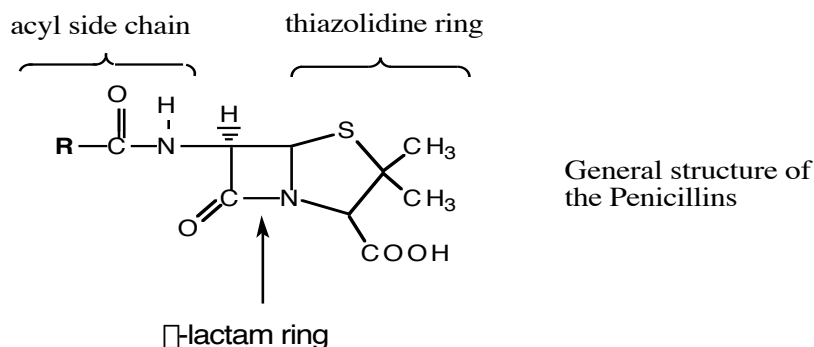


# The Penicillins

## I. CHEMISTRY AND MECHANISM OF ACTION



### Structural Features of Penicillins:

- $\beta$ -lactam antibiotics composed of a dipeptide of cysteine and valine. Intact  $\beta$ -lactam ring is essential for activity.
- Variation of the side chain - improved activity vs. Gm - bacteria compared to Penicillin G (see Table 10 for structures)
  - Aminopenicillins – enhance Gm - bacteria
  - penicillinase-resistant penicillins (bulky side chains in nafcillin & oxacillin)
  - carboxy penicillins (ticarcillin) – activity vs. Enterobacteriaceae and *Pseudomonas*
  - ureido penicillins (piperacillin) – broad spectrum penicillins (esp. *Pseudomonas*)
- Penicillin is produced by *Penicillium chrysogenum*. Alteration of the culture medium by feeding precursors, phenylacetic acid for Penicillin G or phenoxyacetic acid for Penicillin V is used for large scale production.
- Other penicillins are produced semi-synthetically.

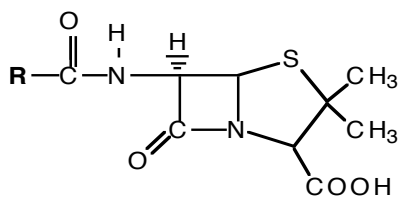
### Mechanism of Action

- Penicillins are dipeptide analogs of D-ala-D-ala.
- Radiolabelled Penicillin G binds to several different proteins in the cell wall of bacteria (Table 1).
- Bactericidal action is primarily due to inhibition of PBPs 1a & 1b and PBP3 that function as transpeptidases in the biosynthesis of the peptidoglycan.
- Inhibition is result of acylation of the enzyme by attack of serine on the  $\beta$ -lactam ring

**Table 9. Penicillin Binding Proteins (PBPs) of *E. coli***

Penicillin Binding Protein	% of total $^3\text{H}$ -penicillin G Bound	Protein Function
1a 1b	8	transpeptidases (inhibition is lethal)
2	0.7	maintenance of rod shape
3	2	septum formation
4	4	D-alanine carboxypeptidase (non-lethal inhibition)
5	65	
6	2	

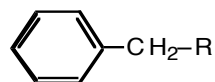
Table 10. Structure of Representative Penicillins



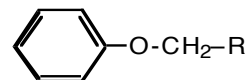
Penicillin

Side Chain

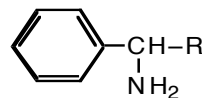
Penicillin G



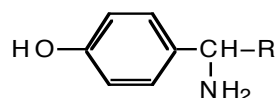
Penicillin V



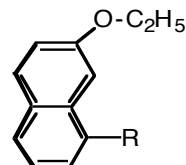
Ampicillin



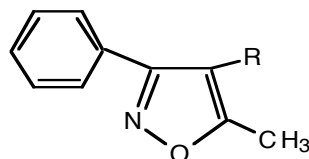
Amoxicillin



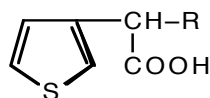
Nafcillin



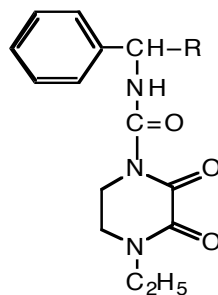
Oxacillin



Ticarcillin



Piperacillin



## II. CLASSIFICATION OF THE PENICILLINS

**Table 11. Classification, Route of Administration, and Trade Names of Penicillins**

Type and Generic Name	Route of Administration	Trade Names
<b>Natural Penicillins</b>		
Penicillin G (benzylpenicillin)	IV, PO	Pentids, Pfizerpen
Penicillin G procaine	IM	Wycillin, Duracillin
Penicillin G benzathine	IM	Bicillin L-A, Permapen
Penicillin V (phenoxymethyl penicillin)	PO	Pen-Vee K, Veetids
<b>Penicillinase-Resistant Penicillins</b>		
Methicillin	IV, IM	Staphcillin
Oxacillin	IV, IM, PO	Bactocill, Prostaphlin
Nafcillin	IV, IM, PO	Unipen, Nafcil,
Cloxacillin	PO	Tegopen, Cloxapen
Dicloxacillin	PO	Dynapen, Dycill
<b>Extended-Spectrum Penicillins (Aminopenicillins)</b>		
Ampicillin	IV, IM, PO	Omnipen, Polycillin
Amoxicillin	PO	Amoxil, Trimox, Wymox
Bacampacillin	PO	Spectrobid
<b>Broad-Spectrum Penicillins (Anti-Pseudomonal Penicillins)</b>		
<i>Carboxypenicillins</i>		
Carbenicillin indanyl	PO	Geocillin
Ticarcillin	IV	Ticar
<i>Ureidopenicillins</i>		
Piperacillin	IV	Pipracil
<b><math>\beta</math>-Lactamase Combinations</b>		
Amoxicillin-clavulanic acid	PO	Augmentin
Ampicillin-sulbactam	IV	Unasyn
Ticarcillin-clavulanic acid	IV	Timentin
Piperacillin-Tazobactam	IV	Zosyn

