AMERICAN COLLEGE OF CLINICAL PHARMACY

Pharmacotherapy Review Program for Advanced Clinical Pharmacy Practice

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March 25–27, 2013
Riyadh, Kingdom of Saudi Arabia

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American College of Clinical Pharmacy

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American College of Clinical Pharmacy
Lenexa, Kansas
United States of America

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Nephrology

Renal Function Assessment

1. Answer: D

An elderly sedentary woman does not likely have much muscle mass, the source of creatinine (Cr). In the Cockcroft-Gault equation, serum creatinine (SCr) is in the denominator; consequently, a very low value (0.4 mg/dL) will make the final calculated vale very high, probably much higher than the actual glomerular filtration rate (GFR).

Acute Kidney Injury

2. Answer: D

Estimating the creatinine clearance (CrCl) in a patient with unstable kidney function is difficult. The Jeliffe or Brater equation has been recommended as preferable to other equations. In this case, the patient is anuric; hence, a CrCl (GFR) of 10 mL/minute or less (Answer D) should be assumed. Answer A (Cockcroft-Gault) is inappropriate because Cockcroft-Gault should only be used with stable kidney function. The use of the Modification of Diet in Renal Disease (MDRD) (study) (Answer B) in unstable kidney function is also inappropriate. Although Answer C, the Brater equation, may be used, it would still overestimate kidney function in this patient because the patient is anuric.

3. Answer: B

This patient very likely has acute tubular necrosis (ATN), which is a type of intrinsic renal failure (Answer B). The rapid rise in SCr, the blood urea nitrogen (BUN)/Cr ratio of about 10, and the muddy casts all point to ATN. There is no evidence of prerenal causes (hypotension, volume depletion) (Answer A). Naproxen is associated with functional acute kidney injury (AKI), but the urine of patients with AKI is bland without casts. Answer C is incorrect because there is no evidence of obstruction in this patient.

4. Answer: D

One strategy in the management of AKI is to remove potentially nephrotoxic drugs, either direct toxins or medications that alter intrarenal hemodynamics. It is common to see the following orders for patients with AKI: no angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), or intravenous contrast. It is also important to remove (or reduce the dose of) agents that are cleared renally. Metformin, which accumulates in decreased kidney function with an increased risk of lactic acidosis, should be temporarily discontinued at this time. In this case, metformin, naproxen, and lisinopril should be discontinued.

5. Answer: C

This patient presents with ATN, anuria, and volume overload. Although loop diuretics have not been shown to improve clinical outcomes in patients with AKI, they may increase urine output, which will help with fluid and electrolyte balance. In addition, this patient is hypervolemic, so a trial of intravenous loop diuretic would be appropriate (Answer C). Adding 0.9% sodium chloride (NaCl) (Answer A) would worsen fluid overload. Hydrochlorothiazide (Answer B) would not be appropriate because thiazide diuretics are not likely to be effective with such poor kidney function. Fluid restriction (Answer D) may be required if furosemide fails to increase urine output, but it would not be the first-line approach.

Drug-Induced Kidney Damage

6. Answer: B

Intravenous 0.9% NaCl is considered the most effective hydration for the prevention of contrast-induced nephropathy (Answer B). The other solutions, particularly the oral solution, would not be appropriate.

7. Answer: B

Many data have been published on the use of oral acetylcysteine in the prevention of contrast-induced nephropathy. Although many of the studies are observational and some are conflicting, the low risk of the product has made it the standard of care in this situation. Fenoldopam (Answer A) should not be used on the basis of the results obtained in the CONTR AST trial. Although some data exist with ascorbic acid (Answer C), they are limited. Hemofiltration (Answer D) has also been studied, but it is not generally recommended because of the questionable benefits and the real risk of complications.

Chronic Kidney Disease (CKD)

8. Answer: B

The patient is currently at stage 3 CKD (GFR 30–59 mL/minute/1.73m^2), which can be calculated by the MDRD formulae or Cockcroft-Gault. The five stages correlate from mild kidney damage (stage 1) to kidney failure (stage 5).

9. Answer: C

On the basis of this patient's diabetes mellitus diagnosis and overt proteinuria, the patient likely has diabetic nephropathy. Progression will be accelerated by smoking, poor diabetes control, and poor blood pressure (BP) control. In patients with diabetes, a target hemoglobin A_{1c} of less than 7% is associated with a decrease in the rate of disease progression. Blood pressure control of less than 130/80 mm Hg in patients also decreases the progression of kidney disease. The standard of care in patients with diabetic nephropathy is ACEIs (evidence for a reduction in morality and reduced progression of CKD) or ARBs (evidence for a reduction in progression but no mortality data), so enalapril (Answer C) is the best choice. A nondihydropyridine (Answer B) might be initiated in patients who cannot tolerate ACE or ARB therapy but would not be a first choice. Dihydropyridine therapy (Answer A) is not recommended in diabetic nephropathy because of conflicting literature on its efficacy. An increase in atenolol (Answer D) might control BP, but inhibition of the renin-angiotensin system is still the best answer. In addition, a recent meta-analysis evaluating atenolol in hypertensive patients with diabetes mellitus found either no difference in outcomes or worse outcomes.

10. Answer: B

The BP is not at goal (should be less than 130/80 mm Hg). To improve BP control and enhance the effect of the ACEI, chlorthalidone should be added to the regimen (Answer B). Monitoring of SCr and serum potassium is appropriate in this patient. There is less than a 30% increase in SCr, so enalapril should be continued, making Answer A and Answer C inappropriate. Adding chlorthalidone would also counter the tendency for hyperkalemia. Answer D would probably lower BP but would not be the preferred route because renal protection would likely not be enhanced.

11. Answer: D

The amount of potassium in that much orange juice could be lethal because most patients with stage 5 CKD are already hyperkalemic and have no way to eliminate potassium. Although ingesting too much sodium (Answer A) or fluid (Answer C) is bad, it is not likely lethal. Aluminum toxicity (Answer B) takes years to develop and is not acutely toxic.

12. Answer: B

Hyperparathyroidism is associated with epoetin resistance in patients on hemodialysis (HD) (Answer B). Although iron deficiency is the most common cause of epoetin deficiency, the laboratory results for this patient do not indicate iron deficiency (Answer A). Phenytoin therapy (Answer C) has been associated with anemia in other patient populations, but not in HD patients. Infection (Answer D) and inflammation are very common causes of epoetin deficiency in patients on HD, but there is nothing in this patient's presentation to suggest an infectious or inflammatory process.

13. Answer: B

D.W. requires treatment for his elevated immunoreactive parathyroid hormone (iPTH) (800 pg/dL), which puts him at high risk of renal osteodystrophy. He has high serum phosphorous and calcium. The corrected calcium is 10.2 mg/dL, and the calcium × phosphorus factor is 80 mg^2/dL^2. The goal/target calcium × phosphorus factor in stage 5 CKD is less than 55 mg^2/dL^2. Current binder therapy is contributing to calcium exposure; therefore, calcium acetate should be discontinued and sevelamer initiated. Cinacalcet will lower the iPTH and potentially serum calcium. Answer A is incorrect because increasing the calcium acetate may worsen the hypercalcemia. Answer C is incorrect for two reasons. First, the patient needs some type of phosphate binder; second, intravenous vitamin D analogs can worsen hypercalcemia and are not very effective at reducing elevated iPTH in the presence of hyperphosphatemia. Answer D is incorrect because intravenous vitamin D analogs can worsen hypercalcemia and are not very effective at reducing elevated iPTH in the presence of hyperphosphatemia.

14. Answer: A

The target hemoglobin in these patients should not be normal. All prospective studies find that trying to normalize hemoglobin with ESAs (erythropoiesis-stimulating agents) results in worse outcomes. The hemoglobin target, as recommended by the FDA (U.S. Food and Drug Administration) (since June 2011), should not be greater than 10 g/dL. Use the lowest dose of ESA sufficient to reduce the need for RBC (red blood cell) transfusions. The other answers are all true.

Renal Replacement Therapy

15. Answer: D

A native arteriovenous fistula is the preferred access for long-term HD. If an arteriovenous fistula cannot be constructed, a synthetic arteriovenous graft (Answer C) is considered second line. A subclavian catheter (Answer A) is a poor choice because of the increased risk of infection and thrombosis and because of the poor bloodflow obtained through a catheter. A Tenckhoff catheter (Answer B) is incorrect because it is for peritoneal dialysis.

