
Supplemental Digital Appendix 1

Interview Guide for Exploratory Study of the Therapeutic Reasoning Underlying Physicians' Choice of Antimicrobial

INTRODUCTORY TEXT

I am interested in the way infectious diseases knowledge is organized among practicing physicians. I am going to ask you a series of questions that attempt to understand the reasoning that underlies empiric choice of antimicrobials. The first part of the survey will be related to vignettes that ask you to reason through empiric antimicrobial selection in a specific case, while the remainder of the interview will be focused on your antimicrobial reasoning more generally. Do you have any questions before we begin?

I'd like to start with a few questions about your clinical experience.

1. Which of the following best describes roughly how many years of clinical practice experience you have (not including training)? 0-4, 5-10, 11-15, >15?

2. What percentage of your work time is dedicated to direct patient care, either as an independent provider or as an attending physician on a team?

3. Do you work in the inpatient setting, the outpatient setting, or both?

VIGNETTES
Now I would like to share three vignettes structured like board-style questions that will help explore your antimicrobial reasoning process.

VIGNETTE #1 [*will be provided to the interviewee to follow along as the interviewer reads*]
A 60-year-old woman with a past medical history of type 2 diabetes mellitus and atrial fibrillation presents with fevers and progressively worsening shortness of breath for the past 3 days. On review of systems, she also endorses fatigue, malaise, and productive cough. She takes metformin, glyburide, metoprolol XL, and warfarin. She has no known drug allergies. She works as a nurse and lives with her spouse in an apartment. She has a 5 pack-year smoking history but quit 37 years ago. She denies alcohol or drug use.

On exam, her vitals are: temperature of 39.3, heart rate of 89, blood pressure of 146/89, respiratory rate of 32, and an oxygen saturation of 88% on room air that corrects to 100% on 3 liters of oxygen via nasal cannula. She appears unwell but is not in acute distress, and there are crackles in her left lower lobe. Laboratory studies reveal:

WBC 16.3	Creatinine 1.4 (baseline is 0.7)
HGB 15	
HCT 47	
Platelets 227	
+Immature granulocytes, Left Shift	

Chest x-ray shows a consolidation in the left lower lobe. She is admitted to the hospital.

4. How would you choose what antibiotics to use in this case? Please explain the steps in your reasoning process as you would to a third-year medical student on your team who has not had to manage this type of patient before.

VIGNETTE #2 [*will be provided to the interviewee to follow along as the interviewer reads*]
A 73 year-old man with a past medical history of type 2 diabetes mellitus, chronic kidney disease stage 2, and hypertension on metformin, lisinopril, and several over-the-counter vitamins and supplements presented two days ago with a right lower extremity redness and pain concerning for severe cellulitis. He denied any fevers. He has improved on vancomycin since admission. He has no known drug allergies. He lives in an assisted living facility and is a retired schoolteacher. He is a lifetime nonsmoker and denies drug use but has approximately 4 alcoholic beverages weekly.

On exam today, his vitals are: temperature of 37, heart rate of 72, blood pressure of 135/84, respiratory rate of 16, and an oxygen saturation of 99% on room air. He appears well. His right lower extremity remains mildly erythematous, but the redness has receded several inches from the line of previous demarcation, and no other skin abnormalities are apparent besides a small

healing abrasion on his right lower shin where he scraped his leg a week ago; the erythema extends from this abrasion. There is trace right lower extremity edema, and the erythematous area remains slightly warm to the touch. You think he is ready for discharge from the hospital.

5. How would you choose what antibiotics to use in this case? Please explain the steps in your reasoning process as you would to a third-year medical student on your team who has not had to manage this type of patient before.