### III. MECHANISMS OF RESISTANCE

#### A. INACTIVATION BY ENZYMES ( $\beta$ -LACTAMASES)

1. Gram positive bacteria secrete  $\beta$ -lactamases outside of cell wall
2. Gram negative bacteria -  $\beta$ -lactamases are present in periplasmic space
3. Over 30 different  $\beta$ -lactamases are known. TEM-1 is most common & has the broadest spectrum (includes cephalosporins). TEM-1 is common in Enterobacteriaceae, *Ps. aeruginosa*, *H. influenzae*, and *N. gonorrhoeae*. SHV-1 & K1 found in *Klebsiella*

Table 12. Classification of  $\beta$ -Lactamases

Organism	Richmond-Sykes Class	Representative Enzymes	Preferred Substrates	DNA Locus	Gene Expression
<i>Ps. aeruginosa</i> <i>Enterobacter</i> sp. <i>Citrobacter</i> sp. <i>Serratia</i> sp.	I		Cephalosporins	Chromosomal	Inducible
<i>Proteus</i> sp.	II		Penicillins	Chromosomal	Constitutive
Enterobacteriaceae <i>H. influenzae</i> <i>Klebsiella</i> sp.	III	TEM-1 TEM-2 SHV-1	Penicillins & Cephalosporins	Plasmid	Constitutive
<i>Klebsiella</i> sp.	IV	K-1	Penicillins & Cephalosporins	Chromosomal	Constitutive
Enterobacteriaceae <i>Ps. aeruginosa</i>	V	OXA 1-7 PSE 1-4	Penicillins	Plasmid	Constitutive
<i>Staph. aureus</i>		PC-1	Penicillins	Plasmid	Inducible
<i>Bacteroides fragilis</i>	resembles I		Cephalosporins	Plasmid & Chromosomal	Constitutive
<i>B. melaninogenicus</i>	resembles V		Penicillins	Unknown	Constitutive

Another classification scheme for  $\beta$ -lactamases has been developed by K. Bush (K. Bush, G.A. Jacoby, A.A. Madeiros, *Antimicrobial Agents and Chemother.* 1211-1233, 1995) based on the substrate activity. This new scheme is being more widely used than the older Richmond-Sykes classification.

Table 13. Bush, Jacoby, Madeiros Classification of  $\beta$ -Lactamases

Group	Characteristics	Typical Enzymes	Organism
1	Cephalosporin-hydrolyzing $\beta$ -lactamases not inhibited by clavulanic acid	P99 ampC S&A	<i>E. cloacae</i> <i>E. coli</i> <i>Ps. aeruginosa</i>
2a	Penicillin-hydrolyzing $\beta$ -lactamases inhibited by clavulanic acid	PC1 569	<i>Staph. aureus</i> <i>B. cereus</i>
2b	Broad spectrum $\beta$ -lactamases inhibited by clavulanic acid	TEM-1 & 2  SHV-1 ROB-1	Enterobacteriaceae & <i>H. influenzae</i> Enterobacteriaceae <i>H. influenzae</i>
2b'	Extended-broad spectrum $\beta$ -lactamases inhibited by clavulanic acid	TEM-3 SHV-2 K1	Enterobacteriaceae Enterobacteriaceae <i>Klebsiella oxytoca</i>
2c	<i>Carbenicillin-hydrolyzing <math>\beta</math>-lactamases inhibited by clavulanic acid</i>	<i>PSE-1,3, &amp;4</i> <i>CARB-3 &amp; 4</i> <i>BRO-1 &amp; 2</i> <i>AER-1</i>	<i>Ps. aeruginosa</i> <i>Ps. aeruginosa</i> <i>Moraxella caryophyllata</i> <i>Aeromonas sp.</i>
2d	Cloxacillin-hydrolyzing $\beta$ -lactamases inhibited by clavulanic acid	OXA-1 PSE-2	Enterobacteriaceae <i>Ps. aeruginosa</i>
2e	Cephalosporin-hydrolyzing $\beta$ -lactamases inhibited by clavulanic acid	L2 SC10950	<i>Stenotroph. maltophilia</i> <i>Proteus vulgaris</i>
2f	Carpapenemase inhibited by clavulanic acid	IMP-1 (C) Sme-1 (C)	<i>Ps. Aeruginosa</i> <i>Serratia mercersceus</i>
3	Metallo- $\beta$ -lactamases	L1 CcrA	<i>Stenotroph. maltophilia</i> <i>B. fragilis</i>
4	Penicillin-hydrolyzing $\beta$ -lactamases not inhibited by clavulanic acid	249 G-237 LCR-1	<i>Ps. cepacia</i> <i>B. fragilis</i>

Adapted from Mandell, Bennett, and Dolin (eds.), *Mandell, Douglas & Bennett's Principles and Practice of Infectious Diseases*, 4th ed., Churchill Livingstone, New York, 1994, p. 215.

## B. ALTERED PERMEABILITY TO PENICILLINS

1. Resistance due to alterations in porins in Gm – outer membrane.  
Mechanism for resistance to broad-spectrum penicillins.

## C. ALTERED PENICILLIN BINDING PROTEINS

1. Operative mechanism for resistance in staphylococci to penicillinase-resistant penicillins and increasing resistance to penicillin G observed in *Strep. pneumoniae*.  
MecA gene in Staphylococci produce penicillin-binding protein (PBP) 2a with reduced affinity for  $\beta$ -lactams.