16. Answer: D

The best-studied agent is midodrine, an α_1-agonist. Levocarnitine (Answer A) has been tried, but there are limited data on its benefit. Fludrocortisone (Answer C) is a synthetic mineralocorticoid, which is used for hypotension in other situations; however, the primary mechanism is caused by Na and water restriction in the kidney; hence, this drug is less likely to work. Sodium chloride tablets (Answer B) would not work acutely and should generally be avoided.

Dose Adjustments in Kidney Disease

17. Answer: B

The presence of kidney failure and low albumin results in an increased free fraction of phenytoin. Using the correction equation gives a corrected level of 12.5, which is therapeutic. A free phenytoin concentration can also be drawn.

Endocrinology

Activity 1: Diabetes Mellitus Diagnostic Criteria

1. Criteria for diagnoses

	Normoglycemia	Prediabetes	Diabetes
FPG	< 100 mg/dL	100–125 mg/dL	≥ 126 mg/dL[a]
PPG (after 75 g OGTT)	< 140 mg/dL	140–199 mg/dL	≥ 200 mg/dL[a]
Random PG			> 200 mg/dL + symptoms[a]
Hemoglobin A_{1c}	< 5.7%	5.7% –6.4%	≥ 6.5%[a]

[a]Should be confirmed by repeat test (preferably the same test) on a different day.

FPG = fasting plasma glucose; OGT T = oral glucose tolerance test; PG = plasma glucose; PPG = postprandial blood glucose.

Activity 2: Type 2 Diabetes Mellitus

2. This patient has the following American Diabetes Association risk factors for type 2 diabetes mellitus (DM):
   Age older than 45 years
   Overweight (body mass index greater than 25 kg/m^2)
   Habitual physical inactivity
   High-risk ethnicity (African American)
   Hypertension (blood pressure [BP] greater than 140/90 mm Hg)
   High-density lipoprotein concentration less than 35 mg/dL
   Presence of prediabetes (impaired fasting glucose or impaired glucose tolerance)

3. Type 2 DM, uncontrolled, newly diagnosed

4. Lifestyle modifications to improve diet and exercise and metformin (increase metformin to maximal tolerated dose [2550 mg] to increase efficacy)

Activity 3: Glycemic and Nonglycemic Goals

5. Appropriate therapeutic goals for a patient with DM

Glycemic Goals	
FPG	70 –130 mg/dL
PPG	< 180 mg/dL
Hemoglobin A_{1c}	< 7%

FPG = fasting plasma glucose; PPG = postprandial blood glucose.

Nonglycemic Goals	
Blood pressure[a]	< 130/80 mm Hg
LDL	< 100 mg/dL < 70 mg/dL (with CVD)
HDL	> 40 mg/dL (men) > 50 mg/dL (women)
Triglycerides	< 150 mg/dL

[a]Lower blood pressure is appropriate in some patients, depending on additional compelling indications. CV D = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Activity 4: Type 2 DM Therapeutic Goal

6. The patient's American Diabetes Association glycemic and nonglycemic goals and the most appropriate agent to recommend at this time are as follows.

Therapeutic Goals			
	Controlled	**Uncontrolled**	**Drug of Choice for Uncontrolled Goals**
FPG	✓		
Hemoglobin A_{1c}		✓	Sulfonylurea (preferable) or basal insulin (intermediate- or long-acting insulin: 10 units/day or 0.2 unit/kg). Titrate basal insulin to obtain FPG between 70 mg/dL and 130 mg/dL
Blood pressure		✓	ACEI or ARB
LDL		✓	Statin (~22% reduction desired)
HDL		✓	Statin (~17% increase desired) ± fibrate, niacin, or gemfibrozil
Triglycerides	✓		

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Activity 5: Type 2 DM Medications

7. Drug class comparison based on hemoglobin A_{1c}–lowering properties and effect on weight

Drug Class	Hemoglobin A_{1c} % Reduction	Effect on Weight (↑, ↓, or no effect)
Amylin analogs	0.5–1	↓
Dipeptidyl peptidase-4 inhibitors	0.5– 0.8	No effect
GLP-1 analogs	0.5–1.1	↓
Meglitinides	0.5–1.5	↑
Metformin	1–2	↓
Sulfonylureas	1–2	↑
Thiazolidinediones	0.5–1.4	↑
α-Glucosidase inhibitors	0.5– 0.8	↓

GLP-1 = glucagon-like peptide-1.

Activity 6: Type 2 DM Medications

8. Hold metformin for 48 hours before cardiac catheterization.
   Hold glyburide while the patient is taking nothing by mouth.

9. The patient is showing early signs of renal impairment with an increase in baseline serum creatinine from 0.8 mg/dL to 1.3 mg/dL. Glipizide might be a better option in renal impairment because active metabolites are renally eliminated. He should be initiated on glipizide 5 mg by mouth 2 times/day.

Activity 7: Insulin Review

10. Ranking of insulin products from shortest duration to longest duration, with 1 being the shortest and 5 being the longest in duration

		Category	Onset	Duration (hours)
___4___	Detemir	Long acting	2–4 hours	6–24
___3___	NPH	Intermediate acting	1–2 hours	10–20
___1___	Lispro	Rapid acting	5–20 minutes	3–5
___5___	Glargine	Long acting	1–2 hours	~24
___ 2___	Regular	Short acting	30–60 minutes	4–6

Activity 8: Type 1 DM Case Review

11. 15 units of glargine subcutaneously every night; 5 units of aspart subcutaneously before meals 3 times/day

    Total daily dose (TDD) = 0.3–0.6 unit/kg/day (insulin-naive patients, typically 0.5–0.6 unit/kg/day)
    60 kg x 0.3 unit/kg/day = 18 units
    60 kg x 0.6 unit/kg/day = 36 units
    Basal/bolus regimen = TDD/2 (50% basal and 50% bolus)
    Basal (glargine or detemir[a]) = 9–18 units
    Bolus (lispro, aspart, or glulisine) = 9–18 units (total bolus dose/3 administered 3 times/day with meals)

    [a]Because of interpatient variability, detemir should be administered two-thirds in the morning and one-third at night (duration of action can be as short as 6 hours).

Activity 9: Insulin Adjustment

12. Appropriate period for determining the dose adjustment for self-monitoring of blood glucose (SMBG)

Insulin Type	Time of Administration	Appropriate SMBG Time (i.e., FPG, PPG, pre-lunch, lunch, pre-dinner, bedtime, overnight)
NPH	Before breakfast	Pre-dinner (efficacy) Midday/lunch (safety)
	Before dinner	FPG (AM) (efficacy) Overnight (safety)
	At bedtime	FGP (AM) (efficacy) Overnight (safety)
Regular	Before breakfast	PPG breakfast/pre-lunch (safety/efficacy)
	Before lunch	PPG lunch/pre-dinner (safety/efficacy)
	Before dinner	PPG dinner/HS (safety/efficacy)
Detemir	Before breakfast	Pre-dinner/HS/FPG ? (efficacy) Overnight (safety)
	Dinner or bedtime	FPG (AM) (efficacy) Overnight (safety)
Glargine	Bedtime	FPG (AM) (efficacy) Overnight (safety)
	AM	FPG (AM) (efficacy) Overnight (safety)
Lispro, aspart, glulisine	Before breakfast	PPG breakfast (safety/efficacy)
	Before lunch	PPG lunch (safety/efficacy)
	Before dinner	PPG dinner (safety/efficacy)

A M = morning; FPG = fasting plasma glucose; HS = at bedtime; PPG = postprandial blood glucose; SMBG = self-monitoring of blood glucose.

Activity 10: Insulin Adjustment Review

13. Appropriate adjustments of insulin regimen and rationale

Insulin	Dose Adjustment? (Yes or No)	Rationale	Recommended Dose (units)
Glargine HS	Yes	FPG consistently above ADA goal for FPG (70 –130 mg/dL)	17[a]
Aspart breakfast	Yes	PPG consistently above ADA goal for PPG (< 180 mg/dL)	7[a]
Aspart lunch	Yes	PPG consistently above ADA goal for PPG (< 180 mg/dL)	7[a]
Aspart dinner	No	PPG consistently within ADA goal for PPG (< 180 mg/dL)	5

[a] Adjustments are typically made in 2- to 5-unit increments; however, total adjustment should not exceed 20% of the TDD. ADA = American Diabetes Association; FPG = fasting blood glucose; PPG = postprandial blood glucose; TDD = total daily dose.