VIGNETTE #3 [*will be provided to the interviewee to follow along as the interviewer reads*]
An 85 year-old woman with a past medical history of hypertension, type 2 diabetes mellitus, and chronic pain presented with fevers and confusion two days ago. She was unable to participate in review of systems at the time of admission. She is on lisinopril, metformin, and methadone. She has no known drug allergies. She lives with her sister and is a retired office manager. She is a lifetime nonsmoker and does not use alcohol or drugs. On initial exam, her vitals were: temperature of 39.3, heart rate of 105, blood pressure of 146/89, respiratory rate of 20, and an oxygen saturation of 98% on room air. She appeared unwell but was not in acute distress. She was confused but had a nonfocal limited neurologic exam. Her abdomen was non-distended and soft, but she groaned and grimaced with palpation of her suprapubic area. There was no costovertebral angle tenderness. Laboratory studies revealed:

WBC 15.7
HGB 14.6
HCT 37
Platelets 335
+Immature granulocytes, Left Shift

Creatinine 1.4 (baseline is 0.5)

Urinalysis: 0 RBCs/hpf, >50 WBCs/hpf, +leukocyte esterase, +nitrite, no squamous cells

She was started on ceftriaxone and admitted to the hospital. Now on hospital day 3, she is back to her neurologic baseline, has normal vital signs, and her creatinine has improved to 0.9. You think she is ready for discharge. However, the following microbiology results from the day of admission return:

Blood Culture: *Escherichia coli* in both bottles
Urine Culture: *Escherichia coli*

The *Escherichia coli* in both cultures has the following susceptibility pattern:

ANTIBIOTIC	**MIC** (mcg/mL)	**INTERPRETATION**
Ampicillin/Sulbactam	16	Resistant
Aztreonam	≤ 1	Sensitive
Cefazolin	2	Sensitive
Ceftriaxone	≤ 0.5	Sensitive
Ciprofloxacin	≤ 0.5	Sensitive

Gentamicin	≤ 2	Sensitive
Levofloxacin	≤ 1	Sensitive
Nitrofurantoin	≤ 32	Sensitive
Piperacillin/Tazobactam	≤ 8	Sensitive
Tobramycin	≤ 2	Sensitive
Trimethoprim/Sulfamethoxazole	≤ 2	Sensitive

6. How would you choose what antibiotics to use in this case? Please explain the steps in your reasoning process as you would to a third-year medical student on your team who has not had to manage this type of patient before.

GENERAL QUESTIONS

Now I would like to ask you some general questions about your infectious diseases reasoning.

7. Think back to the last infection you treated. How did you choose antibiotics in that case?

8. Reflecting on the last few questions, please write out the steps in your general antibiotic reasoning process on these 3x5 notecards and arrange them in the order they occur. If two steps occur at the same time, place them side-by-side.

9. What clinical resources do you use when managing infectious diseases?

9A. When do you use these resources? (In what clinical situations do you use…)

9B. How often do you use these resources?

Supplemental Digital Appendix 2

All Codes Used During Analysis of Data From Interviews and Notecard Exercise in an Exploratory Study of the Therapeutic Reasoning Underlying Physicians' Choice of Antimicrobial

1. NAMING THE SYNDROME

1A. Naming the Syndrome Generally

[PROCESS CODE] Specifically stating the diagnosis, or specifically stating that the diagnosis needs to be defined. Typically a brief factual statement. Can include reasoning that supports the diagnosis, but this is not required. May reference source of infection or site of infection rather than a specific diagnosis. May also mention that the clinician needs to ensure that they have the correct diagnosis.

1B. Features of the Case that Support the Diagnosis

Mention of evidence that supports the naming of a particular syndrome or diagnosis, such as vital signs, exam findings, laboratory studies, etc. Different than "Differentiating Features" code, which describes the nuanced features of a presentation beyond a particular diagnosis.

2. DELINEATING PATHOGENS

[PROCESS CODE] Mention of specific organisms (or classes or types of organisms) likely to cause the patient's presentation, or mention that particular information would help make the pathogens definable or change the microbiologic differential. May mention where this information could be obtained if not known, or may mention that the likely pathogens should be determined or that the clinician should attempt to determine them as part of the reasoning process. May mention data from cultures (which would include co-code of "Microbiologic Data"). Indicating that risk factors for MDR (multi-drug resistant) organisms should be considered would be included in this code.

3. ANTIMICROBIAL (THERAPY SCRIPT) SELECTION

[PROCESS CODE] Mention of the process of choosing between antimicrobials or selecting a particular antimicrobial. May involve the respondent only making a statement of what antimicrobial they would choose, without any reasoning or justification for doing so.