## IV. SPECTRUM & USES

### A. PENICILLIN G AND PEN VK SPECTRUM

1. *Strep. pneumoniae*, *Strep. pyogenes*, Group B Strep., viridans group Strep., however penicillin-resistant strains of *Strep. pneumoniae* are emerging (as high as 60% in endemic areas). If MIC < 0.1 µg/ml - Pen G or V is DOC.
2. *Staphylococcus aureus* (non-penicillinase producing strains)
3. *Enterococcus faecalis*, *E. faecium* (in combination with aminoglycosides)
4. *Neisseria meningitidis*
5. *Treponema pallidum* (syphilis)
6. *Listeria monocytogenes*
7. *Corynebacterium diphtheriae*
8. Anaerobes - *Clostridium perfringens* & *C. tetani* (not *C. difficile*), *Bacteroides fragilis* (non-penicillinase producing strains), *Fusobacterium*, *Peptostreptococcus*

**Table 14. Comparison of MIC Values between Penicillin G and Penicillin V (for non-penicillinase producing strains)**

Organism	MIC for Pen G (µg/ml)	MIC for Pen V (µg/ml)
<i>Staph. aureus</i>	0.03	0.03
<i>Strep. pyogenes</i>	0.007	0.015
<i>Strep. pneumoniae</i>	0.015	0.03
<i>Enterococcus faecalis</i>	2.0	4.0
<i>E. coli</i>	64.0	128.0
<i>Salmonella typhi</i>	4.0	64.0
<i>Neisseria gonorrhoeae</i>	0.007	0.03
<i>N. meningitidis</i>	0.03	0.25
<i>Haemophilus influenzae</i>	1.0	4.0

#### Acid Stability

Pen G is very labile in acid (half-life = 5 min at pH 2, 37°C) compared to Pen V (half-life = 5h at pH 1). Consequently, Pen V should be used when oral penicillin is indicated.

## B. USES FOR PENICILLIN G AND PENICILLIN V

1. **Streptococcal Infections** - Pen G is the most potent compound of all the penicillins and cephalosporins for susceptible Gram + bacteria. Pen V is normally used for oral administration (more acid stable). Resistance is looming as a major problem.
  - a. Strep throat & scarlet fever - *Strep. pyogenes* is generally sensitive
  - b. Streptococcal skin and soft tissue infections (Erysipelas & cellulitis) caused by *Strep pyogenes*,
  - c. Pneumonia & Meningitis due to *Strep. pneumoniae*
    - Intermediate resistance (0.1-1.0  $\mu\text{g/mL}$ ) ~20-30% of all strains
    - Resistant ( $\geq 2.0$   $\mu\text{g/mL}$ ) ~15% of community strains
    - Pen G is DOC for *Strep. pneumoniae* after sensitivity testing. High doses will cover most intermediate-resistant strains.
  - d. Endocarditis due to *Strep. viridans* & *Enterococcus sp.*
    - Enterococcal endocarditis (Pen G in combination with Aminoglycosides)
    - Group B Strep., Viridans group Streptococci - usually sensitive to Pen G alone
  - e. Anaerobic streptococcal infections & *Peptostreptococcus*
2. **Gram positive rods** - *Clostridia* (anaerobic infections) & *Bacillus sp.*
  - a. Tetanus
  - b. Gas gangrene
  - c. Anthrax
3. **Meningococcal Infections** – *Neisseria* (Gram – cocci)
  - Meningitis due to *N. meningitidis* - usually sensitive to high dose Pen G
  - Meningococemia – overwhelming sepsis
4. **Syphilis**
  - Primary syphilis –single dose of Benzathine Penicillin G as *Treponema pallidum* is exquisitely sensitive to low concentrations.
  - Secondary syphilis – Procaine Pen G
  - Neurosyphilis - high dose Pen G (continuous infusion)
5. **Prophylaxis for scarlet fever** - recent local epidemics of scarlet fever (Group A streptococci) have occurred in U.S. – Benzathine Pen G

## C. SPECTRUM and USES OF PENICILLINASE-RESISTANT PENICILLINS

### 1. Staphylococcal Infections

- Spectrum similar to Pen G, but includes *Staph. aureus* & *Staph. epidermidis*.
- Community-acquired Methicillin-resistant forms of *Staph aureus* (MRSA) are infrequent but increasing.
- 50-80% of *S. epidermidis* in hospitals is methicillin-resistant, but *Staph. epi* . is not as invasive or virulent.
- Staphylococci cause skin infections (impetigo), abscesses in many organs, pneumonias, prosthetic joint, catheter, and artificial valve infections, endocarditis, meningitis (rare), & bone infections (osteomyelitis). Osteomyelitis may require months of therapy.

2. Streptococcal infections (use when Staph. is also a possibility) – almost as active as Pen V.

## D. SPECTRUM OF AMINO-PENICILLINS (Amoxicillin & Ampicillin)

1. Have similar Gram + spectrum to Penicillin V & K (slightly less active)
2. *E. coli*, *Proteus mirabilis* - especially for UTIs (however 25-50% make  $\beta$ -lactamase)
3. *Haemophilus influenzae* - resistance is common (30-40%) & *Neisseria sp.*, *Listeria*
4. *Shigella* & *Salmonella* - usually treat with ampicillin for GI infections (resistance is over 50% for Shigella in U.S.)

**Table 15. MIC Values ( $\mu\text{g/ml}$ ) of Extended-Spectrum Penicillins vs. Gm – Bacteria**

Organism	Ampicillin Amoxicillin	Carbenicillin Ticarcillin	Piperacillin
<i>Escherichia coli</i>	3	6	8
<i>Proteus mirabilis</i>	3	1.5	1
<i>Klebsiella sp.</i>	200	>400	16
<i>Enterobacter spp.</i>	>500	50	16
<i>Citrobacter diversus</i>	>100	12	8
<i>Citrobacter freundii</i>	50	12	32
<i>Serratia</i>	>500	100	32
<i>Salmonella</i>	1.5	3	4
<i>Shigella</i>	1.5	3	8
<i>Proteus vulgaris</i>	>500	12	16
<i>Providencia</i>	>500	12	8
<i>Morganella</i>	200	25	8
<i>Pseudomonas aeruginosa</i>	>500	50	16
<i>Acinetobacter</i>	250	25	32
<i>Pseudomonas, other</i>	>500	100	>100