Activity 11: Insulin Adjustment

14. Appropriate adjustments of insulin regimen and rationale

Insulin	Dose Adjustment? (yes or no)	Rationale	Recommended Dose (units)
Glargine HS	Yes	FPG consistently above ADA goal (70–130 mg/dL). The dose should be decreased because 3 AM blood sugars indicate hypoglycemia. Somogyi effect is the likely etiology of the FPG elevation. Decreasing the dose will result in decreased overnight hypoglycemia and decreased FPG	20–23[a]
Aspart breakfast	No	PPG consistently within ADA goal for PPG (< 180 mg/dL)	8
Aspart lunch	No	PPG consistently within ADA goal for PPG (< 180 mg/dL)	8
Aspart dinner	No	PPG consistently above ADA goal for PPG (< 180 mg/dL)	10–13[a]

[a] Adjustments are typically made in 2- to 5-unit increments; however, the total adjustment should not exceed 20% of the TDD.
ADA = American Diabetes Association; FPG = fasting blood glucose; PPG = postprandial blood glucose; TDD = total daily dose.

Activity 12: Hypoglycemia Treatment

15. Ingest 15–20 g of glucose:
    2 or 3 glucose tablets
    1/2 cup (4 oz) of any fruit juice
    1/2 cup (4 oz) of a regular (not diet) soft drink
    1 cup (8 oz) of milk
    Five or six pieces of hard candy
    1 or 2 teaspoons of sugar or honey

    Retest blood sugar in 15 minutes.
    If greater than 70 mg/dL, eat a meal at an appropriate time.
    If n is less than 70 mg/dL, ingest a second 15- to 20-g glucose load and continue to retest at 15-minute intervals until corrected.

Activity 13: Thyroid Laboratory Value

16. Laboratory parameters

	Hyperthyroidism		Hypothyroidism	
	Primar y	Secondar y	Primar y	Secondar y
TSH	↓	↑	↓	↓
T_3/T_4	↑	↑	↓	↓
TRH	↓	↓	↑	↑

TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; T_3/T_4 = triiodothyronine/thyroxine.

Activity 14: Hyperthyroid Case

17. Methimazole 15 mg by mouth daily and propylthiouracil 100 mg by mouth 3 times/day
    Iodines (Lugol's solution and saturated solution of potassium iodide)
    β-Blockers (primarily propranolol) for symptomatic control
    Radioactive iodine (^{131}I)

18. Counseling points to discuss with the patient after her ingestion of radioactive iodine include:

    Flush toilet twice after use with the lid down.
    For 3 days, sleep in separate bed and minimize time with children.
    For 5 days, avoid long trips and public transportation.
    For 7 days, minimize close contact with other people.
    For 7 days, keep dishes and clothes separate, and wash immediately.
    For 10 days, avoid pregnant women.
    Do not breastfeed or become pregnant for 6 months.

Activity 15: Hypothyroid Medications

19. Agent comparison based on thyroid source and equivalent dose

Drug	Thyroid Source	Equivalent Dose
Thyroid USP	Desiccated hog, beef, or sheep thyroid	1 grain (64 mg)
Levothyroxine	Synthetic T_4	100 mcg (0.100 mg)
Liothyronine	Synthetic T_3	25 mcg (0.025 mg)
Liotrix	Synthetic T_4/T_3 ratio = 4 to 1	12.5/50 mcg T_3/T_4

T_3/T_4 = triiodothyronine/thyroxine.

Activity 16: Hypothyroid Case Review

20. Levothyroxine 50–75 mcg by mouth daily

    Liothyronine 25 mcg by mouth daily

21. Levothyroxine 25 mcg intravenously daily (intravenous starting dose is one-half the oral dose)

Activity 17: Syndrome of Inappropriate Antidiuretic Hormone

22. The patient has hyponatremia because his serum sodium is 110 mEq/L, and his volume status is euvolemic because there is no evidence of hypovolemia or hypervolemia. The patient's diagnosis is SIADH (syndrome of inappropriate antidiuretic hormone) because of high urine osmolality and high urine sodium.

23. The desired rate of correction of hyponatremia is 0.5 mEq/L/hour.

24. Osmotic demyelination syndrome

25. 3% NaCl (sodium chloride) 700 mL @ 35 mL/hour for 20 hours

Na deficit = (weight)(% TBW [total body weight])(desired Na - measured Na)
Na deficit = (60 kg)(0.6)(120 mEq/L - 110 mEq/L) = 360 mEq

Volume of intravenous fluid = (360 mEq/514 mEq) x 13,000 mL/L = 700 mL

Time = 10/0.5 = 20 hours

Intravenous fluid rate = 700/20 = 35 mL/hour

Biostatistics and Clinical Trials

Case 1

1. The type of data represented by a Likert scale is ordinal. As such, use a nonparametric type of statistical test. In addition, this case describes a pre-post design with the same subjects; therefore, you would need to use a test that takes into account the paired or matched nature of the comparison groups. The Wilcoxon signed rank test should be used with ordinal-level data and matched or paired comparison groups.

2. Each of these outcomes requires the comparison of percentages or proportions between two groups. Again, the subjects in this case serve as their own controls; thus, the data are considered paired or matched. The statistical test that would be used to compare nominal level data (i.e., proportions) of paired or matched samples is the McNemar test.

Case 2

3A. To evaluate this statement, recall that the standard error of the mean (SEM) is calculated as the standard deviation divided by the square root of the sample size. When solving this equation for the standard deviation, you get a value of 1. Because about 95% of all population members fall within about 2 SD of the mean, this would mean that the cardiac output of 95% of the population falls between 3 L/minute and 7 L/minute. It would indeed be unusual to observe cardiac outputs outside this range.

3B. This interpretation is inconsistent with the data because it is derived using the value for the SEM (i.e., mean cardiac output ± 2 SEM), and the SEM tells us about the precision of the estimate of the mean, NOT the spread in the data.

3C. This statement is inconsistent with the data presented because these are continuous data from a normally distributed population; therefore, the mean is the appropriate measure of central tendency.

3D. This statement is not consistent with the data because it refers to values corresponding to 1 SD, which would encompass only 68% of all population members. Therefore, about 32% of the population could be expected to have values in this range—a frequency not considered "unusual."

Case 3

4A. This statement would not be considered a correct interpretation of the information presented because, for a type I error to have occurred, you must conclude a difference when one does not exist. In this case, with α set at 0.05, there is no statistically significant difference, so there is no possibility of a type I error.

4B. This statement is consistent with the data previously presented. Lack of a statistically significant difference is required to make a type II error. Type II errors occur when "no difference" is concluded on the basis of the p-value when, if fact, a true difference between the groups exists. To minimize the risk of a type II error, the power of a trial, by convention, should be greater than 80%. Because power is calculated as $1 - \beta$, setting β as less than 0.20 would be necessary to result in a power greater than 80%.

4C. As in No. 7, this statement would not be considered a correct interpretation of the information presented because for a type I error to have occurred, you must conclude a difference when one does not exist. In this case, with α set at 0.05, there is no statistically significant difference; thus, there is no possibility of a type I error. In addition, setting α to the even more stringent 0.01 makes it even less likely that a statistically significant difference would be found.

4D. This statement is consistent with the data previously presented because setting β at more than 0.30 would actually decrease the power to detect a difference. Thus, although a type II error may have occurred, the proposed solution is incorrect.

Case 4

5. You can determine whether the result is statistically significant by evaluating the confidence interval and determining the possible values for the difference it contains. If a 95% confidence interval contains within its bounds the value that would represent "no difference," you can conclude that the results are not statistically significant. Conversely, if a 95% confidence interval excludes the value that would represent no difference, you can conclude that the p-value is less than 0.05 and, thus, that the difference is statistically significant.