4. PRE-EXISTING PATIENT CHARACTERISTICS

4A. Pre-existing Patient Characteristics in General

Mention that, in general, pre-existing patient characteristics should be considered without specifying how they would inform the reasoning process or even which specific characteristics should be considered. Use only if mention of pre-existing patient characteristics never further specified in response.

4B. Age

4Bi. Age in General

Mention of patient age in general, without considering specific effects. Does not include statements of the "one-liner," such as: "This is a 60 year-old woman with…"

4Bii. Age Affecting Antimicrobial Choice

Mention that a patient's age may affect which antimicrobial is chosen. Often in reference to adverse effects being common in certain age groups, which would co-code with "Adverse Effects."

4C. Allergies

Mention of a patient's allergies. May be in relation to antimicrobial choice.

4D. Exposures

Mention of specific patient exposures. May or may not be mentioned in the context of raising concern for specific pathogens. Examples include past hospitalizations, place of residence (nursing home, etc), occupation or place of employment, sick contacts, travel. May mention season of the year.

4E. Medical History

4Ei. Comorbidities

4Eia. Comorbidities Generally

Mention of patient comorbidities generally, not including past or current infections. Use only if mention of comorbidities never further specified in response.

4Eib. Comorbidities Affecting the Microbiologic Differential

Mention of specific patient comorbidities – such as immunocompromising condition or structural lung disease – that change the microbiologic differential (such as raising concern for specific pathogens or resistant organisms). Does not include past or current infections.

4Eic. Comorbidities Affecting Treatment Choice

Mention that certain patient comorbidities should be considered in choosing the appropriate antimicrobial. In particular, may mention that certain antimicrobials should be used in patients with certain comorbidities or avoided in patients with certain comorbidities, in many cases due to the potential for adverse effects. Does not include instances in which the respondent is indicating that different antimicrobials should be chosen because of concern for certain pathogens because of the patient's comorbidities (which would be coded as "Comorbidities Affecting the Microbiologic Differential"). May specifically mention renal or hepatic function

affecting drug clearance, which may have a "Clearance/Metabolism" co-code. Does not include past or current infections.

4Eid. Comorbidities Affecting the Illness Trajectory/Risk of Complications

Mention that certain patient comorbidities affect the risk of infectious complications without mentioning treatment selection or the microbiologic differential. Does not include past or current infections.

4Eii. Ability to take Oral Medications

Mention of a patient's ability to tolerate or absorb oral medications. Likely mentioned in relation to its influence on antimicrobial choice.

4Eiii. Past Infections

Mention of a patient's past pathogens or infections, likely in relation to helping define current pathogens or infections. If the respondent mentions past, unrelated infections only in reference to past antimicrobials the patient has taken, this should be coded only as "Prior Exposure to Antimicrobials."

4F. Medications

4Fi. Prior Exposure to Antimicrobials

Mention of prior exposure to antimicrobials, which may be couched in terms of raising concern for resistant organisms. Could also mention that recurrence of an infection after recent antimicrobials might also warrant choosing a different class of antimicrobials. Does not include antimicrobials prescribed for the current presentation/illness, which would be coded under "Illness Trajectory."

4Fii. Current Medications

Mention of the patient's current medication list not including antimicrobials, likely as a factor in antimicrobial selection. Typically in reference to drug-drug interactions (DDIs)with antimicrobials, or compounded adverse effects between current medications and potential antimicrobial choices, which would be co-coded with "DDIs."

4Fiii. Existing Pill Burden

Mention of the patient's existing pill burden, likely in terms of how it affects antimicrobial choice (in relation to the added burden of the new antimicrobial medication).

4G. Social Factors

4Gi. Ability to Adhere

Mention of a patient's ability to adhere, likely in relation to how this affects antimicrobial choice. May also include mention of social support or health literacy.

4Gii. Financial Factors

Mention of cost to patient or insurance issues as factors in antimicrobial choice. Should be specific to the patient and their financial/insurance situation and not just to the drug/health system, which would be coded under "Cost & Pharmacy Considerations."

4Giii. Likelihood of Follow-Up

Mention of a patient's likelihood of follow-up, or ability to get follow-up. Often in relation to antimicrobial choice, as the respondent may indicate that some antimicrobials warrant closer follow-up. May be co-coded under "Monitoring for Adverse Effects" depending on what follow-up is required for a particular drug.

