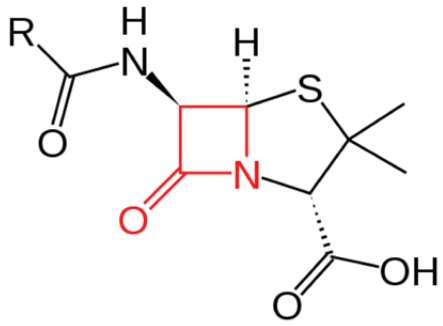
A POSSIBLE WAY TO FIGHT PENICILLIN RESISTANCE

To understand how the antibiotic penicillin works and sometimes fails and how there's hope for a solution, we need to remind ourselves of how bacteria reproduce. The tiny little organisms who constitute separate biological kingdoms make extra copies of themselves through rapid cell division, a growth similar to what our own skin cells use to replace dead ones.

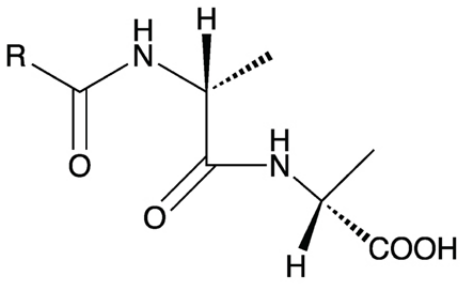
But in order for a bacterium to grow before dividing into two cells, it needs a bigger perimeter in the same manner that one would need more fence if one expanded his yard's boundaries. Bacteria "fences" consist of a cell membrane and cell wall. To build a bigger cell wall requires more of a key cell wall component , a glycoprotein called peptidoglycan and these peptidoglycans have to be linked together. (The only clinically important bacteria that don't use this "brick" are *Mycoplasma pneumoniae*, which can cause atypical pneumonia, and a form of *Chlamydia trachomatis*, which can cause a sexually transmitted disease.)

HOW PENICILLIN WORKS

To bond the" bricks", bacteria use an enzyme which causes a part(D-alanyl-alanine) of one peptidoglycan to a different part of a second peptidoglycan molecule. But penicillin molecules resemble D-alanyl-alanine enough so that they bond strongly to the bacterial enzyme.

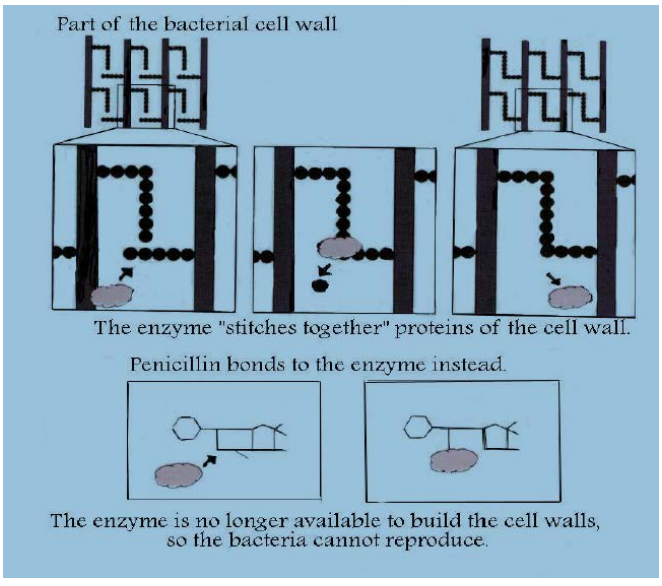


Penicillin



D-Ala-D-Ala

When this happens, it prevents the enzyme from doing its job. (see diagram: From Center for Molecular Modeling). With an incomplete cell wall, water rushes in causing the bacterium cell to explode and die.



RESISTANT BACTERIA

But bacteria can alter themselves through a form of sexual reproduction. Through conjugation they transfer a circular DNA (plasmid) which contain specific genes. One of these genes produces an

enzyme(penicillase), which has the ability to attack and degrade the penicillin molecule. Other bacteria genes can help them expel penicillin or change the enzymes that are vulnerable to penicillin inhibition.

A POSSIBLE SOLUTION

More specifically, it's gram-negative bacteria that produce penicillases known as metallo-β-lactamases such as NDM-1 and VIM. These specifically attack the part of penicillin that would otherwise distract the bacterial enzyme used to build its expanding cell walls. The lactamases are a growing problem , threatening the efficiency of penicillin, cephalosporin and carbapenem antibiotics to treat infections. Are there "retaliatory" substances that in turn attack these lactamases so the penicillin can go undegraded and block the peptidoglycan bonders?

There is hope! June 2014, the journal Nature reported that :

Gerard Wright and colleagues (from Canada's McMaster University) report a screen for naturally produced inhibitors of NDM-1 in an extensive collection of DMSO-dissolved natural product extracts derived from environmental microorganisms. One extract (from A. *versicolor*) exhibited a particularly potent anti-NDM-1 activity and was identified as aspergillomarasmine A (AMA), a natural product first reported some 50 years ago associated with leaf wilting. AMA is a rapid and potent inhibitor of both NDM-1 and VIM-2, and the authors find that AMA fully restores antibiotic efficacy *in vitro* and *in vivo* against bacterial pathogens possessing either VIM- or NDM-type resistance genes. AMA is non-toxic and well tolerated, making it a realistic prospect as an antibiotic adjuvant.

SOURCES:

Principles of Pharmacology
by David E. Golan, Armen H. Tashjian, Jr., Ehrin J. Armstrong, April W. Armstrong

http://cbm.msoe.edu/includes/pdf/smart2007/mwp2007.pdf

Nature.com Volume 510 Issue 7506