   In this case, the difference between hemoglobin A_{1c} is not statistically significant. Note that the confidence interval contains within its bounds the value of zero (i.e., the value representing no difference), and as such, a difference of zero between the hemoglobin A_{1c} values could be the true difference between the groups.

Case 5

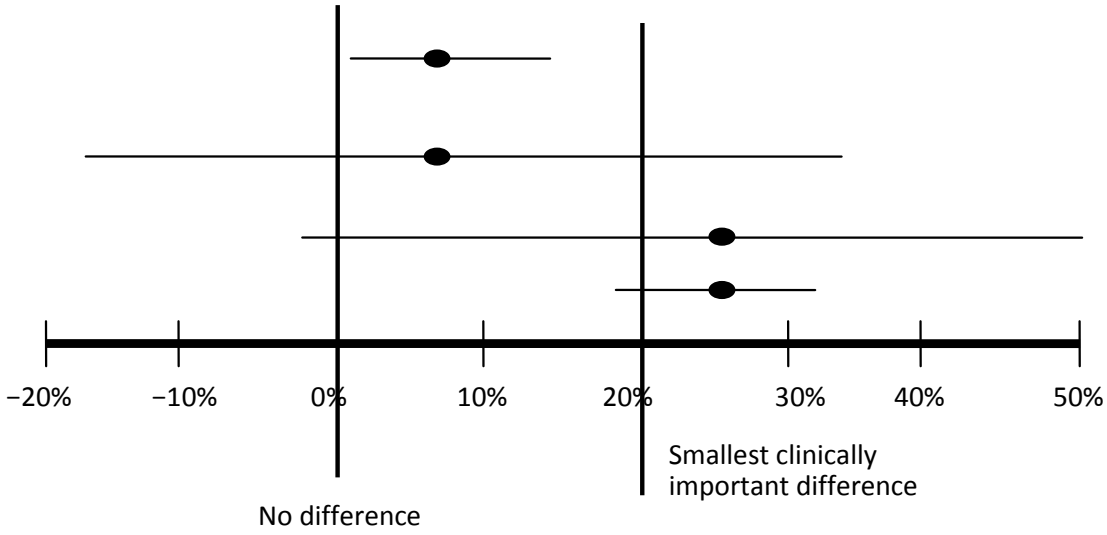
6. You would need to consider the level of data measurement (e.g., nominal, ordinal, continuous), as well as whether the data are normally distributed and whether the data measurements are paired or matched.

7. In this case, the type of comparison described involves a continuous variable using patients as their own control (i.e., matched data). As such, an appropriate statistical test to compare the blood levels of the new medicine with and without the administration of ganciclovir would be a paired t-test.

Case 6

8. To determine the answer to this question, first consider which of the investigations found a statistically significant difference between the response rates. You can do this using the data presented by looking at the p-values for each trial.

   To help assess clinical significance, consider that, for a trial to be clinically significant, there must be at least a 20% difference in response rates. Because none of the trials excludes the possibility that the true difference in response rate could be less than 20%, none of the trials would be considered clinically significant. You know this because the confidence intervals in all the trials contain values less than 20 within their bounds. As such, even the statistically significant trials cannot be said to ensure that the difference between regimens is at least 20%. The following figure represents this graphically (note that all of the confidence intervals contain values less than 20):



CASE 7

9A. Decreasing α would make a type I error less likely. If other study design components were held constant, then decreasing α would increase the sample size needed to conduct your study.

9B. Increasing β effectively decreases your power to detect differences between groups (remember, power is 1 - β). By decreasing the power, you would need to increase your sample size to detect a given level of difference between the groups.

9C. Decreasing the size of the difference you wish to detect would require a larger sample size.

CASE 8

10. To answer this question, look at the 95% confidence interval. A difference in this example is that, in observational study designs (also known as epidemiologic designs), the value that would indicate no difference between the groups is 1. Because the results of these studies (e.g., case-control, cohort) are reported as relative risks or odds ratios, the value 1 signifies no difference in the risk or odds of an event. In this example, the 95% confidence interval does not include the value representing no difference between the groups (i.e., the value 1), so it can be determined that the results are statistically significant with a p-value less than 0.05.

11. Because the odds ratio is less than 1, administering the vaccine would be said to be associated with a decreased risk or chance of having a myocardial infarction (MI). The odds ratio of 0.7 would mean a 30% decrease in the odds of having an MI, and the 95% confidence interval would indicate that the real difference could be anywhere from a 10% reduction to a 50% reduction.

12. For case-control studies, the cases and controls are selected according to on the presence or absence of a disease or outcome. In this example, having or not having the outcome of MI (i.e., the disease) determined the basis for the comparisons. In a cohort trial, the cohorts compared are determined on the basis of the presence or absence of an exposure. Had this been a cohort trial, one possible design would have classified patients on the basis of whether they had received the vaccine and then would have looked back in time, or observed them into the future, to determine whether those exposed had an MI at a rate different from those not exposed to the vaccine.

Case 9

13. Randomization is important because it distributes uncontrolled variables evenly among the group. In other words, it reduces or eliminates the influence of bias or confounders as contributing to any observed differences between the groups and serves to isolate the influence or effect of the intervention. In the trial described in this case, randomization could be important to account for differences in illness burden or complexity among practices, or to account for "leakage" of the intervention to the control group. (In other words, those who are not to receive the intervention receive at least part of it because providers in the practice believe in its value and begin to adopt all or part of it for all patients.)

14. A type of randomization known as cluster randomization may be particularly useful for an investigation of this type. Cluster randomization randomizes groups instead of individuals. In this case, the groups would likely be practice sites. This can minimize the chance of leakage of the intervention to patients who are not supposed to be receiving it.

Case 10

15. The circles each represent the mean difference (i.e., point estimate) between the intervention and control group for each trial included in the meta-analysis. The lines through each circle represent the confidence intervals for the mean difference of each of the trials. The diamond figure at the bottom of the figure represents the results for the estimate of the odds ratio for an asthma exacerbation when summarizing/combining the results of the individual trials. The width of the diamond represents the confidence interval for this summary estimate of effect.

16. For an odds ratio, numbers less than 1 indicate that the outcome of interest is less likely to occur, and numbers greater than 1 indicate that the outcome is more likely to occur.

17. In this example, the new drug appears to have a statistically nonsignificant effect on the number of asthma exacerbations: the estimate of the effect is less than 1, but the confidence interval includes 1 (i.e., no difference) as a possibility.

Case 11

18. Statistical heterogeneity exists in a meta-analysis when differences exist between the trials in the areas of randomization, early termination, measures of risk, or existence of publication bias (to name a few). In a basic sense, heterogeneity is an important consideration to make sure that a meta-analysis is comparing "apples to apples."

19. There are a few common methods to test, statistically, for heterogeneity in a meta-analysis. A χ^2 or a Cochrane *Q* test is a common statistical technique used to assess heterogeneity. Another test is the I^2 test or value.

20. For the χ^2 and Cochrane *Q* tests, a p-value greater than 0.1 is used as a cutoff. For these tests, a high p-value (i.e., greater than 0.1) indicates no heterogeneity. The I^2 test is interpreted in an opposite manner, whereby higher values indicate greater heterogeneity. For this test, values less than 0.25 correspond with low heterogeneity, values of 0.25–0.50 correspond to moderate heterogeneity, and values greater than 0.5 indicate a high level of heterogeneity.

Case 12

21. This is a randomized trial, which indicates that the two groups being compared are independent. The outcome of interest, hospitalization for congestive heart failure symptoms, is a dichotomous

outcome and is thus a variable that would be considered nominal. In this case, a χ^2 test would be appropriate.

22. In the medication group, 27 of 1232 patients had the outcome of interest. This would equal about 2%. In the placebo group, 42 of 1230 patients had the outcome of interest. This would equal about 3.4% of patients. The relative reduction in the number of events would be 3.4% - 2%/3.4%. This represents a 41% relative reduction.

23. The absolute reduction in events between the groups is 3.4% - 2%. Thus, the absolute reduction in events is 1.4%.

24. The number needed to treat (NNT) is calculated as the reciprocal of the absolute reduction in events. As such, the NNT would be 1/1.4% = 1/0.014 = 71.

Case 13

25. The combining of more than one end point into a composite end point has some potential advantages; it 1) alleviates problems of multiple statistical testing, 2) increases event rates, and 3) decreases required sample sizes.

