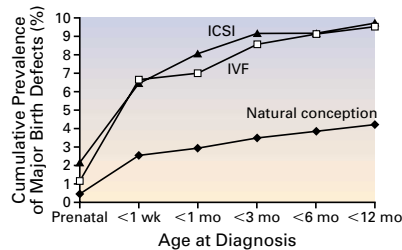




# This Week in the Journal

March 7, 2002



## Birth Defects after Assisted Conception

Intracytoplasmic sperm injection and in vitro fertilization are being used increasingly to treat infertility. It is not known whether infants conceived with these types of technology have a higher risk of birth defects than infants conceived naturally. This study found that infants conceived with intracytoplasmic sperm injection or in vitro fertilization had a risk of a major birth defect diagnosed by one year of age that was twice as high as that in naturally conceived infants. These increased risks persisted after adjustment for potentially confounding factors and did not appear to be attributable to increased surveillance for birth defects among these infants.

*Intracytoplasmic sperm injection and in vitro fertilization are associated with an increased risk of major birth defects, a fact that should be discussed with patients planning to have these procedures.*

see page 725 (editorial, page 769)

*“Singleton infants conceived with assisted reproductive technology were at increased risk for low birth weight.”*

## Low and Very Low Birth Weight in Infants Conceived with Assisted Reproductive Technology

The increased risk of low birth weight among infants conceived with assisted reproductive technology has been attributed in large part to the higher rate of multiple gestations associated with this technology. This study used population-based data to compare the rates of low birth weight in infants from singleton and multiple gestations conceived with this technology with the rates in the general population. Infants conceived with assisted reproductive technology accounted for 0.6 percent of all infants born in the United States to mothers 20 years of age or older in 1997, but they accounted for 3.5 percent of low-birth-weight and 4.3 percent of very-low-birth-weight infants.

*The use of assisted reproductive technology accounts for a disproportionate number of low-birth-weight and very-low-birth-weight infants, mostly because of increases in multiple gestations but also because of increases in the rate of low birth weight among singleton infants.*

see page 731 (editorial, page 769)

## PERSPECTIVE

## Attacking the Pneumococcus — A Hundred Years' War

The battle with pneumococcus over the past century is reminiscent of the Hundred Years' War, the struggle between England and France that was interrupted by truces and stalemates. *Streptococcus pneumoniae* was isolated by Pasteur in 1881 and was soon recognized as the commonest cause of lobar pneumonia. When Dochez and Gillespie divided *S. pneumoniae* into 4 types (there are currently 90) on the basis of capsular antigens, the fatality rate associated with untreated pneumococcal pneumonia was 33 percent. By 1936, the use of type-specific antiserum reduced mortality to about 18 percent.

Sulfonamides were introduced in the 1930s for the treatment of pneumococcal pneumonia. One third of the strains isolated before treatment were resistant to sulfapyridine; strains isolated during treatment were often more resistant. By 1941, sulfadiazine was the drug of choice; mortality was reduced to about 8 percent.

By the mid-1940s, penicillin supplanted prior therapies because of its efficacy, the uniform susceptibility of pneumococcus to it (minimal inhibitory concentration [MIC],  $\leq 0.02 \mu\text{g}$  per milliliter), and the rarity of toxicity. Twenty years later, the MIC of penicillin was  $0.10 \mu\text{g}$  per milliliter or higher for 1 percent of *S. pneumoniae* isolates. A high degree of resistance to penicillin in *S. pneumoniae* emerged in the late 1970s, and worrisome, multidrug-resistant strains then began to appear. In the late 1980s, penicillin resistance in *S. pneumoniae* reached a prevalence of 44 percent in Spain. Resistance soon became worldwide.