## E. USES OF AMINO-PENICILLINS

**Note: Amoxicillin is the number one antibiotic sold in U.S.**

1. Otitis Media - still drug of choice.
  - *Strep. pneumoniae* resistance is increasing. Vaccine should reduce incidence of invasive infections but may not be effective vs. all otitis media strains.
  - *Haemophilus* type b infections are rapidly decreasing due to vaccination, but vaccine is directed against capsular antigens. *Haemophilus* sp. that cause otitis media are not encapsulated, vaccine is not effective. 40-50% are penicillinase +
  - *Moraxella catarrhalis* strains are  $\beta$ -lactamase positive and are resistant.
2. Bronchitis/Pneumonia – may be used, but resistance is a problem.
3. Enterococcal endocarditis (ampicillin or PenG + aminoglycoside is DOC)
4. Meningitis – Ampicillin - alternative choice to 2nd gen. cephalosporins (+ chloramphenicol).
  - Infant meningitis – Ampicillin covers *Strep. pneumoniae*, *N. meningitidis*, *H. influenzae*
  - Neonatal meningitis - group B *Strep.*, *Listeria*, & *E. coli*. (the most common causative organisms)
  - Some strains of *Strep. pneumoniae*, *H. influenzae* & *E. coli* are resistant. DOC for *Listeria* (in combo with gentamicin). Note: cephs are not active vs. *Listeria*
5. Urinary Tract Infections - Covers three most common organisms *E. coli*, *Proteus mirabilis*, & *Staph. Saprophyticus* but resistance is common in *E. coli*
6. Prophylaxis for bacterial endocarditis - 2 gm 1 h prior to dental procedures - DOC
7. Lyme Disease (*Borrelia burgdorferi*) and Erlichiosis (*Erlichia chaffeinsis*) - alternate to doxycycline (1 g amoxicillin + 0.5 g probenecid q 8 h)
8. Alternate for susceptible strains of *N. gonorrhoeae* (3.5 g oral ampicillin or amoxicillin + 1 g probenecid.)

## G. SPECTRUM OF BROAD-SPECTRUM PENICILLINS

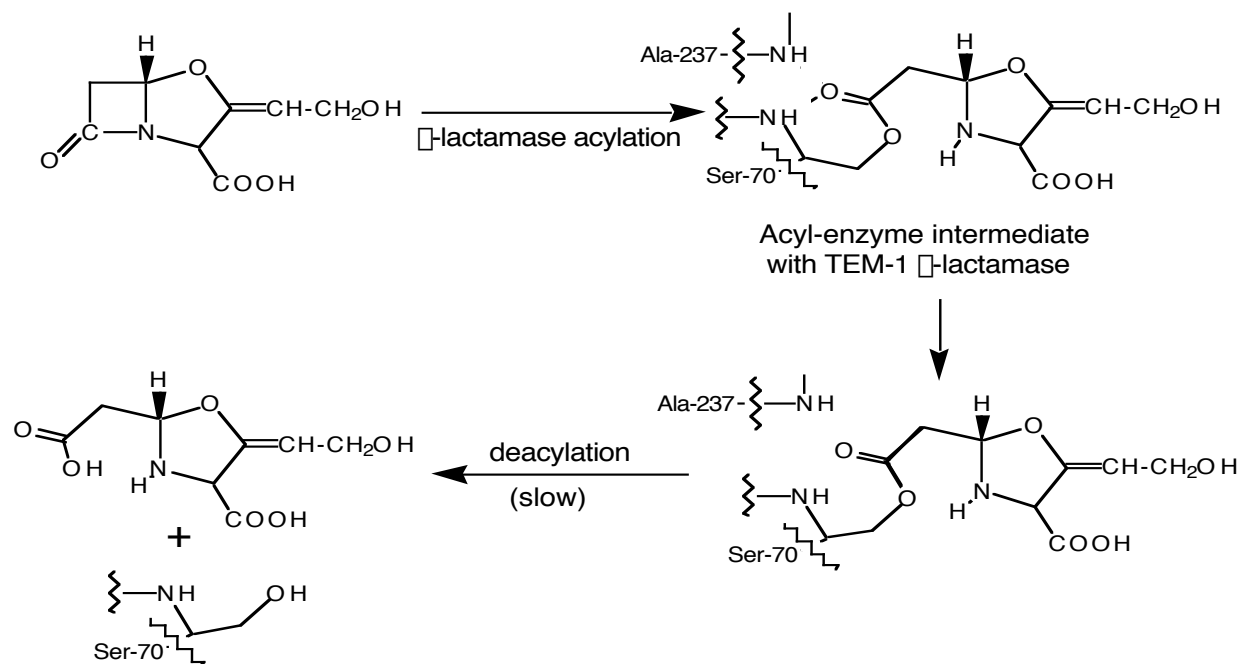
1. *Pseudomonas aeruginosa* - Ticarcillin 2-4 x better than carbenicillin (rarely used). Piperacillin 4-8x more potent, but more expensive.
2. Enterobacteriaceae (see Table 15) - activity is generally OK for urinary tract infections (typical MIC values are 2-16  $\mu\text{g/ml}$ ). Piperacillin has activity vs. *Klebsiella*. Piperacillin generally more potent against other Gm - bacteria.