26. There are many potential difficulties in interpreting and working composite end points. Some of these are as follows:

- Misattribution of statistically beneficial effects of composite measure to each of its component end points
- Dilution of effects
- Negative results for relatively common component of composite end point "hide" real differences in other end points.
- Undue influence exerted on composite end point by "softer" component end points
- For example, hospitalization, retinopathy, vascular death
- Problems when component end points go in opposite directions
- Weighting of end points
- Should death "count" the same as other end points?
- End points that combine death and nonfatal events are subject to biases from competing risks.
- For example, increased death means decreased nonfatal events.

Case 14

27. The strengths/weaknesses of each of the following approaches to analyzing clinical trial data are as follows:

A. Intention-to-treat analysis provides a better estimate of real-world effectiveness because it does not consider adherence. Once patients are randomized to a group (i.e., treatment or placebo), they are analyzed as part of that group regardless of whether they actually adhere to the intervention. This approach to the analysis of clinical trial data has been viewed as providing a conservative estimate of effectiveness that should correspond best with what occurs in practice.

B. Per-protocol analysis analyzes only the data from study subjects who are randomized and then complete the treatment according to the protocol. Those who do not adhere to their assigned treatment (usually at some predefined level) are dropped from the analysis. This type of analysis can give a better estimate of the maximal effectiveness for a particular intervention. However, because patients are dropped from the analysis if they do not adhere to the protocol,

power issues (i.e., lack of sample size) can become a concern by the end of the trial.

C. As-treated analysis, as the name implies, analyzes study participants on the basis of how they were actually treated. If, for example, a trial has active treatment and placebo treatment groups, a patient randomized to active treatment who takes only the first few doses of medicine would, at the end of the trial, be analyzed as a placebo group patient. This approach, compared with per- protocol, minimizes the impact of nonadherent patients on the power by keeping their data in the trial. However, and probably more importantly, this approach is generally considered to greatly jeopardize the benefits of the randomization process and may introduce bias into the analysis.

28. The investigators' stated purpose is to determine the maximal effectiveness of an intervention when it is used correctly. In this case, a carefully planned per-protocol approach to data analysis would give them the best estimate of maximal effectiveness.

Infectious Diseases

Case 1

1. This patient has community-acquired pneumonia requiring hospitalization and admission to a general medicine floor. Because of this, he should receive either a respiratory fluoroquinolone or ampicillin, ceftriaxone, or cefotaxime plus a macrolide, such as azithromycin. Intravenous therapy should be used to start the transition to oral therapy when clinically indicated.

2. Main features include the following.

Pneumonia Subtype	Main Features
Health care associated (HCAP)	Developing in a patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; who resided in a nursing home or long-term care facility; who received intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or who attended a hospital or hemodialysis clinic Possible risk of *Pseudomonas, S. aureus*, and other resistant gram-negative organisms
Hospital acquired (HAP)	Occurs 48 hours or more after admission and is not incubating at the time of admission Risk of *Pseudomonas, S. aureus*, and other resistant gram-negative organisms
Ventilator associated (VAP)	Arises more than 48–72 hours after endotracheal intubation Risk of *Pseudomonas, S. aureus*, and other resistant gram-negative organisms

3. The Joint Commission's core measures for management of pneumonia include the following. Many of these can be addresses by use of preprinted order sets and pharmacists' documentation of assessment in the medical record, particularly for vaccinations. Antibiotic stewardship programs may also play a large role in this process for the antibiotic-associated outcomes.

Measure	Short Name
PN-2	Pneumococcal Vaccination
PN-3a	Blood Cultures Performed Within 24 Hours Prior to or 24 Hours After Hospital Arrival for Patients Who Were Transferred or Admitted to the ICU Within 24 Hours of Hospital Arrival
PN-3b	Blood Cultures Performed in the Emergency Department Prior to Initial Antibiotic Received in Hospital
PN-4	Adult Smoking Cessation Advice/Counseling
PN-5	Antibiotic Timing (Median)
PN-5c	Initial Antibiotic Received Within 6 Hours of Hospital Arrival
PN-6	Initial Antibiotic Selection for CAP in Immunocompetent Patient
PN-6a	Initial Antibiotic Selection for CAP in Immunocompetent – ICU Patient
PN-6b	Initial Antibiotic Selection for CAP Immunocompetent – Non ICU Patient
PN-7	Influenza Vaccination

Case 2

4. This patient is considered to have a complicated pyelonephritis because of existing immunosuppression and should receive empiric intravenous antibiotic therapy with a fluoroquinolone or an extended- spectrum β-lactam. Aminoglycosides should be avoided because of the presence of chronic kidney disease (CKD).

5. Because this patient is symptomatic, the presence of a long-term indwelling catheter would not change antibiotic management; however, the catheter would most likely be replaced with a new one during the treatment course.

6. If the patient is male, then assessing for the presence of prostatitis is indicated because this would dictate a longer treatment course (4-8 weeks), preferably with a fluoroquinolone.

Case 3

7. This patient would meet the criteria for severe disease on the basis of a serum creatinine greater than 1.5 times the baseline value and a white blood cell count greater than 15,000/mm^3.

8. Initial episodes of severe disease should be treated with vancomycin 125 mg 4 times/day for 10–14 days according to the IDSA (Infectious Diseases Society of America) guidelines.

9. The sensitivity should be calculated as follows: Sensitivity = 710/(710 + 185) = 70%

Result	Infection	No Infection	Total
Positive	710	40	750
Negative	185	65	250
Total	895	105	1000

Case 4

10. According to the endocarditis treatment guidelines, the recommended treatment for *Streptococcus viridans* with an MIC (minimum inhibitory concentration) greater than 0.12 mcg/mL with a prosthetic valve is penicillin G plus gentamicin for 6 weeks. Because the patient has CKD, the use of an aminoglycoside may be prohibited. If one is used, however, close monitoring of the renal function should be performed.

11. For future dental procedures, the patient should receive amoxicillin 2000 mg 1 hour before the procedure according to the guidelines.

Human Immunodeficiency Virus

1A. This patient would not qualify for treatment because the diagnosis of human immunodeficiency virus (HIV) infection has not been confirmed. Once a positive antibody test is obtained, the result needs to be confirmed by Western blot. Disease states such as systemic lupus erythematosus can be associated with false-positive HIV antibody results.

1B. This patient, although not symptomatic, would qualify for treatment on the basis of his CD4 count of less than 350/mm^3. The patient has a high viral load, and his history of asthma does not preclude treatment.

1C. This patient, although not symptomatic, would qualify for treatment on the basis of her positive pregnancy status. Her CD4 count of less than 300/mm^3 would also be an indication. Choice of drug therapy should be aimed at reducing risk to the child.

1D. This patient would technically qualify on the basis of his CD4 count of 250/mm^3 and high viral load. However, the patient has active esophageal candidiasis and continues to use intravenous drugs. The candidiasis would require treatment, and the patient would need to abstain from intravenous drug use to be qualified as a good candidate for treatment. Likewise, his hepatitis C virus (HCV) coinfection and nonadherence to follow-up make this a very difficult case in which to justify the use of a complex HCV and HIV regimen.

2. The role of drug classes in the treatment of chronic HIV infection is as follows.

Drug Class	Role in Treatment of HIV
Nucleoside reverse transcriptase inhibitors (NRTIs)	• First-line therapy in combination with protease inhibitors and other NRTIs or NNRTIs
Non-nucleotide reverse transcriptase inhibitors (NNRTIs)	• First-line therapy in combination with PIs and other NRTIs or NNRTIs
Protease inhibitors (PIs)	• First-line therapy in combination with NRTIs or NNRTIs • These agents need to be given at full dose; however, ritonavir is used at a lower dose as a booster for many of these regimens.
Fusion inhibitor (FI)	• Treatment-experienced patients with HIV infection
CCR5 antagonist	• Treatment-experienced patients with HIV infected solely with R5 strains
Integrase inhibitors (INSTIs)	• Treatment-naive or treatment-experienced patients with HIV infection

3A. Efavirenz OR atazanavir/ritonavir OR darunavir/ritonavir OR raltegravir

PLUS

tenofovir/emtricitabine or lamivudine

3B. Efavirenz OR atazanavir/ritonavir OR darunavir/ritonavir OR raltegravir

PLUS

tenofovir/emtricitabine or lamivudine

The patient is receiving drugs that interact with atazanavir (proton pump inhibitor [PPI]) and the protease inhibitors (simvastatin). Could opt to use efavirenz plus tenofovir/emtricitabine to avoid these interactions or change statins to pravastatin and reassess for the need of a PPI and/or consider another acid-suppressive agent.