Penicillin-binding proteins with decreased affinity for the drug are

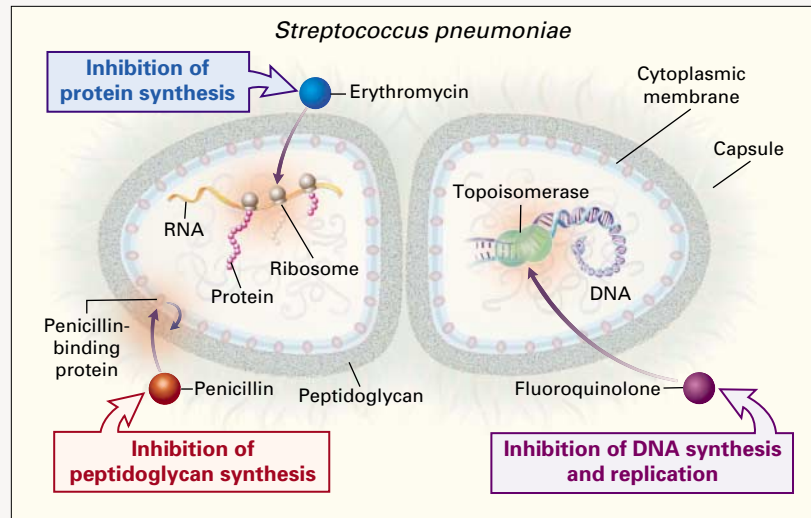


Figure 1. Three Sites of Resistance to Antimicrobials.

responsible for resistance among pneumococci (Fig. 1). The genes encoding the proteins are altered during transformation by heterologous DNA, and the recombinant, penicillin-resistant genes then spread among the pneumococci.

Recommendations for the treatment of community-acquired pneumonia have included the use of newer fluoroquinolones, which are increasingly used as monotherapy. In this issue of the *Journal*, Davidson et al. describe four patients with *S. pneumoniae* pneumonia in whom, not surprisingly, therapy with empirical oral levofloxacin failed because of resistance (see pages 747–50). The resistant isolates bore amino acid substitutions in the *gyrA* and *parC* gene products, which are subunits of topoisomerases.

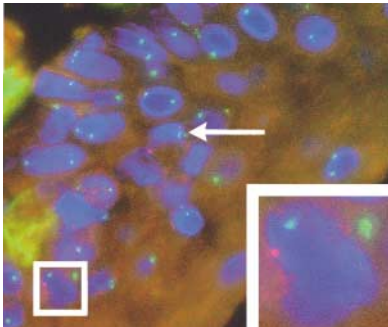
The prevalence of fluoroquinolone resistance among pneumococci remained under 1 percent in the 1990s; that may now be changing. Although routine testing of pneumococci for susceptibility to enhanced-activity fluoroquinolones was previously deemed unnecessary, it now needs to be considered. Caution is particularly warranted in the use of fluoroquinolones for community-acquired pneumonia in patients who have recently received such a drug.

The long battle between pneumococcus and our therapeutic agents provides many lessons. The vast numbers on the bacterial side make possible the appearance of drug-resistant mutants, which under antimicrobial selection emerge in troublesome numbers. This has happened with most bacteria and most antimicrobial agents. It is no surprise that resistance to existing antimicrobial agents has gradually emerged to varying extents among the species, and resistance to drugs of the future is likely. Unnecessary use of antimicrobial agents accelerates the emergence of resistant strains.

How can we counter the advantages of numbers and the genetic plasticity of bacteria? We must recognize that the conflict has no definable end. There is a need for the prudent use of antimicrobial agents aimed at specific bacteria, along with appropriate dosage and duration of therapy. We need to discover new antimicrobial agents that attack novel targets. Finally, immunization of adults against invasive *S. pneumoniae* infections should help reduce drug-resistant pneumococcal infections.

MORTON N. SWARTZ, M.D.

### Hepatocytes and Epithelial Cells of Donor Origin in Recipients of Peripheral-Blood Stem Cells



Male cells were sought in biopsy specimens of liver, skin, and gastrointestinal tract from six women who received a transplant of peripheral-blood stem cells from a brother. In all three types of tissue, small numbers of epithelial cells or hepatocytes containing the Y chromosome were seen. With double staining, cytokeratin (a marker of epithelial cells) and the Y chromosome appeared to be present in the same cell.