4H. Patient Preferences

Mention that a patient may express preferences regarding antimicrobial choice, or that their preferences should be explored/considered. May also mention shared decision-making.

5. CURRENT CASE FEATURES

5A. Differentiating Features of the Current Case

5Ai. Differentiating Features Generally

Mention of features of the current case that help define the clinical situation, without specifying how. Could be an exam feature, laboratory study, radiographic finding, complication, etc. May mention additional data the respondent would want to collect. Should be information that goes beyond naming the syndrome. Does not include microbiologic data like culture results or the desire to obtain cultures/serologies, which should be coded under "Microbiologic Data".

5Aii. Differentiating Features that Affect the Microbiologic Differential

Mention of features of the current case that help define the microbiologic differential. Could be an exam feature, laboratory study, radiographic finding, complication, etc. May mention additional data the respondent would like to collect. May mention that these features are an imperfect

surrogate for microbiologic data. Does not include microbiologic data like culture results or the desire to obtain cultures/serologies, which should be coded under "Microbiologic Data".

5Aiii. Differentiating Features that Affect Treatment Choice
Mention of features of the current case that help define the clinical situation from the standpoint of determining what treatment is warranted. Could be an exam feature, laboratory study, radiographic finding, complication, etc. May mention additional data the respondent would want to collect. Does not include microbiologic data like culture results or the desire to obtain cultures/serologies, which should be coded under "Microbiologic Data".

5B. Microbiologic Data
Specific mention of the presence or absence of microbiologic data (cultures, serologies, respiratory viral testing, etc) within the current case as helping to define the microbiologic differential, or mention of specific organisms obtained from culture. May mention the desire to obtain culture data or that some steps in the reasoning process may be skipped when culture data is available. Likely would be co-coded with "Delineating Pathogens."

5C. Severity of Present Illness

5Ci. Severity of Present Illness in General
Statement of the severity of current clinical presentation as altering how the case is considered, without specifying how. May mention place of treatment as a proxy for severity.

5Cii. Severity of Present Illness Affecting the Microbiologic Differential
Statement of the severity of the current clinical presentation as altering the microbiologic differential. If the respondent indicates that treatment choice also changes as a result of the microbiologic differential changing, would NOT be co-coded with "Severity of Illness Affecting Treatment Choice" but would be co-coded with "Pathogen-Based Treatment." May reference place of treatment as a proxy for severity.

5Ciii. Severity of Present Illness Affecting Treatment Choice
Statement of the severity of the current clinical presentation as affecting treatment considerations without reference to the intervening microbiology (which would be coded as "Severity of Illness Affecting the Microbiologic Differential" AND "Pathogen-Based Treatment"). May reference place of treatment as a proxy for severity.

5D. Trajectory of Present Illness

5Di. Trajectory of Present Illness in General

Mention of a patient's trajectory of present illness - including response (or lack of response) to current antimicrobial treatment and/or the achievement of source control - affecting how the case is considered in general.

5Dii. Trajectory of Present Illness affecting the Microbiologic Differential

Mention of a patient's trajectory of present illness - including response (or lack of response) to current antimicrobial treatment and/or the achievement of source control - affecting the microbiologic differential. Could mention that failure of current antimicrobial therapy might warrant considerations of different pathogens or resistance.

5Diii. Trajectory of Present Illness affecting Treatment Choice

Mention of a patient's trajectory of present illness - including response (or lack of response) to current antimicrobial treatment and/or the achievement of source control - affecting the decision to step-down antimicrobial therapy or switch from IV to PO therapy (which would be co-coded as "Route of Delivery"). Could also mention that failure of current antimicrobial therapy might warrant switch to a different therapy, although should not mention the intervening microbiology (which would be coded as "Trajectory of Present Illness affecting the Microbiologic Differential").

6. PROVIDER AND HEALTHCARE SYSTEM FACTORS

6A. Antibiogram

Mention of the institutional antibiogram (or institutionally-derived/local resistance patterns), often in reference to choosing appropriate empiric antimicrobial therapy.

