. In Hell they are forced to share their very being with hideous reptiles. They blend and meld into clinging lizards, sometimes becoming a monstrous hybrid, sometimes becoming fully reptilian. After spending time as a slithering legged snake, they are transformed back into a shade, only to be attacked and hideously transformed again and again, and again for all eternity.

In our endless battle against the microscopic pathogenic world we face dark and mysterious forces indeed. Some organisms such as the enterococci may freely exchange their very essence, by means of plasmid transmission. This process may create hideous new hybrids, with the combined powers of both the originals. All trace of their first aspect may be erased and the unnatural resulting figure may seem both two and none. It is by this Hellish blending that enterococci may acquire multiresistance to many - if not most - of our most powerful antibiotics.

VANCOMYCIN RESISTANT ENTEROCOCCUS (VRE)

Blue Enterococcus faecalis colonies growing on specialized chromogenic agar, (mykindofscience.com)

Introduction

Enterococci are **gram positive, cocci shaped, bacteria** that commonly colonize the human intestine, the female genital tract and occasionally the urinary tract.

Although these organisms have intrinsically low pathogenicity they also typically show high resistance to antibiotics.

When they acquire resistance to glycopeptide antibiotics, and specifically to **vancomycin** they are termed **vancomycin-resistant enterococci** or **VRE**

Most VRE also have high levels of resistance to β-lactams and aminoglycosides in general

Note that VRE is neither more infectious nor more virulent than sensitive enterococci.

Most of the time VRE does not any disease, however these organisms may invade other parts of the body and cause infection, which is then very difficult to treat because of their high acquired resistance to many first line antibiotics.

VRE are major nosocomial (i.e. hospital acquired) pathogens.

The two most important enterococci are **E. faecalis** and **E. faecium**

Once colonized, it is uncertain for how long VRE organisms persist in the body. Some literature suggests that in the **absence of ongoing recent risk factors**, such as hospitalization or antibiotic use, patients with a remote history of colonization (**> 4 years**) may no longer require contact isolation precautions. [5]

Occasionally VRE may cause infection and treatment is then difficult due to high resistance to multiple antibiotics**,** including **vancomycin.**

Treatment of VRE **infections** must be guided by microbiologists and Infectious Diseases Specialists.

Van A resistance is common in Australia, so many VRE are both vancomycin and teicoplanin resistant

Van B resistant strains are **sensitive** to **teicoplanin**

Antibiotics which may have activity against VRE organisms include:

1. **Teicoplanin (for Van B phenotypes)**
2. **Linezolid**
3. **Daptomycin**
4. **Quinupristin-dalfopristin**
5. **Tigecycline**
6. **Ceftaroline**

Terminology:

It is important to appreciate the difference between colonization and infection.

Colonisation:

- This is the presence, growth and multiplication of microorganisms *without* observable clinical signs or symptoms of infection.

Infection:

- This is the *invasion* of bacteria into tissues with replication of the organism.
- Infection is characterized by isolation of the organism accompanied by clinical signs of illness such as fever, inflammation or pus formation.

History

Vancomycin-resistant enterococci (VRE) were first reported in 1986, approximately 30 years after vancomycin was introduced into clinical practice.

The first detection of a VRE infected patient in Australia occurred in Victoria in 1994.

Epidemiology

Vancomycin resistant enterococci (VRE) have now caused hospital outbreaks **worldwide.**

Pathology

Organism:

Enterococci are **gram positive, cocci-shaped, bacteria** that commonly colonize the human intestine, the female genital tract and occasionally the urinary tract.

When these enterococci acquire resistance to **vancomycin** they are termed **vancomycin-resistant enterococci** or **VRE**

The two most important enterococci are:

1. **E. faecalis:**
    - E. faecalis infection is relatively less severe (around 11% overall mortality)
2. **E. faecium:**
    - E.faecium infection is usually more severe (around 50% overall mortality)

Most commonly, resistance is seen in *E. faecium* and *E. faecalis*, but it has also has been recognized in other enterococci as well including:

3. E. raffinosus
4. E. avium
5. E. durans, and several other enterococcal species

The **VRE phenotype** may be:

1. Acquired resistance:

    Van A or **Van B** depending on the resistance to specific antimicrobial types.

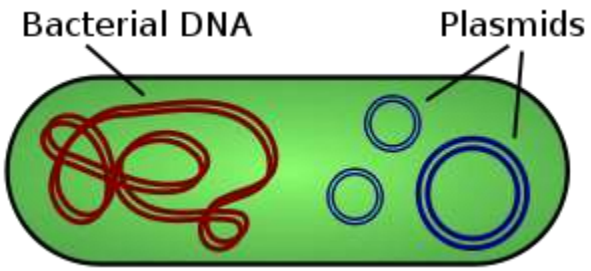
    - **VRE Van A is resistant to vancomycin and teicoplanin**

- **VRE Van B is resistant to vancomycin but sensitive to teicoplanin.**

2. Intrinsic resistance:

   Van C; these are organisms that have their own intrinsic vancomycin resistance (as opposed to plasmid acquired resistance).