4A. This patient would need prophylaxis against *Pneumocystis jiroveci* and *Toxoplasma gondii* based on his CD4 count. Given the patient's sulfa allergy, atovaquone 1500 mg/day or pentamidine 300 mg inhaled monthly could be used for prevention of *P. jiroveci,* but only atovaquone would provide protection against both organisms; therefore, this would be the preferred regimen.

4B. Given this patient's CD4 count, she would need prophylaxis against *P. jiroveci*, *T. gondii,* and *Mycobacterium avium* complex. Given her history of cryptococcal meningitis, she would also require secondary prophylaxis for this infection. Use of trimethoprim/sulfamethoxazole double strength once daily will prevent infections caused by *P. jiroveci* and *T. gondii.* Azithromycin 1200 mg weekly would be preferred for the prevention of *M. avium* complex infection, although clarithromycin or rifabutin could be used as well. Fluconazole 200 mg daily would be the preferred secondary prevention regimen for cryptococcal infection.

5. The following table lists the drug classes associated with and management strategies for each of the provided clinical issues.

Clinical Issue	Associated Drug Class(es)	Clinical Management
Nonadherence	All drug classes present a challenge because several agents are required chronically for treatment.	• The patient's regimen should first be chosen according to viral characteristics (e.g., resistance patterns). • If adherence is a major issue, then an exploration of barriers to adherence should be assessed. Examples include lack of support for comorbid substance abuse, pill burden, cost, and adverse effects. • Regimens that have once-daily dosing or that are supplied as combination products would be the next step in choosing a regimen. Use of pillboxes and dose reminders should be considered. • Patients should be assessed for adverse effects because this is often an underlying reason for nonadherence. Regimens should be adjusted accordingly or adverse effects managed. • Guidelines endorse a multidisciplinary team approach to prevention and management.
Patients receiving chronic warfarin therapy	Protease inhibitors Some NNRTIs (efavirenz, nevirapine, etravirine)	• Monitor INR because most PIs will increase, but some (darunavir) may decrease. • NNRTIs may increase or decrease INR. • May consider alternative anticoagulants; however, some agents (rivaroxaban) may interact as well
Patients receiving chronic proton pump inhibitor therapy	Select agents in various classes have interactions with PPIs.	• Atazanavir/ritonavir is contraindicated in patients receiving > 20 mg daily of omeprazole. Consider an alternative PPI. Avoid PPIs with unboosted atazanavir. Also interacts with antacids and H2RAs • Use of rilpivirine with PPIs is contraindicated. Use alternative acid suppressive or ART. • Darunavir and tipranavir may require an increase in omeprazole dose. • Saquinavir bioavailability is enhanced; monitor for toxicity. Consider alternative acid suppressive

Clinical Issue	Associated Drug Class(es)	Clinical Management
Patients without prescription drug coverage	All therapies may be involved. Patients without prescription drug coverage present a challenge because they require lifelong therapy with multiple agents.	• Use of generically available drugs is preferred; however, many newer agents are not available generically. • Patient assistance programs should be explored to obtain either reduced drug costs or possibly drugs at no cost. This often requires that patients present information regarding assets or financial resources.
Development of dyslipidemia and/or hyperglycemia	All ritonavir-boosted PI-based regimens Efavirenz Abacavir Didanosine Zidovudine Stavudine Indinavir Lopinavir	• Patients should have a cardiovascular risk assessment at baseline, including fasting glucose and lipids. • Consider non–PI-based therapy if high baseline risk • Management of dyslipidemia involves a choice of drugs (e.g., statins) that do not interact with PIs. Monitor fasting lipids 4–8 weeks after initiating PI-based ART and then at 6 and 12 months in the first year. Can be every 12 months thereafter • Check A1c every 3–6 months for the first year and then every 6 months.
Requirement to take medications with food	Rilpivirine Atazanavir Darunavir Saquinavir Elvitegravir Etravirine Lopinavir/ritonavir (oral solution) Nelfinavir Tipranavir	• Patients should be educated on the type and quantity of food that needs to be coadministered. • Some food requirements are specific to certain formulations, so consider alternative formulations if problematic • Consider a food diary or reminders for each meal. • May choose alternative ART therapies if patient cannot adhere to the food requirements.

ART = antiretroviral therapy; H2RA = histamine-2 receptor antagonist; INR = international normalized ratio; NNRTI = non-nucleotide reverse transcriptase inhibitors; PI = protease inhibitor; PPI = proton pump inhibitor.

Cardiology

Activity 1: Hypertension (HTN) Medication

1. MOST appropriate JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) first-line drug class for each of the patient vignettes

Patient Vignettes	First-Line Drug Class
A 60-year-old white man with a history of STEMI BP = 144/82 mm Hg; HR = 80 beats/minute	β-Blocker
A 48-year-old African American woman with stable stage 4 CKD BP = 136/78 mm Hg; HR = 72 beats/minute	ACE inhibitor
A 55-year-old white woman discharged after a cerebrovascular accident BP = 158/92 mm Hg; HR = 80 beats/minute	ACE inhibitor Thiazide
A 32-year-old African American man with no comorbid conditions BP = 150/88 mm Hg; HR = 80 beats/minute	Thiazide

ACE = angiotensin-converting enzyme; BP = blood pressure; CKD = chronic kidney disease; HR = heart rate; STEMI = ST-segment elevation myocardial infarction.

Activity 2: HTN Case

2. This patient has one compelling indication (Framingham risk greater than 10%) resulting in a BP goal of less than 130/80 mm Hg.

3. Nonpharmacologic lifestyle modifications include weight reduction, DASH (Dietary Approaches to Stop Hypertension) diet, dietary sodium restriction (sodium intake, less than 2.4 g), and physical activity (at least 30 minutes most days of the week). The drug of choice in patients with high coronary artery disease (CAD) risk is an angiotensin-converting enzyme inhibitor.

Activity 3: Hyperlipidemia Medication Review

4. Agent comparison based on their lipid-lowering properties

Medications	LDL	HDL	Triglyceride
Fenofibrate	--	++	---
Simvastatin	---	++	--/---
Niacin	--	++	---
Colestipol	--	+	+
Ezetimibe	--	+	--

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Activity 4: Hyperlipidemia Case

5. The patient has three National Cholesterol Education Program (NCEP) risk factors including age (older than 45 years), HTN, and cigarette smoking. Patients with two or more NCEP risk factors, as well as a 10-year CHD risk between 10% and 20%, have a low-density lipoprotein (LDL) goal of less than 130 mg/dL. His current LDL concentration is 161 mg/dL, and he requires a 20% reduction.

6. Nonpharmacologic lifestyle modifications include weight reduction, dietary changes, and physical activity (at least 30 minutes most days of the week). The drug of choice in patients with elevated LDL is an HMG-CoA reductase inhibitor.

Activity 5: Peripheral Arterial Disease Medication Review Key

7. Agent comparison

Medications	Dose	Indicated for PAD or IC	Reduce Leg Pain or CV Morbidity
Aspirin	75–325 mg by mouth daily	PAD	CV morbidity
Clopidogrel	75 mg by mouth daily	PAD	CV morbidity
Cilostazol	100 mg by mouth 2 times/day	IC	Leg pain
Pentoxifylline	400 mg by mouth 3 times/day	IC	Leg pain

CV = cardiovascular; IC = intermittent claudication; PAD = peripheral arterial disease.

Activity 6: Peripheral Arterial Disease Case

8. The patient has an estimated ankle/brachial index (ABI) of 0.73 (right leg) with no signs or symptoms of vascular ischemia. This presentation is consistent with peripheral arterial disease. An ABI of less than 0.90 is consistent with arterial disease resulting in reduced blood perfusion.