## H. USES OF BROAD-SPECTRUM (ANTIPSEUDOMONAL) PENICILLINS

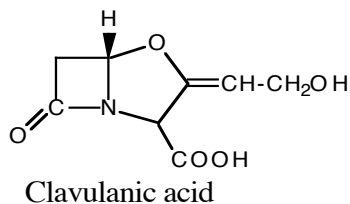
1. *Pseudomonas aeruginosa* infections (often with aminoglycosides)
2. Mixed infections - good gram negative activity, covers most *B. fragilis*
3. Complicated urinary tract infections & prostatitis - Carbenicillin indanyl OK orally.
4. Surgical prophylaxis - intra-abdominal, gynecologic surgery

## I. PENICILLINS IN COMBINATION WITH $\beta$ -LACTAMASE INHIBITORS

The  $\beta$ -lactamase inhibitors that are commercially available are clavulanic acid, sulbactam, and tazobactam. These compounds act as suicide inhibitors of the  $\beta$ -lactamases. Unlike the penicillins and cephalosporins which are released from the enzyme site after opening of the  $\beta$ -lactam ring, these compounds are very slowly released after attack of the enzyme resulting in irreversible inhibition of the enzyme, i.e. the enzyme remains acylated. This protects the penicillins from degradation and expands the utility of these drugs.



1. Amoxicillin + clavulanic acid (**Augmentin**<sup>®</sup> - Glaxo-SK)

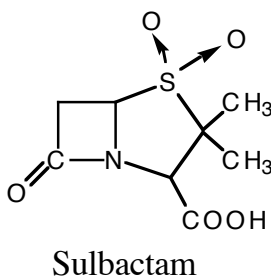


- Clavulanic acid extends spectrum to  $\beta$ -lactamase-producing organisms. Inhibits PC-1  $\beta$ -lactamase of *Staph.aureus* and of anaerobic *Bacteroides sp.*
- Extended spectrum towards gram negative bacteria. Activity towards Richmond-Sykes Class II, III, IV, and V  $\beta$ -lactamases. Some Gm –  $\beta$ -lactamases are not inhibited (Richmond-Sykes Type I).
- Clavulanic acid has some weak antibacterial activity itself. Binds to PBP-2. Combination with amoxicillin is synergistic for *Klebsiella sp.*

Indications for Augmentin<sup>®</sup> are as follows:

- Otitis media, sinusitis, and respiratory tract infections (acute exacerbations of bronchitis or chronic obstructive pulmonary disease, COPD) due to  $\beta$ -lactamase producing *H. influenzae* & *Moraxella catarrhalis*.
- High strength formulation (Augmentin ES – 90 mg/kg) recently approved for otitis media due to *Strep. pneumoniae*
- Skin and Skin-structure infections caused by  $\beta$ -lactamase-producing strains of *Staph. aureus*, *E. coli*, and *Klebsiella sp.*
- UTIs due to  $\beta$ -lactamase-producing strains of *E. coli*, *Enterobacter sp.*, and *Klebsiella sp.*

2. Ampicillin + Sulbactam (**Unasyn**<sup>®</sup>-Roerig)



- Similar to Augmentin<sup>®</sup>, but Unasyn<sup>®</sup> available for IV use.
- Sulbactam similar to clavulanic acid. Slightly more active against cephalosporinases. Less active toward TEM-2 of Enterobacteriaceae.

Indications for Unasyn<sup>®</sup> are:

- Skin & soft tissue infections due to  $\beta$ -lactamase-producing strains of *Staph. aureus*, *E. coli*, and *Klebsiella sp.*, *Proteus mirabilis*, *Bacteroides fragilis*, *Enterobacter sp.*, and *Acinetobacter calcoeticus*.

- ii. Intra-abdominal infections due to  $\beta$ -lactamase-producing strains of *E. coli*, *Klebsiella sp.*, *Enterobacter sp.*, and *Bacteroides fragilis*.
  - iii. Gynecologic infections caused by  $\beta$ -lactamase-producing strains of *E. coli* and *Bacteroides fragilis*.
  - iv. Useful in combination with aminoglycosides for treatment of endocarditis caused by *Enterococcus sp.* and Group D *Strep*.
3. Ticarcillin + clavulanic acid (**Timentin®** - Glaxo-SK)
- a. Extends spectrum towards  $\beta$ -lactamase-producing Enterobacteriaceae & *Pseudomonas*. For *Pseudomonas* infections, often combined with aminoglycosides. Indications are as follows:
    - i. Septicemia due to  $\beta$ -lactamase-producing strains of *Klebsiella sp.*, *E. coli*, *Staph. aureus*, & *Ps. aeruginosa*
    - ii. Lower respiratory tract infections due to  $\beta$ -lactamase-producing strains of *Klebsiella pneumoniae*, *S. aureus*, *H. influenzae*, & *Moraxella catarrhalis*
    - iii. Bone & joint infections due to  $\beta$ -lactamase-producing *Staph. aureus*.
    - iv. UTIs (complicated & uncomplicated) due to  $\beta$ -lactamase-producing strains of *E. coli*, *Klebsiella*, *Ps aeruginosa*, *Citrobacter sp.*, *Enterobacter sp.*, *Serratia marcescens*, & *Staph.*
    - v. Gynecologic infections: endometritis due to  $\beta$ -lactamase-producing strains of *Prevotella* (formerly *Bacteroides*) *melaninogenica*, *Enterobacter sp.*, *E. coli*, *Klebsiella pneumoniae*, *S. aureus*, and *Staph. epidermidis*.
    - vi. Treatment of mixed infections and for presumptive therapy prior to identification of the causative organisms.
4. Piperacillin + tazobactam (**Zosyn®** - Aventis)
- a. Extended spectrum. Indications are as follows:
    - i. Appendicitis or peritonitis caused by  $\beta$ -lactamase-producing *E. coli* or *Bacteroides fragilis*
    - ii. Uncomplicated & complicated skin and skin structure infections caused by piperacillin-resistant  $\beta$ -lactamase-producing *Staph. aureus*
    - iii. Post-partum endometritis or pelvic inflammatory disease caused by piperacillin-resistant  $\beta$ -lactamase-producing strains of *E. coli*
    - iv. Community-acquired pneumonia (moderate severity only) caused by piperacillin-resistant  $\beta$ -lactamase-producing strains of *H. influenzae*