Resistance acquisition by enterococci:



A **plasmid** is a small DNA molecule within a cell that is physically separated from its normal chromosomal DNA and can replicate independently.

They are most commonly found in bacteria as small circular, double-stranded DNA molecules; however, plasmids are sometimes present in archaea and eukaryotic organisms as well.

In nature, plasmids often carry genes that may benefit the survival of the organism, for example **antibiotic resistance.**

While the chromosomes are big and contain all the essential genetic information for the organism under normal conditions, plasmids usually are very small and contain only a small number additional genes that *may* become useful to the organism under certain situations or particular conditions.

Plasmids can be passed from organism to organism and so provide one mechanism for gene transfer between them.

Plasmids may carry genes that provide resistance to naturally occurring antibiotics in a competitive environmental niche, or the proteins produced may act as toxins under similar circumstances, or allow the organism to utilize particular organic compounds that would be advantageous when nutrients are scarce.

Vancomycin resistance is plasmid mediated, meaning that vancomycin sensitive enterococci can acquire resistance from other organisms that contain a plasmid that encodes for genes that confer vancomycin resistance.

Risk Factors:

Known risk factors for VRE **carriage** include:

1. Recent or **extended** hospitalisation
2. Recent critical illness
3. Admission to an Intensive Care Unit
4. Severe underlying disease
5. Prolonged or broad spectrum antibiotic use, in particular Vancomycin
6. Indwelling urinary catheter
7. Patients in proximity to a VRE colonised / infected patient.

Risk Factors for Transmission:

Certain VRE patients are more likely to contaminate the environment and hands of healthcare workers:

These include:

1. Patients with diarrhoea or faecal incontinence
2. Patients with enterostomies
3. Patients with discharging wounds
4. Catheterised patients with VRE colonisation of the urinary tract
5. Patients incapable of maintaining own personal hygiene.

Healthcare workers providing direct care to these patients are at increased risk of transient acquisition of VRE on their hands if standard and transmission based precautions are not followed.

Risk factors for acquiring VRE infection:

Known risk factors for VRE **infection** include:

1. Severe neutropenia
2. Immunosuppression (in general)
3. Solid organ transplantation

4. Admission to an intensive care unit or a neonatal unit

5. Invasive device insertion

The Complications of VRE:

1. Potential transmission of resistance:

    - Plasmid transmission to previously Vancomycin sensitive organisms.

    - There may also be some **inter-species** plasmid transmission, in particular to **Staphylococcus aureus**

2. Infection with VRE in the predisposed:

    - Patients with VRE bacteremia are more likely to die than patients with vancomycin-sensitive enterococcal bacteremia

    - Patients infected with VRE are at higher risk of all-cause mortality. [4]

3. Colonisation, of other patients and/or staff

Reservoir

VRE are part of the normal flora of the human intestine and the female genital tract.

These organisms can also colonise the skin, particularly in the lower half of the body.

Once colonised with VRE patients can harbour these organisms for **years.**

VRE is a *resilient* organism and can **survive in the environment for many weeks.**

Transmission

VRE is readily spread from colonised or infected patients within acute health care settings.

It can be transmitted via:

1. Direct contact via contaminated hands

2. Indirect contact via a contaminated objects (or "**fomites**') e.g. patient care equipment, such as stethoscopes, shower chairs, bed tables etc.

Clinical features

Colonization:

Colonization is the presence, growth and multiplication of microorganisms without any observable clinical signs or symptoms of infection.

Though the person is well, they have to potential to spread VRE organisms to other patients

Infection:

Infection is the *invasion* of bacteria into tissues with replication of the organism.

It is characterized by isolation of the organism accompanied by **clinical signs of illness such as fever, inflammation or pus formation.**

Investigations

Diagnosis:

VRE is definitively diagnosed by the growth of enterococci, on specialized chromogenic agar culture screening plates, (Brilliance VRE Agar) that subsequently shows resistance to vancomycin.

Vancomycin susceptibility is specifically based on minimum inhibitory conentrations (MICs) of vancomycin as follows:

- Susceptible ≤ 4 μg/ml
- Intermediate 8 - 16 μg/ml
- Resistant ≥ 32 μg/ml

Cultures may be grown, from screening swabs or from swabs of infected material including blood, urine, wounds or sputum.

Culture plates develop indigo-purple or light blue coloured colonies of bacteria. These are treated as presumptive VRE growths and are then subjected to additional testing to confirm VRE. Further testing then determines the VRE phenotype.