9. Peripheral arterial disease should be managed with antiplatelet therapy to reduce cardiovascular risk. Either aspirin 75–325 mg by mouth daily or clopidogrel 75 mg by mouth daily can be recommended.

Activity 7: Stable Angina Medication Review

10. Agent comparison

Agent	Effect on Heart Rate (↑, ↓, no effect)	Effect on CV mortality (↑,↓, no effect)	Effect on Demand (↑,↓, no effect)	Effect on Angina Pain (↑,↓, no effect)
Isosorbide mononitrate	↓ or no effect	No effect	↓	↓
Ranolazine	No effect	No effect	↓	↓
Metoprolol	↓	↓	↓	↓
Enalapril	No effect	↓	↓	No effect
Diltiazem	↓	No effect	↓	↓

CV = cardiovascular.

Activity 8: Acute Coronary Syndrome Quality Review

11. The 2008 American College of Cardiology/American Heart Association (ACC/AHA) Quality Performance Measures met are as follows:

Agents	Met	Missed	Not Applicable
Aspirin at arrival		✓	
Aspirin prescribed at discharge	✓		
β-Blocker prescribed at hospital discharge	✓		
Statin prescribed at hospital discharge		✓	
ACE inhibitor or ARB for LVD prescribed at discharge		✓	
Evaluation of LV function	✓		
Time to fibrinolytic therapy for patients with STEMI or LBBB			✓
Time to PCI for patient with STEMI			✓
Smoking cessation counseling		✓	

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LBBB = left bundle branch block; LV = left ventricle; LV D = left ventricular dysfunction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Activity 9: Acute Coronary Syndrome Case

12. Thrombosis in myocardial infarction (TIMI) risk score

TIMI risk score	Age > 65 years	0 point
	> 3 CAD risk factors (family history, HTN, hyperlipidemia, DM, or smoking)	1 point
	Known CAD (> 50% stenosis)	0 point
	Aspirin use in past 7 days	1 point
	Recent severe angina (> 2 anginal events in previous 24 hours)	0 point
	Elevated cardiac markers	1 point
	ST-segment elevation	1 point
		4 points

13. Acute coronary syndrome plan for this patient

	List Medications (No Doses Needed)
ED to cardiac catheterization laboratory	Morphine Oxygen Nitroglycerin Aspirin β-Blocker
Within cardiac catheterization laboratory	Thienopyridine Glycoprotein IIb/IIIa inhibitor (with any anticoagulant except bivalirudin) Anticoagulant
Cardiac catheterization laboratory to discharge	β-Blocker Aspirin Nitrate ACE inhibitor Nitroglycerin Statin Thienopyridine

ACE = angiotensin-converting enzyme; ED = emergency department.

Activity 10: Heart Failure Medication Review

14. Agent comparison

Agents	Initiated in Which ACC/AHA Stage	Reduces Morbidity and Mortality? (yes/no)	Effect on Serum Potassium (↑,↓, none)
Digoxin	C	N	None
Quinapril	A	Y	↑
Carvedilol	B	Y	None
Spironolactone	C	Y	↑
Torsemide	C	N	↓

ACC/AHA = American College of Cardiology/American Heart Association.

Activity 11: Heart Failure Case

15. Decrease lisinopril to 10 mg by mouth daily. The vasodilator therapy should be down-titrated when hypotensive symptoms are related to a recent up-titration of a β-blocker. A decrease in metoprolol XL (extended release) to 25 mg by mouth daily should be considered if the down-titration of the vasodilator therapy fails. The benefits of a β-blocker are well recognized, so if hypotension alone is the problem, the dose of ACE inhibitor should be lowered first. An increase in furosemide to 80 mg by mouth daily is not recommended at this time because of the patient's low BP and lack of hypervolemic symptoms.

16. The discharge activity that meets the 2005 ACC/AHA Heart Failure Performance Measures is Answer C (provide discharge counseling on cardiac medications).

Activity 12: Atrial Fibrillation Case

17. Patient's $CHADS_2$ score:

Congestive heart failure	=	1 point
Hypertension	=	1 point
Age > 75 years	=	0 point
Diabetes	=	0 point
Previous stroke	=	0 point
		2 points

18. A stroke prophylaxis plan for this patient and the most appropriate dose of each agent are as follows:

Aspirin	Warfarin	Dabigatran	Rivaroxaban
Not indicated with a CHADS score of 2 or greater (81–325 mg/day)	Dose adjusted to INR 2–3	150 mg 2 times/day	20 mg once daily

CHADS = congestive heart failure, hypertension, age older than 75 years, diabetes, previous stroke; INR = international normalized ratio.

19. Amiodarone 400 mg 2 or 3 times/day x 2 weeks; then 400 mg/day for 4 weeks, followed by 200 mg/day. Amiodarone is indicated in patients with atrial fibrillation and systolic heart failure. Dofetilide can also be used in this situation; however, the baseline QTc interval is greater than 440 milliseconds.

Activity 13: Anticoagulation Medication Review

20. Clotting factors inhibited by each of the listed agents:

Unfractionated heparin	Factors II and X
Dalteparin	Factors II and X
Rivaroxaban	Factor X
Argatroban	Factor II

Activity 14: Intravenous Heparin Titration and Monitoring

21. Decrease infusion rate by 2 units/kg/hour.

Initial bolus: (80 units/kg) x 70 kg	=	5600 units
Initial infusion: (18 units/kg/hour) x 70 kg	=	1260 units/hour (round to 1250 units/hour)
New infusion rate	= = =	1250 units/hour - [(2 units/kg/hour) x 70 kg)] 1250 units/hour - [140 units/hour] 1110 units/hour (round to 1100 units/hour)

Activity 15: Warfarin Monitoring and Titration

22. The MOST appropriate recommendation for this patient is Answer C (decrease to warfarin 6 mg by mouth daily).

The patient's INR is supratherapeutic at 4.5 with an INR goal of 2.5. The patient is not experiencing signs or symptoms of bleeding and has an INR of less than 5.0, so a reversal agent is not required. One or two doses of warfarin should be held, and the total weekly dose should be decreased by 10% –15%.

7 mg/day x 7 days = 49 mg/week

49 mg x 10% = 4.9 mg = ~5-mg/week reduction	49 mg x 15% = 7.35 mg = ~7-mg/week reduction
49 mg - 5 mg = 44 mg/week	49 mg - 7 mg = 42 mg/week
44 mg/7 days = 6.3 mg/day = ~6 mg/day	42 mg/7 days = 6 mg/day

GASTROENTEROLOGY

1. This patient presents with troublesome gastroesophageal reflex disease (GERD) symptoms that frustrate him. Given that the symptoms occur after meals and are improved with positional changes makes GERD most likely. The patient's amlodipine and metformin could be causing increased symptoms as well. Initiation of targeted lifestyle modifications, including dietary changes and weight loss, should be recommended. Initiation of acid-suppressive therapy would also be appropriate. Because this patient has symptoms more often than 2 days/week, use of a proton pump inhibitor (PPI) on a scheduled basis would be recommended. Given the patient's age, he would also be appropriate to refer for endoscopy, particularly if he does not respond to therapy.

2. This patient presents with symptoms that may be consistent with GERD. Because she has symptoms only 1 or 2 days/week, she may be able to use an on-demand therapy, with either an antacid or a histamine receptor antagonist. Low dose daily PPI therapy would also be acceptable as an alternative strategy. The patient has end-stage renal disease, so avoidance of magnesium- and aluminum-containing products would be preferred. Calcium-based antacids may be preferred. If a histamine receptor antagonist were used, appropriate dosing on the basis of renal function would be needed. Cimetidine should be avoided because of a potential interaction with clopidogrel. Likewise, if a PPI were used, avoidance of omeprazole and esomeprazole would be preferred to prevent reductions in clopidogrel effectiveness.

3. The PPIs have been associated with several types of adverse effects with long-term use. These include risk of infection such as pneumonia and *Clostridium difficile* infection; increased risk of fracture; reductions in serum magnesium; and anemia. This patient has esophagitis, for which PPIs are the best therapy. The risk of the potential adverse effects listed above has generally been reported with odds ratios of 1–2.5, with most studies being observational or retrospective. For this patient, the benefit of using the PPI would outweigh the risk. Because the patient is not at high risk of fracture, the patient should not require calcium or vitamin D supplementation, although measurement of a serum vitamin D concentration could be performed.

