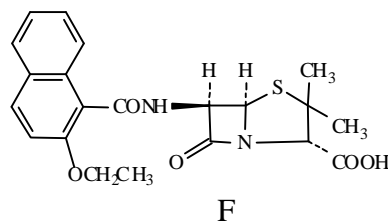
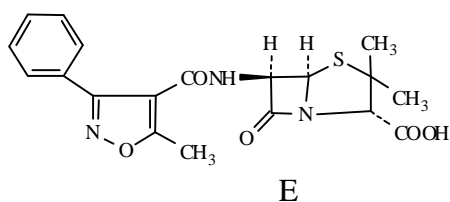
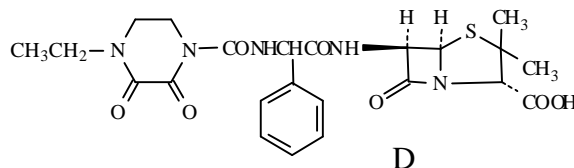
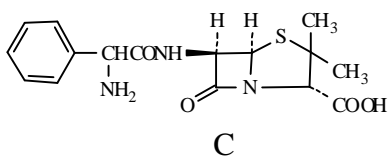
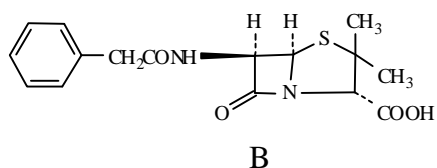
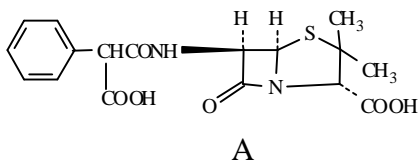


KEY

Problem Set: Penicillin Concepts

Answer the following questions for the penicillins shown below:



1. Which of these compounds are "semi-synthetic" penicillins? **Answer: All penicillins, except Pen G (B) are semi-synthetic derivatives. (1 point)**
2. Which compounds can form water soluble sodium salts? **Answer: All of the penicillin derivatives shown have at least one acidic (carboxyl) group and thus can form sodium salts upon treatment with an appropriate base. These salts will be water soluble since they readily dissociate in water and can participate in ion (COO⁻)-dipole and hydrogen bonds with water. Now, when are these salts used and what problems may be associated with their use? (1 point)**
3. Which compounds are chiral? **Answer: All of the penicillins shown are constructed from chiral amino acids and have chiral centers at positions 2, 5 and 6 of the ring system. Some of the penicillins shown also have an additional chiral center in the 6-acylamino side chain (A, C and D) the configuration of which may or may not be an important determinant of activity (binding to PBPs). And what is the importance of stereochemistry for overall antibacterial activity? (1 point)**
4. Which have a net negative charge at physiologic pH? **Answer: A, B, D, E, F. All of the penicillins shown have at least one acidic carboxyl group with a pKa from 4-5 and this group will be ionized at physiological pH (≈7). Ampicillin also has a**

basic amino group ($pK_a \approx 9$) at the alpha-position of the 6-acylamino side and thus is a zwitterion at pH 7 (amino group predominantly positively ionized, carboxyl group predominately negatively ionized). Other penicillins (D and E) have additional nitrogen functionality in their 6-side chain, but these atoms are not basic! Why is the acidic carboxyl and ionic nature of penicillins important? (1 point)

