STUDY GUIDE
THE BETA-LACTAM ANTIBIOTICS: PENICILLINS INTRODUCTION

1. How is the penicillin beta-lactam ring numbered? Why are penicillins and related antibiotics referred to as “beta lactams”?

2. Which amino acids compose the 6-APA ring system of penicillins. How does biosynthesis determine stereochemistry and why is stereochemistry an important determinant of antibacterial activity?

3. What are the "semi-synthetic" penicillins and what is their source?

4. Identify the various contributions the overall ring structure (bicycle), and beta lactam, 6-acylamino substituent and 3-acidic group make toward overall activity.

5. Why are the penicillins acidic and what is their pKa range? How is penicillin acidity taken advantage of in drug product formulation (water soluble and insoluble salts)? How does penicillin acidity influence elimination profile and mechanism of elimination?

6. Why is the beta-lactam carbonyl of the penicillins more reactive toward nucleophiles than a "typical" amide carbonyl?

7. Why may the beta lactam ring open in the presence acid (know the mechanism)? What role does the 6-acylamino side chain play in this process? What is the mechanism of beta lactam ring opening in the presence of base and nucleophiles?

8. What is the general role of beta-lactam ring reactivity in terms of drug stability, administration, drug action, drug resistance and drug allergy?

9. How does the 6-acylamino side chain contribute to penicillin acid stability or instability? What other factors does this group influence?

10. How are aqueous formulations of penicillins protected from decomposition reactions?

11. What are the primary lethal targets for the penicillins (and other beta-lactams)? What are PSEs and PBPs? Which are essential and non-essential PBPs?

12. What general role do the PBPs play in bacterial cell viability? What are the specific roles of the PBPs transpeptidase, transglycosylase, carboxypeptidase and endopeptidase?

13. Why are the penicillins capable of inhibiting transpeptidase? What is the chemical mechanism and how does structure dictate activity? Do all penicillins have equal or comparable affinities for all PBPs?
14. What is the primary bacterial barrier for penicillins in gram positive bacteria? Gram negative bacteria? By what mechanisms can a penicillin reach its target site of action within gram negative bacteria? Which is more important for most penicillins?

15. What are the optimal structural features for penicillin diffusion through porin channels? Do all penicillins diffuse through the porin channels of all bacteria equally well?

16. What are the major mechanisms (3) of resistance to the penicillin and other beta-lactam antibiotics? What mechanism is observed most commonly for the broad spectrum of bacteria?

17. Which reaction does a beta-lactamase catalyze and what is the significance of this reaction? List the primary properties of staphylococcal (gram positive) beta-lactamases. Generally how do beta-lactamases produced by gram negative bacteria compare to those produced by staphylococci?

18. What is the genetic origin of the beta-lactamases? How do beta-lactamases differ? You do not need to memorize Table 3. It is for your information only and represents only one classification scheme (see Resistance chapter for more details).

19. What are the primary factors (3) that will determine the net impact of beta-lactamases on penicillins relative to their clinical use?

20. What are methicillin-resistant staphylococci (MRSA)? What are MRSE? Why are they resistant to penicillins and how is this resistance transferred? What is the relationship between methicillin-resistance and beta-lactamase resistance?

21. By what mechanism do some bacteria reduce entry of the penicillins? Name several bacterial strains that have acquired resistance by this mechanism.

22. What are the major pharmacodynamic properties that define the actions of the penicillins. Know what each of these terms mean and their significance.

23. Identify each penicillin by class as listed in Table 4.

24. You should know the antibacterial spectrum for each product and class of pencillins and the relationship between penicillin structure and activity as defined below. These properties are described in the text and Tables 5 and 6:

   a. How does the structure of each penicillin of each class differ from benzyl penicillin (Pen G)? Is stereochemistry important for activity? What are the acid/base properties of each class? Does lipophilicity play a role in activity (isoxazoles)?
   b. Which organisms are each penicillin class effective against and what is the role of structure in efficacy?
   c. Which organisms are each penicillin class not very effective against and what is the role of structure in lack of efficacy?
25. What are the major beta-lactamase inhibitor combinations and how beta-lactamase inhibitors extend the spectrum of the penicillins in combination?