*These studies add to the evidence that stem cells can differentiate into multiple lineages. The results must be viewed in the light of the difficulty of ensuring that the sex-marked cells were not simply donor lymphocytes. Mindful of this caveat, the authors argue persuasively that blood contains such versatile cells.*

see page 738 (editorial, page 770)

*“Recent exposure to a fluoroquinolone should be a contraindication to the use of another fluoroquinolone for the empirical treatment of community-acquired pneumonia.”*

### Levofloxacin Resistance in Pneumococcal Pneumonia

This report describes four patients with pneumococcal pneumonia in whom empirical treatment with levofloxacin failed. In these patients, the isolates of *Streptococcus pneumoniae* were resistant to levofloxacin, and in two of them the resistance appeared to have been acquired during the current course of treatment with fluoroquinolones.

*These case reports are cause for concern because fluoroquinolones such as levofloxacin are now being used in some patients for the empirical treatment of community-acquired pneumonia. Currently, fluoroquinolone-susceptibility testing of pneumococci is not routinely performed. Routine susceptibility testing may be needed, however.*

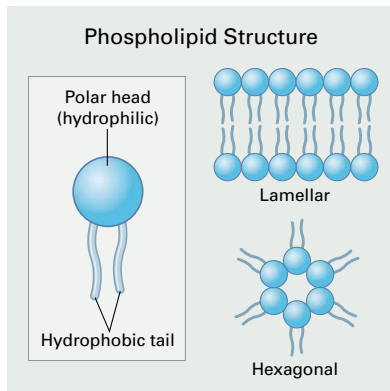
see page 747 (Perspective, page 722)



### Images in Clinical Medicine: Massive Air Embolism in a Neonate with Pulmonary Hypoplasia

At birth this baby girl was found to have left pneumohydrothorax and marked pulmonary hypoplasia that was treated with mechanical ventilation. After continued deterioration, she received high-frequency oscillatory ventilation. Her intraarterial pressure wave form dampened, and surgical exploration revealed air, but no blood, in the carotid artery.

see page 751



### Medical Progress: The Antiphospholipid Syndrome

The antiphospholipid syndrome is an autoimmune disorder of hypercoagulability characterized by the presence of autoantibodies to various phospholipids or phospholipid-binding proteins. The autoantibodies include anticardiolipin antibodies, lupus anticoagulant antibodies, and antibodies to  $\beta_2$ -glycoprotein I (a phospholipid-binding protein). These autoantibodies have both procoagulant and anticoagulant effects, but the procoagulant effects predominate, resulting in syndromes of venous and arterial thrombosis and pregnancy loss.

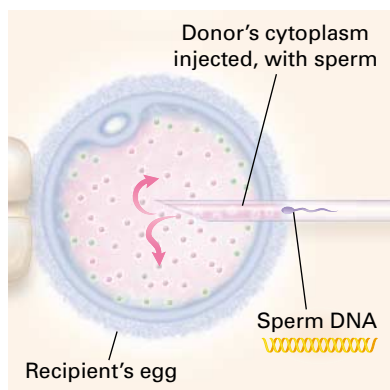
see page 752



### Clinical Problem-Solving: Where Are You From?

A 52-year-old man with human immunodeficiency virus infection who had emigrated from Guyana 15 years earlier presents with fever. He has a long history of anemia and thrombocytopenia but no history of opportunistic infections.

see page 764



### Sounding Board: Ooplasmic Transfer

Ooplasmic transfer is a novel approach to the treatment of infertility due to recurrent failure of oocyte implantation after in vitro fertilization. To restore oocyte viability, ooplasm from a normal donor is removed with a micropipette and injected into an oocyte from the infertile woman. The resulting oocyte, which is fertilized by intracytoplasmic sperm injection, contains mitochondrial DNA from both women. The author discusses the potential benefits and risks, as well as the ethical aspects, of this new approach to the treatment of infertility.

see page 773