## V. ABSORPTION, DISPOSITION, AND METABOLISM

**TABLE 16. PHARMACOKINETIC PROPERTIES OF THE PENICILLINS**

Penicillin (Dose)	% Oral Absorp.	Food <input type="checkbox"/> Absorp.	% Protein bound	% Metab.	Total Conc. ( $\mu\text{g/ml}$ )	Free Conc. ( $\mu\text{g/ml}$ )	t <sub>1/2</sub> (hrs) normal	t <sub>1/2</sub> (hrs) renal imp
Pen G	30	Yes	55	20	2	0.9	0.5	10
Pen V	60	No	80	55	4	0.8	1.0	4
Methicillin	Nil		35	10			0.5	4
Oxacillin (0.5 g po)	30	Yes	93	45	6	0.4	0.5	1
Cloxacillin (0.5 g po)	50	Yes	94	20	10	0.6	0.5	1
Dicloxacillin(0.5 g po)	50	Yes	97	10	15	0.45	0.5	1.5
Nafcillin (1g)	Erratic	Yes	87		1.2	0.16	0.5	1.5
Ampicillin (0.5g po)	40	Yes	17	10	3.5	2.9	0.5	1.5
Amoxicillin (0.5g po)	75	No	17	10	7.5	6.2	1	8
Bacampicillin (0.8g)	95	No	17	10	12.9	10.7	0.5	1
Carbenicillin indanyl	30	No	50	2	15	7.5	1.1	15
Ticarcillin (3 g)	Nil		50	15	190	85	1.2	15
Piperacillin (2g IV)	Nil		30		300	150	1.3	4
Clavulanic acid (0.125 g po)	90	No	25	55-75	3.3			
Sulbactam (0.5g IV)	Some		38	10	13	7.8	1	4
Tazobactam	Nil							
Temocillin	Nil		85	10			4	17

Adapted from Mandell, Douglas, & Bennett, *Principles and Practice of Infectious Diseases, 3rd ed.*, Churchill Livingstone, New York, 1990.

1. All penicillins have short half-lives (0.5-2 h) and must be given 3-4 times per day.
2. Penetration into CSF - very low when meninges are not inflamed. Penicillins with highest CSF penetration are ampicillin (mean 35% of serum, range 2-100%), ticarcillin (mean = 9.5% and 40% in 2 different studies), and piperacillin - (mean = 23% and 32% in 2 studies). Penicillinase-resistant penicillins (methicillin & nafcillin) show very poor penetration.

## V. ADVERSE EFFECTS

**TABLE 17. ADVERSE REACTIONS ASSOCIATED WITH PENICILLINS**

<i>Type of Reaction</i>	<i>Frequency (%)</i>	<i>Occurs most frequently with:</i>
<b>Allergic</b>		
Anaphylaxis (IgE mediated) Early urticaria (<72 h)	0.004-0.4	Penicillin G
Hemolytic anemia due to cytotoxic antibodies	Rare	Penicillin G (high dose)
Serum sickness (Ag-Ab complex disease)	Rare	Penicillin G Amoxicillin
Delayed hypersensitivity Contact dermatitis	4-8	Ampicillin
<b>Idiopathic reactions</b>		
Maculopapular skin rash Fever Late onset urticaria	4-10	Ampicillin Amoxicillin
<b>Gastrointestinal</b>		
Diarrhea	2-5	Ampicillin
Enterocolitis	<1	Ampicillin
<b>Hematologic</b>		
Hemolytic anemia	Rare	Penicillin G
Neutropenia	1-4	Penicillin G, Oxacillin, Piperacillin
Platelet dysfunction	3	Carbenicillin
<b>Hepatic</b>		
Elevated SGOT level	1-4	Oxacillin, Nafcillin Carbenicillin
<b>Electrolyte Disturbances</b>		
Sodium overload	Variable	Carbenicillin, Pen G (Na) Ticarcillin, Piperacillin
Hypokalemia	Variable	Piperacillin, Ticarcillin
Hyperkalemia (acute)	Rare	Pen G, K salt
<b>Neurologic</b>		
Seizures	Rare	Penicillin G
Bizarre sensations	Rare	Procaine Penicillin G
<b>Renal</b>		
Interstitial nephritis	1-2	Methicillin
Hemorrhagic cystitis	Rare	Methicillin

Adapted from *Mandell, Douglas, & Bennett's Principles and Practice of Infectious Diseases, 4th ed.*, Mandell GL, Bennet JE, and Dolin R (eds.), Churchill Livingstone, New York, 1995, p. 239

### A. Rashes and Anaphylactic shock

1. Severe and potentially life-threatening anaphylaxis - should have epinephrine on hand if unsure. Rate is 4-15 per 100,000 courses of penicillin.
2. Caused by formation of hapten-protein complex. Anaphylaxis and rashes usually occur after an initial exposure. Skin testing is important tool to identify penicillin-allergic patients.
3. "Ampicillin rash" - idiopathic reaction resulting in a maculopapular, late-developing rash. This is not a true penicillin allergy. May go away with continued treatment. May not occur again with repeated dosing. Incidence is less with amoxicillin

## B. Seizures

1. Seizures may be precipitated if penicillins are infused intravenously at high doses too quickly. Should administer slowly over at least 10-15 minutes.

## VI. DRUG INTERACTIONS

**TABLE 17. DRUG INTERACTIONS OF THE PENICILLINS**

Precipitating drug	Object drug	Effect	Description
Parenteral penicillins	Aminoglycosides	☐	Incompatibility. Penicillins and AGs form insoluble complex. Do not mix together in IVs. May occur <i>in vivo</i> .
Parenteral penicillins	Anticoagulants Heparin	↑	Large IV doses increase prothrombin time.
Penicillins	Oral contraceptives	☐	Interruption of steroid enterohepatic recycling. Results in ineffectiveness and breakthrough bleeding.
Penicillins, oral	Atenolol	☐	Decreased absorption of atenolol with ampicillin.
Allopurinol	Amoxicillin	↑	Rate of ampicillin rash appears to be much higher with co-administration of allopurinol
Bacteriostatic antibiotics e.g Tetracycline, Macrolides, Chloramp.	Penicillins	☐	Decreased effect of penicillins. Penicillins require growing cell wall to have an effect.