5. Which are eliminated renally by tubular secretion? **Answer: All of the penicillins are eliminated renally by tubular secretion (TS) and glomerular filtration (GF). The more acidic penicillins (A, B, E and F) are eliminated to a greater extent by TS than GF. The less acidic penicillins (i.e. C) are eliminated to a greater degree by GF (lower %TS). You should not be confused by the data in the table on page 28 of the notes. The overall extent of nafcillin elimination by TS is relatively low because the majority of the dose ($\approx 70\%$) is cleared hepatically! In which cases is route and mechanism of elimination important? (1 point)**
6. Which is most likely to undergo beta-lactam ring opening in the presence of aqueous acid? **Answer: F. F (nafcillin) contains an aromatic ring with an electron donating substituent (OCH_2CH_3) in conjugation (resonance) with the 6-side chain carbonyl. Thus this substituent would participate more in acid-catalyzed opening of the beta-lactam ring as discussed generally on page 3 and in more detail on page 30 in the chapter. Carbenicillin (A) has an alpha-carboxyl group in the 6-acylamino side chain and this group spontaneously decarboxylates in acid as described on page 33 of the notes to yield Pen G, which has a beta-lactam ring more stable than F. Also the acylureido moiety of penicillin D is susceptible to acid hydrolysis, but not at the same rate as the beta-lactam ring of F. Answers B, C and E are in no way correct (by any interpretation of the question) since the side chain carboxyl of A is more reactive than any of these compounds, and the beta-lactam of F is more reactive than any of these compounds. I gave credit for answers A or F since I didn't define the reaction more precisely. (1 point)**
7. Which would yield penilloic acids in aqueous base? **Answer: All penicillins may be hydrolyzed to penilloic acids in the presence of base as described on page 4. The rate of reaction may vary (some beta-lactams are more stable than others), but can undergo the ring-opening reaction. What is the role of this reaction in penicillin formulations and stability? (1 point)**
8. Which are capable of acylating transglycosylases? **Answer: Penicillins produce their bactericidal actions by "acylating" (reaction of the beta-lactam carbonyl with an enzyme nucleophile) essential PBPs (1-3). Recall that the essential PBPs have multiple catalytic activities including transpeptidase (coupling of amino acids of the peptidoglycan) and transglycosylase (coupling of sugars) actions. Review the table on page 6 and the text on pages 5-6. (1 point)**
9. Which are stable to penicillinases produced by *S. aureus*? **Answer: E and F. Those penicillins with bulky, aromatic substituents incorporated into the alpha-carbon**

of the 6-acylamino side chain are resistant to many penicillinases produced by *S. aureus*. These include the isoxazole (i.e. E) and aroylamino (i.e. F) penicillins. The rationale for this is described on pages 20 and 21 of the course notes and involves decreased binding to the penicillinases produced by this organism (the steric bulk is not tolerated by penicillinases, but can still be accommodated by the target PBPs, so the compounds retain activity). (1 point)

10. Which are effective against MRSA? **Answer: None.** All penicillins, not just methicillin, are ineffective against MRSA since this organism elaborates a very different PBP2 (pages 12 and 13) with low penicillin affinity. Don't be confused by the "name" of this organism! It involves all penicillins (and beta-lactams), not just methicillin! (1 point)
11. Which display concentration-dependent bactericidal activity? **Answer: None.** All of the beta-lactams display time-dependent (concentration-independent) bactericidal activity based on their killing mechanism and other factors. Of course you recall that this assumes that therapeutic levels (above MIC/breakpoint) are maintained, so concentration is not "irrelevant". (1 point)
12. Which are effective against bacteria present in phagocytes? **Answer: None.** One of the limitations of this drug class is their inability to penetrate phagocytes (and some other key tissues and cell types). By the way, why is this? (1 point)
13. Which display significant PAE in gram negative organisms? **Answer: None.** The beta-lactams in general display a PAE only against (some) gram positive organisms. We discussed this briefly in class (page 14). (1 point)
14. Which display pharmacologic synergism with aminoglycosides? **Answer: ALL (A-F)** can potentially display synergism with aminoglycosides due to different and complimentary mechanisms of action as describes on page 14 of the notes. Do not confuse this with formulation/pharmacokinetic antagonism that may occur when these agents are administered concurrently, particularly in the same infusion mixture (page 43)! (1 point)
15. Which are orally effective against penicillinase producing *S. aureus*? **Answer: E.** Question 9 above asks about penicillinase stable penicillins. Here I ask which were orally effective against penicillinase-producing *S. aureus*. Oxacillin (E) is the only orally active antistaphylococcal penicillin on the list (A-F). Do you know why it is effective against penicillinase-producing staphy AND is orally active (while F is not)? You better know! (1 point)
16. Which are generally ineffective versus enterococci? **Answer: E and F,** the antistaphylococcal penicillins. The carboxypenicillins (A), natural penicillins (B), aminopenicillins (C) and ureidopenicillins (D) display variable activity against enterococci, but may be generally effective. The antistaphylococcal

penicillins have virtually no significant affinity for the somewhat unique PBPs present in enterococci. (1 point)

