C. Narrow spectrum of activity

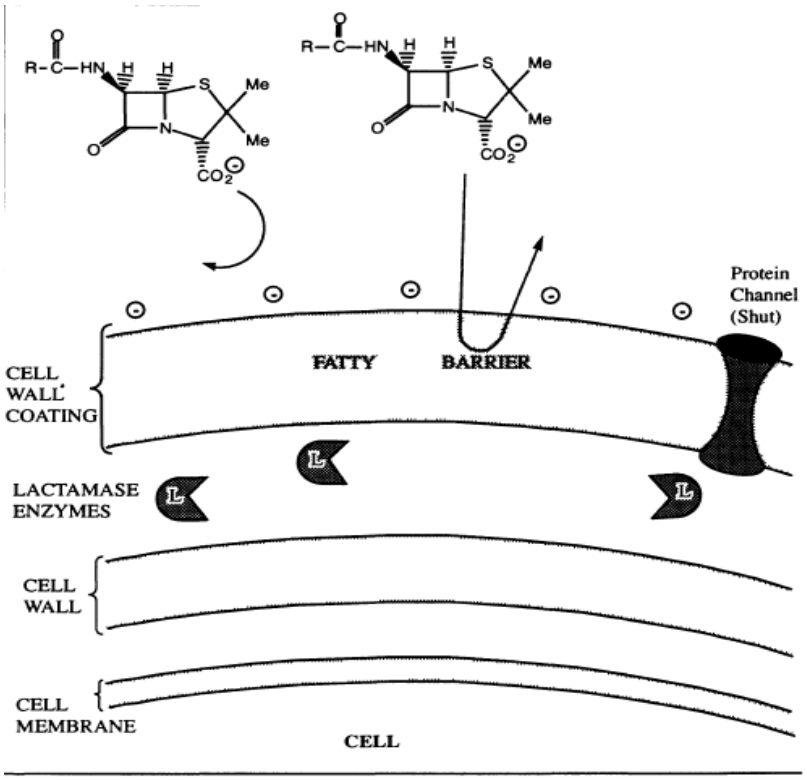
One problem has cropped up in everything described so far; most penicillins show a poor activity against Gram-negative bacteria. There are several reasons for this resistance:

1- Permeability barrier.

The outer surface may have an overall negative or positive charge depending on its constituent **triglycerides**. An excess of **phosphatidylglycerol** would result in an overall **anionic** charge whereas an excess of **lysylphosphatidylglycerol** would result in an overall **cation** charge. Penicillin has a free carboxylic acid which if ionized would be repelled by the former type of cell membrane.

Alternatively, the fatty portion of the coating may act as a barrier to the polar hydrophilic penicillin molecule.

The only way in which penicillin can negotiate such a barrier is through protein. channels in the outer coating. Unfortunately, most of these are usually closed.



Permeability barrier of a Gram-negative bacterial cell.

2- High levels of transpeptidase enzyme produced.

The **transpeptidase** enzyme is the enzyme attacked by penicillin. In some gram negative bacteria, a lot of transpeptidase enzyme is produced, and the penicillin is incapable of inactivating all the enzyme molecules present.

3- Modification of the transpeptidase enzyme.

A mutation may occur which allows the bacterium to produce a transpeptidase enzyme which is not antagonized by penicillin.

4- Presence of β-lactamase.

We have already seen that (β-lactamases) are enzymes which degrade penicillin. They are situated between the cell wall and its outer coating.

5- Transfer of the (β-lactamase enzyme).

Bacteria can transfer small portions of DNA from one cell to another through structures called **plasmids**. These are small pieces of circular bacterial DNA. If the transferred DNA contains the code for the (β-lactamase enzyme), then the recipient cell acquires immunity.

