STUDY GUIDE:

THE CEPHALOSPORINS AND CEPHAMYCINS

1. How does the cephalosporin and cephamycin ring system differ from that of the penicillins? What is the difference between a cephalosporin and a cephamycin? Why is this important?

2. What is the source of most cephalosporins used in therapy today?

3. What is the difference between a cephem and cepham ring? Be able to number this ring. What are the three key reactive groups present in many cephalosporins/cephamycins? Which of these groups are required for antibacterial activity?

4. Compare the reactivity of the beta-lactam of a cephalosporin to a penicillin. Why is there a difference in reactivity?

5. What is a cephalosporanic acid? What is the significance of the 3-acetoxymethyl group (metabolic and chemical reactivity and its influence on activity and use)?

6. Given a cephalosporanic acid, show and name the decomposition products formed by metabolic/hydrolytic reactions on the 3-acetoxymethyl group.

7. Show the product formed from chemical and metabolic hydrolysis of the 7-acylamino side chain. How important is this reaction clinically?

8. What is the mechanism by which cephalosporins kill bacterial cells? How does this compare to the penicillins in mechanism and PBP affinity?

9. What are the major mechanisms of resistance to the cephalosporins (list three)? How do these compare to the penicillins?

10. How do they cephalosporins compare, generally, to the penicillins in terms of beta-lactamase inactivation (more or less)? Are all cephalosporins similarly susceptible to beta-lactamase inactivation?

11. How has the structure of the cephalosporins been modified to yield beta-lactamase resistant derivatives? How does this differ from the penicillins? (You need not memorize Table 1).

12. Which cephalosporins/cephamycins induce beta-lactamases?

13. Be able to identify each cephalosporin as a first, second, third or fourth generation agent (Table 2).
14. In terms of general antibacterial spectra of activity, which bacteria are resistant to all cephalosporins? How does antibacterial vary from 1st to 2nd to 3rd generation?

15. Know the sub-classification of first generation agents (oral versus parenteral) and the chemical rationale for this difference (the 3 substituent). How do the oral agents compare with ampicillin in structure and stereochemistry? Why are they orally effective? Why are the others NOT orally effective?

16. What is the general spectrum of activity of the first generation agents? Which gram positive organisms? Are they effective against gram negative organisms? Why is Cefazolin often the first generation cephalosporin of choice?

17. Know the sub-classification of second generation agents. What roles do various 7-side chain substituents play in the enhanced activity in this generation? Which members of this class may induce beta-lactamase production?

18. Identify other key functionality that contributes significantly toward the overall therapeutic profile of the second generation agents. Which are acid stable? Metabolically stable? Prodrugs? Stereochemistry?

19. Compare the second generation agents to the first generation agents in terms of their activity toward S. aureus, and gram negative organisms in general. Which are effective against B. fragilis and what structural feature do they share?

20. Know the sub-classification of third generation agents. Why is moxalactam NOT a cephalosporin and how does it compare to carbenicillin? How does cefoperazone compare to the acylureide penicillins in structure and action? Are they beta-lactamase resistant?

21. What is a “N-methyl-thiotetrazole” moiety and what is it’s significance?

22. How are all of the other third generation cephalosporins structurally related? How are they different? Why are they beta-lactamase resistant?

23. Compare the antibacterial spectrum of the third generation agents to the first and second (general gram positive and gram negative). Which are active against Pseudomonas?

24. Which cephalosporin has been classified as a “fourth” generation agent? How does it’s structure compare to the third generation agents?

25. Generally how does the antibacterial spectrum of cefepime compare to the other cephalosporins and why is it “extended”??
26. **For ALL cephalosporins and cephameycins be sure you identify if the 3-substituent is chemically (acid) unstable, metabolically (esterase) unstable or both. You should be able to classify them all as orally active or orally inactive, and know why!**

27. Know which cephalosporins/cephamycins are orally active or which are not and why. Focus on the nature of the 3- and 7-substituents. Know which substituents are chemically and/or metabolically unstable and why.

28. Which cephalosporins/cephamycins are available as free amino acids (amphoteric compounds)?

29. Which cephalosporins/cephamycins are available as salts and which salt forms? Which are available as “disalts”? How are the salt forms administered? Why must most salts dosage forms be used shortly after preparation (reconstitution)?

30. Which cephalosporins/cephamycins are available as prodrugs? What is the purpose of prodrug formulation, and how are they administered?

31. You need not memorize time to peak plasma level data. You should be aware that generally food may delay absorption of most cephalosporins and cephameycins, and which products are exceptions.

32. You need not memorize specific distribution information for cephalosporins/cephamycins. You should know which drugs distribute to CSF.

33. What is the relationship between the structure of the cephalosporin/cephamycin 3-substituent and degree of plasma protein binding? You should be able to predict relative degrees of plasma protein binding and half-life by simply analyzing structures of the 3-substituent (as in the Table 2).

34. Which cephalosporins/cephamycins are “significantly” metabolized and which are not and why? Be sure you know the metabolic pathway and significance of metabolism.

35. Generally how are the cephalosporins eliminated? What is the primary pathway (renal or other) and mechanism (GF, TS or both)? Do doses need to be reduced in renal impairment?

36. Why do the oral first generation agents have relatively short half lives? How are they eliminated?

37. Why does cefazolin have a “significantly greater half life” than other parenteral first generation cephalosporins?

38. Why are the second generation cephalosporins/cephamycins not significantly inactivated by metabolism? How are they second generation agents eliminated?
39. Why is plasma protein binding a major determinant of half-life in the second generation cephalosporin series? Explain the relationship between structure, ppb and half-life for these drugs as shown in Table 3.

40. Which third generation cephalosporins/cephamycins are significantly inactivated by metabolism and which are not?

41. How are the third generation cephalosporins/cephamycins eliminated (route and mechanism if renal)? Is dosage reduction required in renal impairment?

42. How do the third generation cephalosporins/cephamycins differ in their plasma protein binding profiles and why? Which third generation cephalosporin has the longest half-life and why?

43. What is the distribution, metabolism and elimination profile of cefepime (using the properties discussed in the questions above for the other cephalosporins)?

44. What unique metabolic reaction does cefepime undergo?

45. What is the most common type of adverse reaction associated with the cephalosporins or cephamycins? How does this compare to the penicillins?

46. Why is CDAD a significant problem with many cephalosporins/cephamycins?

47. Why is “pseudocholelithiasis” more common with ceftriaxone and most other cephalosporins or cephamycins?

48. What is chemical mechanism and rationale for the “disulfiram reaction”? Which cephalosporins/cephamycins are more likely to produce this interaction and why?

49. Which cephalosporins/cephamycins are more likely to induce hypoprothrombinemia and why?