17. Which may be generally effective against *Pseudomonas*? **Answer: A and D. Only the carboxypenicillins (A) and ureidopenicillins (D) penetrate *Pseudomonas* with sufficient reliability to be effective (pages 22-24) due to their unique 6-acylamino side chains. Remember, however, that these agents are not resistant to beta-lactamase inactivation. (1 point)**
18. Which may be combined with a beta-lactamase inhibitor to enhance efficacy against Amp-C beta-lactamase producing *Pseudomonas*? **Answer: D. Only carboxypenicillins (A) and ureidopenicillins (D) have "somewhat reliable" activity against *Pseudomonas*. And only tazobactam retains efficacy against Amp-C beta-lactamases (found in *Pseudomonas*). Currently, the only antipseudomonal penicillin combined with tazobactam is piperacillin. (1 point)**
19. Which compound displays the lowest oral bioavailability? **Answer: A. But this is a tough question. Pen G (B) has low oral activity due to significant acid-catalyzed decomposition. Ampicillin (C) has somewhat higher oral activity than Pen G because it is more acid stable, but it is an amphoteric molecule which is poorly soluble in the gut and this limits absorption (that's why amoxicillin is "better" than ampicillin). Piperacillin (D) has very low oral activity because both the ureido side chain and beta-lactam ring can undergo acid-catalyzed decomposition. Oxacillin (E) is acid stable and relatively lipophilic, so it is generally well absorbed. Nafcillin (F) is more acid unstable for reasons outlined numerous times in this key (and discussed in the chapter). Carbenicillin has an alpha-COOH group in the side chain which spontaneously decomposes in acid, yielding Pen G (and loss of carbenicillins unique spectrum of activity). Thus virtually none of the parent compound (carbenicillin) reaches the systemic circulation. Remember, bioavailability refers to the amount of the parent drug reaches the systemic circulation, not metabolites. Also note that the carbenicillin derivative in the table on page 28 with 49% oral bioavailability is the indanyl ester (the acid-stabilized prodrug form)! (1 point)**
20. Which compound displays greater oral bioavailability than Penicillin G? **Answer: Either C or E. Both of these compounds display higher oral bioavailabilities than the other penicillins in the list, but for different reasons. These reasons are discussed in the answer to question 19 above. (1 point)**
21. Which compounds are more acid stable than Pen G? **Answer: C and E. I wanted to illustrate the difference in acid stability of different penicillins, relative to Pen G (B). Carbenicillin (A) is more unstable in acid than Pen G because it has an alpha-COOH in the 6-side chain which may decarboxylate. Piperacillin (D) is more unstable in acid because its acylureido side chain and beta-lactam ring can be hydrolyzed in the gut. Nafcillin is more unstable in acid because of its electron-donating (+R) ethoxy-aromatic side chain which assists in beta-lactam**

ring hydrolysis. Ampicillin (C) is more acid stable than Pen G due to the electron withdrawing alpha-amino group (-I effect) which reduces side chain carbonyl nucleophilicity and therefore slows beta-lactam ring hydrolysis. Oxacillin (E) is more acid stable because the isoxazole ring is electron withdrawing and therefore reduces side chain carbonyl nucleophilicity and therefore slows beta-lactam ring hydrolysis. These trends are described throughout the notes, mainly in the pharmacokinetic section (pages 27-33 and elsewhere). (1 point)