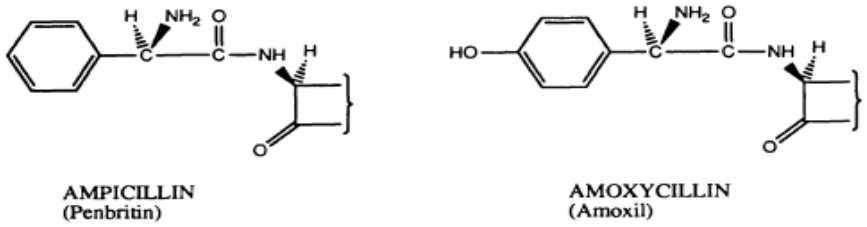
Solving the problem of narrow activity spectrum

Enhancement of Gram-negative activity is found to be greatest **if the hydrophilic group (e.g. NH_2 , OH, CO_2H) is attached to the carbon, alpha to the carbonyl group on the side-chain.**

Those penicillins having useful activity against both Gram-positive and Gram negative bacteria are known as **broad-spectrum antibiotics**. There are two classes of broad-spectrum antibiotics. Both have an **alpha-hydrophilic group**. However, in one class the hydrophilic group is an **amino function** as in **ampicillin** or **amoxicillin**, while in the other the hydrophilic group is an **acid group** as in **carbenicillin**.

Class I broad-spectrum antibiotics—ampicillin and amoxicillin.

Ampicillin is the second most used penicillin in medical practice. Amoxicillin differs merely in having a **phenolic group**. It has similar properties, **but is better absorbed through the gut wall**.



AMPICILLIN (Penbritin)

AMOXYCILLIN (Amoxil)

Class I broad spectrum antibiotics.

Properties:

- Active versus Gram-positive bacteria and against those Gram-negative bacteria which do not produce penicillinase.
- Acid-resistant **due to the NH_2 group**, and is **therefore orally active**.
- Non-toxic.
- Sensitive to penicillinase (no 'shield').
- Inactive against *Pseudomonas aeruginosa* (a particularly resistant species).
- Can cause diarrhea due to poor absorption through the gut wall leading to disruption of gut flora.

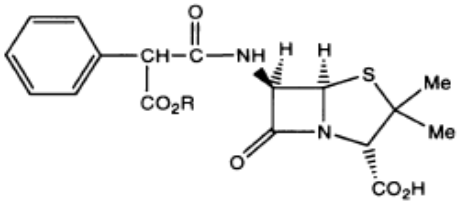
The last problem of poor absorption through the gut wall is due to the dipolar nature of the molecule since it has both a free amino group and a free carboxylic acid function. This problem can be alleviated by using a prodrug where one of the polar groups is masked with a protecting group. This group is removed metabolically once the prodrug has been absorbed through the gut wall.

Class II broad-spectrum antibiotics—carbenicillin

In general, **carbenicillin** is used against penicillin-resistant Gram-negative bacteria. The broad activity against Gram-negative bacteria is **due to the hydrophilic acid group** (ionized at pH 7) **on the side-chain**. It is

particularly interesting to note that the stereochemistry of this group is important. The alpha-carbon is chiral and only one of the two enantiomers is active. This implies that the acid group is involved in some sort of binding interaction with the target enzyme.

Carfecillin is the prodrug for carbenicillin and shows an improved absorption through the gut wall.



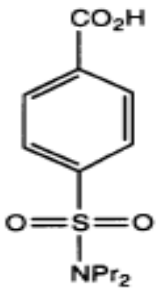
R = H CARBENICILLIN

R = Ph CARFECILLIN

Synergism of penicillins with other drugs

There are several examples in medicinal chemistry where the presence of one drug enhances the activity of another. In many cases this can be dangerous, leading to an effective overdose of the enhanced drug. In some cases it can be useful. There are two interesting examples whereby the activity of penicillin has been enhanced by the presence of another drug.

One of these is the effect of **clavulanic acid**, The other is the administration of penicillins with a compound called **probenecid**. Probenicid slows down the rate at which penicillin is excreted by competing with it in the excretion mechanism. As a result, penicillin levels in the bloodstream are enhanced and the antibacterial activity increases—a useful tactic if faced with a particularly resistant bacterium.



Probenicid.