26. Know the mechanism by which the beta-lactamase inhibitors function as “suicide inhibitors”.

27. What are the keys to an effective beta-lactam/beta-lactamase inhibitor combination?

28. Are the beta-lactamase inhibitors effective against all beta-lactamases?

29. Do the beta-lactamase inhibitors possess clinically significant antibacterial activity?

30. Table 7 compares some of the key kinetics parameters of most of the penicillin products. You will not be asked to learn any specific “numbers” (%oral bioavailability, %ppb, %GF or %TS, %metabolism), but you should know the relative trends (i.e. higher or lower bioavailability than Pen G, more or less ppb, more or less TS, etc) the chemical/structural rationale for the differences. You should know:

a. Dosage forms:
   - What salt forms are available and how they are administered (oral, injection)?
   - What prodrug forms are available (ampicillin), why were they designed, what are their chemical and disposition properties (higher blood levels)? Also which enzymes or other conditions are responsible for the conversion prodrug forms to the parent drug?
   - Why are the various dosage forms used (i.e. hyperkalemia, increased duration, etc)?
   - What are the chemical properties of penicillin solutions (i.e. methicillin) and how should they be stored?

b. Oral Bioavailability:
   - Which penicillins are orally effective and which are not?
   - What is the oral bioavailability and what factors (acid instability, decarboxylation, lipophilicity, dissolution, etc.) influence bioavailability?
   - Compare all penicillins to Pen G and Ampicillin with respect to acid stability and know the reasons for the differences.
   - Other than drug structure, what factors influence oral bioavailability (food, age, drugs)

c. Distribution:
   - What is the general tissue distribution profile (good, moderate or poor)? Which are distributed into the CSF and when (inflammation)?
   - What is percent protein binding for pencillin? What is the role of the 6-acylamino group in ppb (lipophilicity, the presence of acidic or basic moieties)? Compare each penicillin to Pen G and know why they are more or less ppb.
   - What role does ppb play in half-life? In tissue distribution and antibacterial activity?

d. Metabolism and Elimination:
   - What is the major route of elimination for each penicillin (renal, hepatic)
   - What is the relative contribution of GF or TS to elimination for each penicillin and why?
• What role does probenecid play in elimination? What role does probenecid play in transport out of the CNS?
• For each penicillin is dose reduction required in renally impaired patients? Why?
• Which penicillins are significantly metabolized (compared to Pen G)? Which isoxazole is most extensively metabolized?
• What are the half-lives for the individual penicillins relative to Pen G and why?

31. Which penicillins require dosage adjustment in renally impaired patients? Which penicillins are dialyzable?

32. Which penicillins have prolonged half-life in severe hepatic impairment? Is dose adjustment required?

33. Describe the two types of penicillin-induced hypersensitivity reactions. What is the incidence of these? What tests are available to determine hypersensitivity?

34. What are the chemical mechanism(s) of hypersensitivity?

35. Why might ampicillin be most frequently implicated in CDAD?

36. What are the relationships between penicillin elimination, penicillin CSF levels, meningeal inflammation, uremia and probenecid relative to penicillin-associated convulsions?

37. What is the relationship between penicillin reactivity, serum sickness and nephropathy?

38. Explain the relationships between “hyperkalemia”, hypopkalemia” and the penicillins.

39. Why is hepatotoxicity observed more commonly with methicillin and nafcillin than other penicillins?

40. Why are platelet aggregation and electrolyte disorders observed more commonly with the carboxypenicillins than other penicillins?

41. What are the major pharmacokinetic and pharmacodynamic drug interactions observed upon coadministration of the penicillins and aminoglycosides, anticoagulants, beta-blockers, probenecid, oral contraceptives, cyclosporine, lithium, methotrexate, neuromuscular blockers and rifampin.
The general structures of the major penicillin classes are shown below. Copies of this sheet can be used to make **summary comparisons** of important differences/similarities between the penicillins including structure, spectrum of activity, susceptibility to beta-lactamases, key pharmacokinetic properties, etc.

- **Aminopenicillin**
- **Carboxypenicillin**
- **Acyllureides**
- **Methicillin**
- **Nafcillin**
- **Isoxazolyls**
- **Penicillin G**
- **Penicillin V**