Natural penicillins (penicillin G and penicillin V) have activity against (Miller 2002; Bush and Bradford 2016):

- Non-beta-lactamase-producing Gram-positive cocci, including *viridans* streptococci, group A streptococci, *S. pneumoniae*, enterococci, *S. aureus*, coagulase-negative staphylococci, and anaerobic streptococci (*Peptostreptococcus*, *Peptococcus* spp.).
- Gram-positive bacilli such as *Listeria monocytogenes, Erysipelothrix rhusiopathiae, and Bacillus anthracis*.
- Gram-negative cocci such as *Neisseria meningitidis* and non-penicillinase producing *Neisseria gonorrhoeae* strains.
- *Treponema pallidum* and many other spirochetes.
- Anaerobic organisms such as *Clostridium* spp. (excluding *Clostridium difficile*), *Actinomyces* spp., and non-beta-lactamase-producing Gram-negative rods.

3.3.1.2 Semisynthetic Penicillins

Semisynthetic penicillins are prepared by using 6-APA as starting block and adding side chain to the 6-amino group.

3.3.1.2.1 Penicillinase-Resistant Penicillins

The addition of an isoxazolyl side chain to the 6-amino group of the penicillin compound protects the beta-lactam ring from hydrolysis by penicillinases produced by staphylococci. However, the agents in this group, also known as antistaphylococcal penicillins, showed lower activity against streptococci than natural penicillins and a null activity against enterococci. Anaerobic activity ranges from minimal to none and Gram-negative activity is virtually nonexistent (Miller 2002; Bush and Bradford 2016). Methicillin, oxacillin, and cloxacillin are included in this group.

3.3.1.2.2 Aminopenicillins

Aminopenicillins (ampicillin and amoxicillin) were developed by adding an amino group to benzylpenicillin. This modification improved coverage against Gram-negative organisms, whereas the spectrum of activity against Gram-positive organisms remained similar to that of the natural penicillins.

These agents showed activity against streptococci and had slightly greater activity against *Enterococcus* spp. and *L. monocytogenes* than the natural penicillins. Among Gram-negative bacilli, these drugs showed activity against *Haemophilus influenzae*, *Escherichia coli*, *Proteus mirabilis*, *Salmonella* spp., and *Shigella* spp. However, the side chain added did not inhibit hydrolysis by staphylococcal penicillinases or Gram-negative beta-lactamases (Bush and Bradford 2016).