STUDY GUIDE

THE MACROLIDE/AZALIDE ANTIMICROBIAL AGENTS

1. Why are these antibiotics derivatives called "macrolides"? Classify each drug in this chapter as a macrolide or azalide, and as an antibiotic or semi-synthetic derivative.

2. What are the key structural differences between erythromycin, clarithromycin, azithromycin and dirithromycin?

3. Generally how does spiramycin and josamycin differ in structure from the commercial macrolides/azalides (2 reasons)?

4. What are the “ketolides and how do they differ in structure from the commercial macrolides?

5. What is the biosynthetic source of erythromycin? What is the lactone moiety of erythromycin called? What sugar moieties are present and what are their properties?

6. What hydrolysis product forms from erythromycin in aqueous acid or base? What is the significance of this reaction? Can it occur with other macrolides?

7. When does the “intramolecular cyclization” reaction occur with erythromycin? What is it's significance (two reasons) and how does it occur? Which functional groups are important for this reaction?

8. What salt forms of erythromycin are available? Which are water soluble? Which are water-insoluble? How is each salt form formulated and used (oral or parenteral)?

9. What ester and ester salt derivatives of erythromycin are available? What is the estolate? How is each salt form formulated and used (oral or parenteral)? What are the advantages of these esters dosage forms?

10. How does clarithromycin differ in structure from erythromycin? Why was this macrolide developed (the role of the 6-methoxy)?

11. How does azithromycin differ in structure from erythromycin? Why was this macrolide developed?

12. How does dirithromycin differ in structure from erythromycin? Why was this macrolide developed? What is the active form of this prodrug?

13. How does troleandomycin differ in structure from erythromycin and oleandomycin? What unique structural feature is present in troleandomycin?
14. What is the target site of action for the macrolides and what processes are blocked as a result of binding to this target? How is this mechanism of action different/similar to the aminoglycosides, tetracyclines, chloramphenicol and clindamycin?

15. What is the basis for antibacterial selectivity for the macrolides?

16. Are the macrolides bactericidal or bacteriostatic in action generally?

17. What are the mechanisms of resistance to the macrolides? Are they plasmid or chromosomal? Which is most common and what is its significance for other antibiotics?

18. What is MLS\textsubscript{B}? Which macrolides induce MLS resistance and which do not?

19. What are the primary enzymes implicated in resistance to the macrolides and which reactions to they catalyze?

20. Which organisms are innately resistant to erythromycin?

21. Characterize the efficacy of macrolide products versus important gram positive pathogens. What is the relative antibacterial activities of the macrolides against these pathogens?

22. Characterize the efficacy of macrolide products versus important gram negative pathogens. What is the relative antibacterial activities of the macrolides against these pathogens?

23. Characterize the efficacy of macrolide products versus important gram negative bacilli and why?

24. Characterize the efficacy of macrolide products versus important obligate anaerobic pathogens. What is the relative antibacterial activities of the macrolides against these pathogens?

25. Characterize the efficacy profile of the macrolides against “atypical” bacteria? Which of these organisms are these drugs effective against and why is this significant?

26. What factors limit erythromycin oral bioavailability?

27. Describe the absorption properties and prodrug function from the gut of the erythromycin salts and ester salts. How do they differ? When does food interfere?

28. When are the IV salt forms of erythromycin used and what major problem is associated with their use?

29. Why do all erythromycin salts and esters display comparable distribution and elimination profiles post-absorption?
30. Compare clarithromycin, azithromycin, dirithromycin and troleandomycin to erythromycin in terms of oral bioavailability. Rationalize differences in absorption. Also, does food interfere with absorption of these drugs?

31. Compare azithromycin, clarithromycin and dirithromycin to erythromycin in terms of distribution, focusing on distribution to CSF, respiratory tissues/secretions, bile, placenta, breast milk, macrophages (and like cells). What are the relative plasma protein binding profiles of these drugs?

32. Is erythromycin metabolized? What is the importance of metabolism? What is the primary route of elimination? How does renal impairment or hepatic impairment impact of erythromycin half-life?

33. How do clarithromycin, azithromycin and dirithromycin compare to erythromycin in their metabolism and elimination profiles. What is the importance of metabolism for each agent, and what are the major metabolites? Are active metabolites formed?

34. List three significant adverse reactions linked to macrolide use.

35. What is the relationship between drug structure/reactivity and the GI tract effects? Are the newer macrolides free of GI tract adverse effects? Why?

36. What role does the antibacterial profile of macrolides play in GI tract side effects?

37. What is the incidence and important of macrolide-associated hepatotoxicity? Does it occur with all erythromycin products and the newer macrolides?

38. What are the symptoms of hepatotoxicity? Characterize the onset, reversibility of this adverse reaction?

39. What is the relationship between macrolide structure, metabolism and hepatotoxicity? What is the role of the tertiary amine and overall structure?

40. What is the frequency, characteristics and risk factors for ototoxicity?

41. What is basis for most significant drug-interactions observed with the macrolides? What is the relationship between macrolide structure and the incidence of metabolic-based drug interactions?