

## What are Antibiotics?

Antibiotics are a type of antimicrobial selected to target the specific microbe responsible for the infection. They work through a variety of mechanisms but all aim to inhibit or interfere with a particular microbial molecular mechanism to either arrest cell growth or promote cell death. Different classes of antibiotics have characteristic molecular targets. Examples of microbial targets include: the cell wall, cell membrane, ribosomes, DNA, RNA, and metabolic enzymatic biochemical pathways<sup>[1]</sup>. Microbes can acquire resistance to specific anti-microbial agents if they develop specific mutations that prevent the antibiotic from acting upon the molecular target.

## The Clinical Scenario

Prescribing Antibiotics:

Given the clinical scenario, this wound would be:

- Cultured- to determine precisely which microbe is responsible)
- Biopsied- to assess histopathology
- Tested for Drug Sensitivity- to determine to which antibiotics the microbe is susceptible or resistant to

Pending these results, decisive and targeted therapy based on drug sensitivities would be selected. The IV route would be the optimal route of delivery, as this is a non trivial skin infection which could be quite capable of becoming a serious, systemic infection.

Recommended Therapy for Infection:

Initial empiric therapy would consist of broad spectrum antibiotic agents to cover a wide variety of possible offending agents. Then, according to UpToDate<sup>[2]</sup>, recommended empiric therapy would consist of:

1. Cefazolin or clindamycin (to cover expected gram positives)
2. Vancomycin (to cover MRSA which would expected clinically due to presence of pus)
3. With or without a fluoroquinolone (to cover gram negatives and pseudomonas which could both be expected due to inoculation of the wound with foreign material.

## Treating Difficult Infections

*Pseudomonas aeruginosa*, like many other bacteria, can be treated with antibiotics. Unfortunately, pseudomonal infections are increasingly resistant to certain antibiotics, and can therefore be more challenging to treat<sup>[3]</sup>. In certain infections, where bacterial resistance is high or the organism is multi-resistant, combination therapy must be used to treat the infection.

What is Combination Therapy?

A type of antibiotic treatment which involves the use of a  $\beta$ -lactam antibiotic, with an aminoglycoside or fluoroquinolone antibiotic<sup>[4]</sup>. This combination of antibiotics has shown to be effective in the treatment of infections with gram-negative bacteria, such as *Pseudomonas*.

Antibiotics and their Mechanisms of Action:

1.  $\beta$ -lactam antibiotics

$\beta$ -lactams, such as antipseudomonal penicillins and cephalosporins, are characterized by their four-membered, nitrogen-containing beta-lactam ring at the core of their structure. This ring is crucial to their mode of action.  $\beta$ -lactam antibiotics target a group of enzymes called 'Penicillin-Binding Proteins' (PBPs)<sup>[5]</sup>. PBPs are found anchored in the cell membrane of the bacterial cell, and are involved in the cross-linking of the bacterial cell wall elements. The beta-lactam ring binds to these different PBPs, and renders them unable to perform their role in cell wall synthesis. Since the bacteria are unable to synthesize their cell walls, osmotic instability or autolysis may occur, leading to death of the bacterial cell<sup>[5]</sup>.

2. Aminoglycoside antibiotics

Aminoglycosides, such as gentamicin and amikacin, work by inhibiting the process of protein synthesis in the bacteria. The antibiotic is able to bind to ribosomes in the bacteria, and prevent them from being able to engage in translation<sup>[6]</sup>. Since protein synthesis is blocked, the bacteria is unable to produce any of the necessary enzymes, receptors, and other biochemical building blocks needed for growth and functioning<sup>[6]</sup>. These protein-inhibiting antibiotics have shown to be

effective when administered in a concentration-dependent manner against certain gram negative anaerobic bacterias, like *Pseudomonas* <sup>[6]</sup>. Another mechanism, used in

### 3. Fluoroquinolones

Ciprofloxacin and ofloxacin are examples of Fluoroquinolones. These antibiotics work by inhibiting bacterial reproduction by disrupting DNA replication. The enzyme DNA gyrase plays a crucial role at the replication fork; it is responsible for relieving strain in the DNA whilst it is being unwound by the helicase enzyme, in preparation for replication! Another enzyme, called topoisomerase IV, also plays a similar role to DNA gyrase during replication, in addition to being responsible for decatenating the DNA once replication is complete<sup>[7]</sup>. This particular group of antibiotics bind the DNA-enzyme complex, to create breaks in the DNA strands. The damage to the bacterial genome, in turn, can lead to bacterial cell death.

The use of the combination of different killing mechanisms allows for better clearance of the infection. In addition to these, other antibiotics such as carbapenams, polymyxins and tigecyclins have been used in the treatment of *Pseudomonas* infections <sup>[3]</sup>.

### Antibiotic Resistance in *Pseudomonas aeruginosa*

Despite the various antibiotic treatment options, resistance is a very real issue in the treatment of *Pseudomonas* infection<sup>[3]</sup>, and a lot of research is being undertaken in order to better understand the mechanisms of resistance. *Pseudomonas* have developed a variety of mechanisms of resistance, thus *Pseudomonas* infections can sometimes be more challenging to treat.

Mechanisms of Resistance:

#### 1. The Cell Wall

One mechanism of resistance is the use of the cell wall as a barrier<sup>[8]</sup>. Most major classes of antibiotics are too large to cross the cell wall of the *Pseudomonas* bacteria, thus must enter via channels<sup>[8]</sup>. This, nonetheless, helps the bacteria stay protected from the antibiotics.

#### 2. Multidrug Efflux Pumps

The bacteria have developed multi drug efflux pumps in their outer membranes, which use active transport to remove ('pump') the antibiotics from the cell<sup>[8]</sup>. Together, with the cell wall, penetration of the antibiotic into the bacteria is very challenging, and makes it difficult for larger antibiotics to be used for treatment.

#### 3. Antibiotic Modification/ Inactivation

Another very interesting mechanism of resistance comes from the *P. aeruginosa*'s ability to inactivate or modify antibiotics. A key example of this comes from the *ampC* gene, for the production of  $\beta$ -lactamase. This gene in the *pseudomonas* codes for an enzyme which is able to break down the core  $\beta$ -lactam ring in the antibiotics, thus inactivating the antibiotic<sup>[8]</sup>.

#### 4. Biofilm formation

Lastly, another mechanism of resistance comes from the bacteria's ability to form biofilms, which help the bacteria establish firm colonies. The *pseudomonas* is thought to use quorum sensing, in order to aggregate and initiate biofilm formation. The core of the biofilms often contain dormant cells, which may be able to reactivate under the correct environmental pressures. This makes the bacteria very difficult to kill and clear from the site<sup>[9]</sup>.

## References

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