SA to PRSA to MRSA to LRSA

Bad news: From MRSA to LRSA

Categories: drug development - infectious disease - resistance
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Via the Journal of the American Medical Association, a report from Spain: the first recorded outbreak, in a Madrid hospital, of *Staphylococcus aureus* resistant to linezolid (Zyvox), one of only a few drugs still available to treat very serious infections of drug-resistant staph, MRSA. This is bad news.

Background: The M in MRSA stands for methicillin, the first of the semi-synthetic penicillins, created by Beecham Laboratories in 1960 in response to a worldwide 1950s outbreak of penicillin-resistant staph. The central feature of the chemical structure of both penicillin and methicillin is an arrangement of four atoms, known as the beta-lactam ring, that governs both drugs' ability to interfere with bacterial cell-wall synthesis. That structure was copied into the formulas of a number of other drug families -- the cephalosporins, carbapenems and monobactams -- and so MRSA is resistant to them as well. And in addition, the bug has picked up resistance to yet other drug families through horizontal transfer; so increasing the census of new drugs that can treat resistant staph infections is a high priority for drug development. It's especially critical for severe infections such as ventilator-associated pneumonia, osteomyelitis, endocarditis and bacteremia, since all the remaining last-resort drugs have challenges from toxicities to ineffectiveness in certain organs.

Linezolid is a relatively new drug, out since 2000 (and, as a downside, still under patent and, according to patients who have been prescribed it, very expensive). It was the first of a
Resistance to Linezolid Is Mediated by the \textit{cfr} Gene in the First Report of an Outbreak of Linezolid-Resistant \textit{Staphylococcus aureus}

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ZYVOX™

linezolid injection
linezolid tablets
linezolid for oral suspension

PHARMACIA

DESCRIPTION

ZYVOX I.V. Injection, ZYVOX Tablets, and ZYVOX for Oral Suspension contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-Fluoro-4-[(4-morpholino)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide.

The empirical formula is C_{16}H_{20}FN_{3}O_{4}. Its molecular weight is 337.35, and its chemical structure is represented below:

![Chemical Structure of Linezolid](image)
http://www.youtube.com/watch?v=JnIULojUhSQ&playnext_from=TL&videos=d9XiJH5WmwU
(a) Hair

A ripe boil

Leukocidin and enzymes lead to pus formation

Apocrine sweat gland

Coagulase leads to fibrin formation, and fibrin walls off infection

(b) A ruptured boil

Escaping pus

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FIGURE 1. Gram stain of *Staphylococcus aureus* in pustular exudate
A Novobiocin-Sensitive strain of *S. aureus*
Penicillium-sensitve S. aureus

Penicillium sp.
A Nitric Oxide–Inducible Lactate Dehydrogenase Enables *Staphylococcus aureus* to Resist Innate Immunity

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*Staphylococcus aureus* is one of the most successful human pathogens, colonizing 2 billion individuals worldwide and causing invasive infections even in immunocompetent hosts. *S. aureus* can evade multiple components of host innate immunity, including the antimicrobial radical nitric oxide (NO•) produced by activated phagocytes. We show that *S. aureus* is capable of metabolically adapting to nitrosative stress by expressing an NO•–inducible L–lactate dehydrogenase (*ldh1, SACOL0222*) divergently transcribed from the NO•–detoxifying flavohemoglobin (*hmp*). L–Lactate production allows *S. aureus* to maintain redox homeostasis during nitrosative stress and is essential for virulence. NO•–inducible lactate dehydrogenase activity and NO• resistance distinguish *S. aureus* from the closely related commensal species *S. epidermidis* and *S. saprophyticus*. 