## VII. PRODUCTS and DOSAGES

### **Penicillin G Potassium** (250 mg = 400,000 units)

Oral tablets - 200,000 units, 250,000 units, 400,000 units, 500,000 units, 800,000 units  
Powder for oral solution - 400,000 units per 5 ml when reconstituted (Pentids® 400, Apothecon)  
Powder for Injection - 1,000,000 units, 5,000,000 units, 10,000,000 units, 20,000,000 units

### **Procaine Penicillin G (intramuscular)**

Injection vials - 300,000 units/ml and 500,000 units/ml in 10 or 12 ml vials (Crysticillin®, Apothecon)  
Unit dose injections - 600,000 units and 1,200,000 units in 1 and 2 ml Tubex (Wycillin®, Wyeth)  
Syringes - 2,400,000 units per 4 ml disposable syringe (Wycillin®, Wyeth-Ayerst)

For Gonorrhea: 4.8 million units (2.4 million) in each buttock + 1 g oral probenidic  
For primary, secondary, and latent Syphilis: 600,000 units daily for 8 days  
For Neurosyphilis: 2-4 million units per day plus 500 mg probenidic q 6 h for 10-14 days.  
For Neonatal (congenital syphilis) - 50,000 units/kg

### **Benzathine Penicillin G (intramuscular)**

Injection: 300,000 units per ml in 10 ml vials (Bicillin L-A®, Wyeth-Ayerst)  
Unit dose: 600,000 units, 1,200,000 units in 1 and 2 ml Tubex, (Bicillin L-A®, Wyeth-Ayerst)  
Syringes: 1,200,000 units in 2 ml syringe (Permapen®, Roerig), 2,400,000 units in 4 ml syringe (Bicillin L-A®, Wyeth-Ayerst)

For rheumatic fever prophylaxis: 1.2 million units as single dose in adults every 4 weeks  
For syphilis: 2.4 million units IM in single dose  
For syphilis of >1 yr duration: 2.4 million units IM every week for 3 weeks.

### **Penicillin G Benzathine and Procaine Combined**

Injection: 300,000 units, 600,000 units, 1.2 million units, or 2.4 million units per dose containing 1:1 mixture of procaine and benzathine penicillin G. (Bicillin® C-R, Wyeth-Ayerst)  
Injection: 900,000 units benzathine penicillin + 300,000 units procaine penicillin G (Bicillin® C-R 900/300, Wyeth-Ayerst)

For Groups A,C,G, H, L, M streptococcal infections: 2.4 million units for adults  
For pneumococcal infections (except meningitis): 1.2 million units for adults, 600,000 for children.  
Note: resistance in *Strep. pneumonia* is rising. No longer indicated for empiric therapy.

### **Penicillin V Potassium**

Tablets: 125, 250, and 500 mg (Pen-Vee K® - Wyeth-Ayerst; V-Cillin K® - Lilly; Veetids® - Apothecon; Beepen VK® - Glaxo SK)  
Powder for Oral Solution: 125 mg per 5 ml and 250 mg per 5 ml when reconstituted

Adults: 250-500 mg q 6 h. Children: 25-50 mg/kg/day in divided doses q 6 h

### **Nafcillin sodium**

Capsules: 250 mg (Unipen® - Wyeth-Ayerst)  
Powder for Injection: 500 mg, 1g, 2 g in vials, piggyback vials, & ADD-Vantage vials. 10g in bulk vials. (Unipen® - Wyeth-Ayerst, Nafcil® - Apothecon, Nallpen® - Glaxo SK)

IV doses, adults: 3-6 g per 24 h. IM dose, adults: 500 mg q 4-6 h. Oral dose, adults: 250-500mg q 6h  
Infants and children: 25mg/kg twice daily, IM or 50 mg/kg/day in 4 divided doses orally.

### **Oxacillin sodium**

Capsules: 250 and 500 mg (Bactocill®-Glaxo SK, Prostaphlin®-Apothecon)  
Powder for Oral solution: 250 mg/5ml when reconstituted.  
Powder for Injection: 250 mg, 500 mg, 1 g, 2 g, 4 g in vials, piggyback vials, and ADD-Vantage vials. (Bactocill®-Glaxo SK, Prostaphlin®-Apothecon). 10g in bulk vials.

## **Oxacillin sodium**

Oral doses: 500 mg-1 g q 4-6 h for at least 5 days.

IV doses, adults:  $\geq 1$  g q 4-6 h for severe infections up to 12 g/day

## **Cloxacillin sodium**

Capsules: 250 and 500 mg (Cloxapen®-Glaxo SK)

Powder for Oral solution: 125 mg/5ml when reconstituted.

Adults: 250 mg q 6 h for mild to moderate infections.  $\geq 500$  mg q 6h for severe infections.

Children 50 mg/kg/day in divided doses q 6 h.

## **Dicloxacillin sodium**

Capsules: 250 and 500 mg (Dycill®-Glaxo SK, Dynapen®-Apothecon)

Powder for Oral solution: 62.5 mg/5ml when reconstituted. (Dynapen®-Apothecon)

Adults: 250 mg q 6 h for mild to moderate infections.  $\geq 250$  mg q 6h for severe infections.

Children: 25 mg/kg/day in divided doses q 6 h.

## **Ampicillin**

Capsules: 250 mg and 500 mg either as trihydrate or anhydrous. (Omnipen®-Wyeth-Ayerst, , Totacillin® - Glaxo SK, Principen® - Apothecon)

Powder for Injection: 125 mg, 250 mg, 500 mg, 1g, 2 g in vials, piggyback and ADD-Vantage vials. (Omnipen-N®-Wyeth-Ayerst, Polycillin-N® - Apothecon, Totacillin-N® - Glaxo SK) as sodium salt (contains 3 mEq Na/ g).