4. This patient would be considered high risk because of the presence of two or more risk factors, including age older than 65 years, use of corticosteroids, and use of high-dose NSAID (nonsteroidal anti-inflammatory drug) therapy.

5. Potential pros and cons of these *H. pylori* treatment regimens include the following.

Regimen	Pros	Cons
Amoxicillin/ clarithromycin + PPI	• Less pill burden than quadruple therapy	• Potential for reduced effectiveness because of high rates of clarithromycin resistance • Cannot use in patients with penicillin allergy • Drug interactions and adverse effects with clarithromycin (dyspepsia, metallic taste) • Requires 14 days of therapy for maximal effectiveness
Bismuth + metronidazole + tetracycline + PPI	• Generally more effective than triple therapy • Can use in patients with penicillin allergy • Metronidazole resistance can be overcome with increases in dose	• Higher pill burden than triple therapy • Adverse effects with bismuth (dark stool) and metronidazole (nausea, metallic taste), tetracycline (photosensitivity) • Requires 14 days of therapy for maximal effectiveness

PPI = proton pump inhibitor.

6. This patient should have received at least 10–14 days of therapy according to the treatment guidelines. Retesting for eradication of *H. pylori* should be performed no sooner than 4 weeks after treatment to prevent false-negative tests. The serum IgG (immunoglobulin G) test should not be used for retesting because it remains positive, even after eradication. Use of the urea breath test or fecal antigen test is preferred. Thus, this patient should be retested in at least another 2 weeks using the urea breath test or fecal antigen test.

7. This patient would be at risk of SRMB and require preventive therapy because of the presence of coagulopathy (INR [international normalized ratio] greater than 1.5), one of the two major independent risk factors for SRMB. The patient also has hepatic failure, which is additive in risk.

8. Potential pros and cons of these treatment regimens for encephalopathy include the following.

Regimen	Pros	Cons
Lactulose	• Inexpensive • Proven efficacy • Flexible dosing	• Not well tolerated because of titration on the basis of stool frequency • May not be palatable to some patients • Requires many doses a day • May be combined with other agents
Neomycin	• Inexpensive • Proven efficacy similar to lactulose • Minimal absorption	• Requires many doses a day • Possible risk of nephrotoxicity in patients with CKD • May be combined with other agents
Rifaximin	• Efficacy similar to that of lactulose and neomycin • Minimal absorption • No risk of nephrotoxicity	• Expensive • FDA approved only for prevention • 2 or 3 times/day dosing • Widespread use may promote resistance

CKD = chronic kidney disease; FDA = U.S. Food and Drug Administration.

9. This patient has evidence of portal hypertension because of the presence of esophageal varices and ascites. The patient, who has undergone variceal band ligation, should receive therapy to prevent variceal bleeding. Nonselective β-blockers are preferred; however, given the presence of asthma, they would be a contraindication. This patient would need to have an annual screening endoscopy with variceal band ligation as the preventive therapy of choice. For management of ascites, the patient should receive diuretic therapy, preferably with furosemide and spironolactone at a starting dose of 40 mg/100 mg. The patient's ascetic fluid does not meet the criteria for spontaneous bacterial peritonitis, so antibiotic therapy is not indicated.

10. Provide the role of the following drug therapies in the treatment of chronic viral hepatitis.

Drug Therapy	Role in Treatment of Viral Hepatitis
Lamivudine	Second-line (nonpreferred) therapy for HBV per guidelines
Entecavir	First-line monotherapy option for HBV per guidelines
Tenofovir	First-line monotherapy option for HBV per guidelines
Adefovir	First-line monotherapy option for HBV per guidelines
Telbivudine	Second-line (nonpreferred) therapy for HBV per guidelines
Pegylated interferon alfa 2a or 2b	First-line monotherapy option for HBV per guidelines and first-line option for chronic HCV in combination with ribavirin and telaprevir or boceprevir (genotype 1)
Telaprevir	First-line option for chronic HCV genotype 1 in combination with ribavirin and pegylated interferon alfa 2a or 2b

Drug Therapy	Role in Treatment of Viral Hepatitis
Boceprevir	First-line option for chronic HCV genotype 1 in combination with ribavirin and pegylated interferon alfa 2a or 2b
Ribavirin	First-line option for chronic HCV in combination with pegylated interferon alfa 2a or 2b and telaprevir or boceprevir (genotype 1)

PULMONARY DISEASES

CASE 1

1. Using the National Heart, Lung and Blood Institute (NHLBI) guidelines, this patient would be classified as having moderate persistent asthma. This is based on the most severe category of classification using his forced expiratory volume in 1 second (FEV_1) of 68% of predicted.

2. Exposure to potential environmental triggers, family history, and insurance status may be useful information for making an assessment and a plan.

3. The NHLBI guidelines recommend initiating treatment at step 3, with the preferred treatment being a low-dose inhaled corticosteroid (ICS) plus a long-acting β-agonist (LABA) OR a medium-dose ICS alone. Given the recent safety concerns with LABAs, it would be preferable to initiate a medium-dose ICS (see Table 4 of Pulmonary Diseases chapter). The patient would also need a short-acting β-agonist (SABA) as needed for rescue. Modification of trigger exposure and construction of an action plan would also be preferred.

CASE 2

4. Using the NHLBI guidelines, this patient would be classified as having a life-threatening asthma exacerbation on the basis of her minimal response to a SABA and her FEV_1 of less than 25% of predicted.

5. This patient should receive oxygen with a nebulized SABA plus ipratropium as well as a dose of intravenous corticosteroids, such as methylprednisolone, with continuous oxygen saturation monitoring.

6. Both the NHLBI guidelines for asthma and the GOLD (Global Initiative on Obstructive Lung Disease) guidelines for COPD have adopted the use of the following rating scale to rate the strength of evidence. Not all guidelines use the same rating scale to grade evidence. Clinicians need to familiarize themselves with the scale to be used for the respective guideline to accurately interpret the recommendations. Therapeutic recommendations should be made using the highest level of evidence, if possible; however, based on the body of evidence, data may be limited, requiring the use of clinical judgment.

Evidence Category	Sources of Evidence
A	Randomized clinical trials Rich body of data
B	Randomized clinical trials Limited body of data
C	Nonrandomized trials Observational studies
D	Panel judgment consensus

Case 3

7. Assessment of inhaler technique, presence of potential adverse effects, ability to afford the medication given the loss of work, and continued exposure to potential environmental triggers would be helpful in assessing this patient's control.

8. This patient would be classified as not well controlled on the basis of SABA use greater than 2 times/week. This patient is using a low-dose ICS (beclomethasone 160 mcg/day), which is consistent with step 2 therapy according to the NHLBI guidelines. Recommendations for patients who are not well controlled are to increase to the next step of therapy. Options include adding a LABA or increasing to a medium dose of the ICS. Given the recent safety concerns with LABAs, it would be preferable to increase to a medium dose of beclomethasone.

Case 4

9. This patient would be classified as patient group D stage III (severe) on the basis of an FEV_1 between 30% and 50% of predicted, less than 2 exacerbations per year and a CAT score greater than 10.

10. A complete plan for this patient would include the initiation of a SABA as needed with one or more long-acting bronchodilators. According to the GOLD guidelines, the first choice for patient group D would be an inhaled corticosteroid plus a long-acting β-agonist or a long-acting anticholinergic, such as tiotropium, alone. The patient should be educated on the proper use of inhalers. Assessment for pneumococcal and influenza vaccinations, initiation of smoking cessation, use of home oxygen therapy, and potential referral for pulmonary rehabilitation would be preferred as well.

11. This patient would be considered to have a moderate-severe exacerbation on the basis of her oxygen saturation of less than 90% and tachypnea. The patient was admitted to a general medicine floor for management and did not require admission to an intensive care unit or have a need for mechanical ventilation.

12. The patient should receive oxygen therapy and a nebulized SABA plus an anticholinergic, as well as an oral corticosteroid at a dose of 30–40 mg/day of prednisone equivalent. Use of antibiotics is technically not indicated because only two of the three cardinal symptoms are present (dyspnea and increased sputum volume). Had increased sputum purulence been present, antibiotics would have been indicated.

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