5

Current Macrolide Antibiotics and Their Mechanisms of Action

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5.1 Introduction

Macrolide antibiotics are characterized by a large macrocyclic lactone ring to which one or more deoxy sugars (usually cladinose and desosamine) are attached. More than 2000 macrolides have been isolated from a variety of natural sources as diverse as actinobacteria, fungi, plants, insects, and vertebrates (Ōmura 2002). Nearly all of the macrolide antibiotics used today are chemical derivatives of naturally occurring macrolides, especially erythromycin that is derived from the actinobacteria now known as *Saccharopolyspora erythraea* (Labeda 1987). Clinically relevant macrolide antibiotics fall into the category of 14-, 15-, or 16-membered lactone ring macrolides, while those with other antimicrobial and immunosuppressive activities may have more varied ring structures. The prototypical erythromycin has a 14-membered lactone ring as seen in Figure 5.1.

Erythromycin, the first macrolide antibiotic, was discovered in 1952 (McGuire et al. 1952). Erythromycin is a mixture of related compounds, erythromycins A, B, C, and D, with erythromycin A the primary active compound. Most modern macrolides are second-generation macrolides and are derived from erythromycin A, including clarithromycin, dirithromycin, roxithromycin, and azithromycin, among others. Other macrolides are available for use in humans outside of the United States (spiramycin, josamycin, midecamycin, and miocamycin) or are used exclusively in animals (including tylosin, ivermectin, and kitasamycin, among many others).

By modifying the structure of erythromycin A, pharmacokinetics and tolerance were improved, resulting in the second-generation macrolides. Derivatives of second-generation macrolides are characterized as third-generation

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