Adults: 1-12 g daily in divided doses every 4-6 hours

Children: 50-200 mg/kg/day in divided doses q 6 h

*Prevention of bacterial endocarditis:* 2 g IM or IV 30 minutes before dental procedure.

## **Ampicillin sodium plus Sulbactam sodium**

Powder for Injection: 1.5 g (1 g ampicillin + 0.5 g sulbactam) or 3 g (2 g ampicillin + 1 g sulbactam) in vials, bottles, and Add-Vantage vials (Unasyn® - Pfizer).

May be reconstituted in sterile water for injection, 0.9% NaCl, or 5% dextrose however it is less stable in 5% dextrose than in normal saline.

Adults: 1.5-3 g q 6 hours. Do not exceed more than 4 g/day of sulbactam.

Not indicated for children  $\leq 12$  years old.

## **Amoxicillin**

Capsules: 250 mg and 500 mg as trihydrate (Amoxil® - Glaxo SK, Wymox® - Wyeth-Ayerst, Polymox® & Trimox® - Apothecon)

Chewable tablets: 125 mg and 250 mg (Amoxil® - Glaxo SK)

Powder for Oral Suspension: 125 mg per 5 ml and 250 mg per 5 ml when reconstituted.

(Amoxil® - Glaxo SK, Wymox® - Wyeth-Ayerst, Polymox® & Trimox® - Apothecon)

### Amoxicillin Dosing:

*For URIs, otitis, UTIs, and skin & soft tissue infections:*

Adults: 250-500 mg q 8 hours Children: 20-40 mg/kg/day in divided doses q 8 h.

*Gonococcal infections:* 3 g single dose plus 1 g probenidic followed by doxycycline

*Prevention of bacterial endocarditis:* 2 g 1 hour before procedure.

*For Genetourinary or GI procedures:* 3 g 1 hour before procedure, then 1.5 g 6 hours after initial dose.

*For Chlamydia trachomatis in pregnancy:* 500 mg q 8 h for 7 days.

### **Amoxicillin and Potassium Clavulanate** (Augmentin® - Glaxo SK)

Tablets: 250 mg amoxicillin + 125 mg clavulanate; 500 mg amox. + 125 mg clavulanate;  
875 mg amoxicillin + 125 mg clavulanate

Chewable Tablets: 125 mg amox/31.25 mg clav. (lemon-lime); 200mg amox/28.5 mg clav. (cherry-banana); 250 mg amox./62.5 mg clav. (lemon-lime); 400 mg amox./57 mg clav. (cherry-banana).

Powder for oral suspension: 125 mg amox + 31.25 mg clav. per 5 ml when reconstituted (banana flavor); 200 mg amox. + 28.5 mg clav. per 5 ml (orange-raspberry flavor); 250 mg amox. + 62.5 mg clav. per 5 ml. (orange flavor); 400 mg amox. + 57 mg clav. per 5 ml (orange-raspberry flavor).

Augmentin ES (Approved 2001 by Glaxo SK to provide 90mg amox/6.4 mg clav per kg per d) - Powder for oral suspension: 600 mg amox. + 42.9 mg clav. per 5 ml

**Note: chewable tablet cannot be substituted with regular tab**

Augmentin dosing (based on amoxicillin content):

Adults: One 250 mg tablet every 8 hours or one 500 mg tablet q 12h.

*Severe infections and respiratory tract infections:* One 875 mg tablet q 12h or one 500 mg tablet q 8h

To minimize GI effects, should take at the start of meals.

Children  $\leq$ 40 kg: usually 20 mg/kg/day.

*Otitis media, sinusitis, lower respiratory infections and severe infections in children:* 80-100 mg/kg/d

### **Carbenicillin indanyl sodium**

Film-coated tablets: 382 mg carbenicillin (Geocillin® - Pfizer)

Urinary tract infections: 1 or 2 tabs QID

Prostatitis: 2 tabs QID

### **Ticarcillin disodium** (Ticar® - Glaxo SK)

Powder for injection: 1g, 3g, 6g, 20 g, and 30 g in vials. 3g in piggyback and ADD-Vantage vials. (Ticar® - SK-Beecham)

For systemic infections: 200-300 mg/kg/day by IV infusion in divided doses every 3, 4, or 6 h

For UTIs: 100-200 mg/kg/day every 4 to 6 hours. For uncomplicated infections in adults 1gm IM or IV every 6 hours.

### **Ticarcillin and Clavulanate potassium** (Timentin® - Glaxo SK)

Powder for injection: 3g ticarcillin + 0.1g clavulanate in vials, piggyback bottles and ADD-Vantage vials.

Also available in 31g bulk vials. Contains 4.75 mEq of sodium/g.

Reconstitute in Sodium chloride injection, 5% dextrose injection, or Lactated Ringer's.

Solution: 3g ticarcillin + 0.1g clavulanate in 100 ml premixed, frozen vials. Contains 18.7 mEq sodium per 100ml

Adult dose: 3.1 g every 4 hours (reduce dose and give less frequently if renally impaired)

### **Piperacillin sodium** (Pipracil® - Aventis)

Powder for injection: 2 g, 3 g, 4 g in vials, infusion bottles, and ADD-Vantage vials. 40g in bulk vials

Severe infections: 12-18 g/day IV in divided doses every 4-6 hours

UTIs: 8-16 g/day IV in divided doses every 6 to 8 hours

Surgical prophylaxis: 2 g IV just prior to surgery, 2 g in surgery, 2 g q 6h post-op up to 24 hours

### **Piperacillin sodium plus Tazobactam sodium** (Zosyn® - Aventis)

Powder for injection: 2 g piperacillin/0.25 g tazobactam, 3 g piperacillin/0.375 g tazobactam, and 4 g piperacillin/0.5 g tazobactam in vials.

Adult dose: 12 g piperacillin/1.5 g tazobactam in divided doses of 3.375 g every six hours (adjust dose in patients with renal dysfunction)