Beta-lactam antibiotics

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Constantin Cojocel passed away in 2007. This chapter was updated by the editors. The editors wish to dedicate this chapter to his memory.

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Introduction

The large family of β-lactams comprises penicillins, cephalosporins, cephamycins, monobactams, carbacephems and carbapenems and are so named since they all containing the β-lactam moiety.

Penicillin was the first β-lactam antibiotic and was discovered in 1928 by Sir Alexander Fleming at St. Mary’s Hospital, London [1]. The β-lactam chemical structure for penicillin was first proposed by Abraham and Chain in 1943 and finally established in 1945 by X-ray crystallographic analysis. In the same year, Giuseppe Brotzu, a Sardinian professor of bacteriology, isolated Cephalosporium acremonium from the sea near a sewage outfall at Cagliari, which produced antibiotic material with a broad spectrum of activity. It was almost eight years later in 1953 when Newton and Abraham, while studying the production of antibiotics by Brotzu’s Cephalosporium, that they discovered a penicillin-like substance providing resistance to hydrolysis by penicillinases which was named cephalosporin C.

By 1959, Rolinson and coworkers completed the isolation of the penicillin nucleus, 6-aminopenicillanic acid, (Figure 1) in quantity. At about the same time the β-lactam-dihydrothiazine structure for the cephalosporin C was proposed [2] and confirmed subsequently by X-ray crystallographic analysis. In 1962, Morin and coworkers established a chemical method for the production of 7-aminocephalosporanic acid (Figure 1) from cephalosporin C in quantity. These developments opened the way to the preparation of a large number of semi-synthetic cephalosporins with hopes of being used as therapeutic agents. Cephalothin was prepared in 1962 and was the first semi-synthetic cephalosporin to find extensive clinical use in the 1960s. Cephalothin was followed by cephaloridine, in which the acetoxy group at C-3’ of cephalothin was replaced by a pyridinium group (Figure 2). These cephalosporins were followed by four generation of cephalosporins that are now categorized based on their spectrum of activity.

Figure 1. Core structure of penicillins, cephalosporins, carbapenems and monobactams.

Figure 2. Various side chains attached to the β-lactam nucleus, which are involved in renal toxicity.