22. Which compounds are eliminated by tubular secretion to a lesser extent than penicillin G? **Answer: This is just a bad question and there's almost no "fixin' it". I wanted you to realize that ampicillin (C) as an amphoteric compound has a lower TS/GF elimination ratio (or more balanced TS/GF excretion profile) than Pen G. I also wanted to illustrate that like nafcillin (F) displays a relatively low TS% because a large fraction of the dose is cleared hepatically. (1 point)**
23. Which compounds may be formulated as ester prodrugs to enhance oral absorption? **Answer: A and C, but this is a bit tricky (I know, you think all of my questions are!). In theory any of the penicillins could be converted to esters (of the 2-carboxyl group) to increase lipophilicity and, perhaps, enhance passive absorption from the intestine. In practice (commercial products), only carbenicillin (A) and ampicillin (C) have been converted to esters to enhance absorption (pages 32 and 33 of the notes). Note that the primary ampicillin prodrug is an ester of the 2-carboxyl to enhance lipophilicity and therefore absorption. The ester derivative of carbenicillin (carbenicillin indanyl) involves the side chain carboxyl group. This prodrug was developed to retard acid-catalyzed decomposition, specifically decarboxylation of the alpha-COOH in the upper GI tract. This is an important difference! (1 point)**
24. Which compound is most extensively bound by plasma proteins? **Answer: E. The isoxazole penicillins have the appropriate balance between lipophilicity and 6-side chain functionality to provide optimal interactions with plasma (as well as other) proteins. Protein binding is high with nafcillin (F) and some acylureides (D), and low with penicillins with ionized alpha-side chain substituents (A and C). Overall, protein binding does not significantly impact on therapeutic considerations (half-life, drug interactions, etc.) due to the clearance profile of these drugs (mainly renal of unmetabolized drug). (1 point)**
25. Which compounds are distributed to the CSF when the meninges are inflamed? **Answer: All. For most penicillins CSF penetration to any significant degree at therapeutic concentrations occurs only when the meninges are compromised by inflammation (or other disease). This is due, in part, to the polar nature of most penicillins. Of course any penicillin which can distribute to the CSF when the meninges are not compromised will distribute better when there is inflammation. (1 point)**

26. Which compounds are eliminated primarily in the bile? **Answer: F. The lipophilic penicillin nafcillin (F) displays the highest biliary/renal clearance ratio. Compound E (oxacillin) also is eliminated in part via the bile, but nafcillin is the to the greatest extent (70%). (1 point)**
27. Which display significant prolongation of half-life in patients with severe renal impairment? **Answer: Those compound eliminated completely (or nearly completely) by renal mechanisms only (no metabolism or significant biliary component) will display prolonged half-life in severe renal impairment. This would include compounds A-D. Oxacillin (E) has a significant hepatic contribution toward elimination and nafcillin (F) is eliminated primarily by hepatic mechanisms. Again, the more lipophilic compounds display lower renal to hepatic clearance ratios. Why is this (covered in PDA1 and PDA2)? (1 point)**
28. Which display significant prolongation of half-life in patients with severe hepatic impairment? **Answer: Compound F (although E is not a poor choice). Nafcillin (F) is one of the more lipophilic penicillins and displays greater hepatic distribution and metabolism (70%) as described on page 35 of the notes. As a general rule, the more lipophilic compounds within a structurally similar series (i.e. penicillins, tetracyclines, etc.) the greater the fraction eliminated by non-renal routes. The elimination/clearance profile can impact on drug therapy several ways. Do you know them? (1 point)**
29. Which compound is most commonly associated with diarrhea and CDAD? **Answer: Compound C (ampicillin) as described on page 40 of the notes? Can you provide TWO REASONS to account for this! (1 point)**
30. Which compound is most commonly associated with interstitial nephritis? **Answer: None. Methicillin is most commonly associated with this adverse reaction and would have been the best choice if included in the choices. (1 point)**
31. Which compound is most commonly associated with bleeding/coagulation adverse reactions? **Answer: The carboxy penicillins, particularly carbenicillin (A), have additional pharmacologic actions as described on page 42 of the chapter which result in interference with platelet aggregation.**