Enterococcus faecalis colonies are light blue.

Enterococcus faecium colonies are indigo-purple.

The VRE phenotype may be either **Van A** or **Van B** depending on the resistance to specific antimicrobial types.

- **VRE Van A is resistant to vancomycin and teicoplanin**

- **VRE Van B is resistant to vancomycin but sensitive to teicoplanin.**

Screening:

Routine screening for VRE carriage is not currently recommended, but may be initiated in the event of outbreaks.

Routine screening of staff is not currently recommended.

Selective admission and interval screening is required for patients who are at **increased risk** of colonisation or infection

Specimens for VRE screening include **faecal specimens** and **perianal swabs.**

Local policies may vary, but one suggested program is as follows:

Target patients	**Frequency of screening**
Any patient admitted to ICU	On admission, weekly & on discharge
Patients transferred from metro ICU, liver transplant or renal units.	On admission
Patients with recent admission to overseas health facility (within 12 months)	On admission
Patients sharing a room or bathroom with a VRE confirmed or VRE presumptive (purple or blue colonies) patient for greater than 24 hours - all wards	Immediately on confirmation or when the source patient is identified has having (purple or blue colonies)

Re-admission testing:

VRE carriage can persist for long periods. When re-admission to an acute care facility is required there must be a **specific mechanism to alert the hospital staff that the patient may still be VRE colonised.**

On re-admission the VRE status of the patient may be **re-assessed.**

Meanwhile, consideration as to whether the patient should be isolated should be determined on factors such as whether they are faecally continent and capable of self care with good

hygiene, the presence of discharging lesions and the type of unit to which they are being admitted.

Management

VRE Colonization:

Strict adherence to infection control measures is essential.

VRE is now endemic in many Australian hospitals. Previously hospitals routinely isolated all patients with VRE colonization. However with the large numbers of patients now presenting with multi-resistant organisms this is not always possible, or indeed necessary, depending on the exact circumstances.

The usual **contact precautions** should be maintained in all situations, but the need for **isolation** of patients found to be colonised with VRE, may be done on a **risk-based strategy.** [5]

Risk stratification will vary according to local polices, but in general terms the following is reasonable:

Patients who will definitely require **isolation**, (i.e. in single room accommodation with a dedicated ensuite bathroom) include those who are VRE presumptive (i.e. purple - blue colonies) or already confirmed colonization **and** any one of the following:

- Diarrhoea and/or faecal incontinence
- Receiving broad spectrum antibiotics
- Discharging wound present
- Stoma present
- Patient is unable/unwilling to comply with hand hygiene practices

If *none* of these conditions are present then the patient may be considered for placement with **contact** precautions in a shared room provided that other patients in that room are classified as **low risk.**

Patients at **low risk** of colonization include:

- No indwelling or invasive devices (e.g. IDC, PICC, IVC etc.)
- No wounds
- Not immunocompromised or undergoing immunosuppressive therapy
- No multi resistant organisms present- e.g. MRSA, ESBL, HVISA

VRE Infection

Van A resistance is common in Australia, so many VRE are both vancomycin and teicoplanin resistant

Van B resistant strains are **sensitive** to **teicoplanin**

Antibiotics which may have activity against VRE organisms include:

1. **Teicoplanin (for Van B phenotypes)**

2. **Linezolid**:

   Although teicoplanin is commonly used in many hospitals with VRE strains that are sensitive, linezolid may be preferred over teicoplanin due to: [3]

   - Greater efficacy
   - Better tissue penetration (it is poorly protein bound, so volume of distribution approximates to total body water)
   - No dosage reduction is necessary in renal or hepatic failure
   - Van A resistance is common in Australia, so many VRE are teicoplanin resistant

3. Fifth generation cephalosporins: (**Ceftaroline / Ceftolozane & Tazobactam):**

   - Limited experience to date

Third line options include:

4. **Daptomycin**

5. **Quinupristin-dalfopristin**

6. **Tigecycline**

Clearance screening:

Once colonized, it is uncertain for how long VRE organisms persist in the body. Some literature suggests that in the absence of ongoing recent risk factors, such as hospitalization or antibiotic use, patients with a remote history of colonization (> 4 years) may no longer require contact isolation precautions. [6]

Another study showed that the median time to clearance after discharge was around 9 weeks. Risk factors for prolonged carriage in this study were surgery, antibiotic use during admission, dialysis, and discharge to a nursing home or other health care institution. [7]

There is no universally accepted definition of what constitutes "**clearance**" of VRE.

One suggested definition has been, defined as **VRE negative rectal (or stool) cultures on at least three consecutive occasions a minimum of 1 week apart.** [7]

Disposition:

Treatment of VRE **infections** must be guided by **microbiologists** and **Infectious Diseases Specialists**.

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