6B. Clinical Experience

Mention that part of the treatment decision is based on what, in the respondent's experience, has worked for similar patients in the past. May mention that these decisions could be different from other physicians and/or change over time. May involve individual provider treatment preferences.

6C. Institution-Specific Practices

Mention that treatment selection might be related to institution-specific practice patterns. May mention that these practices change over time or could be influenced by senior or extremely knowledgeable members of the healthcare system. Should not specifically reference institutional guidelines or protocols, which would be coded under "Evidence-Based/Guideline-Supported Treatment."

6D. Supporting Trainee Choices

Mention that, if working with trainees, the respondent tries to support trainee choices as long as they are reasonable, even if the respondent might choose something slightly different if working independently.

7. TREATMENT PRINCIPLES

7A. Pathogen-Based Treatment

Mention that the antimicrobial selection will be or should be based on the pathogen(s) or likely pathogen(s).

7B. Evidence-Based/Guideline-Supported Decisions

Mention that guidelines (national, local, etc) or data/literature should support the treatment choice or that the respondent would want to consult the literature/data/guidelines before making a decision. Could also mention that the studies or guidelines don't fit a particular patient or that data are lacking in a certain clinical realm.

7C. Narrow Coverage

Mention that antimicrobial coverage should be as narrow as possible or should be narrowed as soon as sufficient time has passed or additional information is available – possibly in relation to starting more broadly for sicker patients and then narrowing. May mention the need to preserve broader choices for situations when they are actually needed.

7D. Parsimony

Mention that the fewest possible number of antimicrobials should be used. May mention "elegance" in an antimicrobial regimen.

8. ANTIMICROBIAL (THERAPEUTIC) SCRIPT CONTENT

8A. Adverse Effects

Mention that certain adverse effects may make the antimicrobial a less attractive choice. Conversely, could mention that fewer or less severe adverse effects may make the antimicrobial an attractive choice.

8B. Cost & Pharmacy Considerations

Mention of an antimicrobial's availability within a pharmacy or its formulary status, typically as a factor in antimicrobial choice. May also mention the cost of the antimicrobial to the institution or patient, as well as whether it is generic or not. Should reference the cost of an individual drug, not just the patient's financial situation. If mentions a particular patient's financial situation, would be co-coded as "Financial Factors."

8C. Dosing

8Ci. Dosing Generally

Mention of an antimicrobial's dosing characteristics generally and not specific to antimicrobial choice. Dose adjustments related to metabolic/clearance issues should be coded under "Clearance/Metabolism," although these may be co-coded.

8Cii. Dosing Affecting Treatment Choice

Mention that an antimicrobial's dosing characteristics – such as number & frequency of pills – might affect antimicrobial choice. Dose adjustments related to metabolic/clearance issues should be coded under "Clearance/Metabolism" although these may be co-coded if it affects antimicrobial choice. May be co-coded with "Pill Burden" if the patient's pre-existing medication list is mentioned in relation to antimicrobial dosing.

8D. Drug-Drug Interactions

Mention of any known drug-drug interactions that the antimicrobial has, especially in relation to the patient's current medications. Or may mention any plan to check for DDIs even if the interactions are not known by the respondent specifically.

8E. Duration of Therapy

Mention that a particular antimicrobial might be preferred because of a shorter duration of therapy or less preferable because of a longer duration of therapy. Should be specific to a particular antimicrobial. If respondent only discusses duration of therapy in relation to the syndrome, should be coded as "Other."

8F. Evidence of Efficacy/Guideline Support

Mention of any evidence in favor of a particular antimicrobial, or that the available evidence should be compared between antimicrobials. Often will be co-coded with "Evidence-Based/Guideline-Supported Decisions" if that seems to be a treatment principle guiding the respondent's reasoning. Could be data (in vitro,

in vivo, retrospective analyses, trials), other literature, guidelines, expert opinion, references to efficacy, etc.

8G. Monitoring for Adverse Effects

Mention of the monitoring required for certain antimicrobials & how this might influence antimicrobial selection, or be required if a certain antimicrobial were chosen as a way of choosing between antimicrobial options.

8H. Pharmacodynamics

Mention of how the antimicrobial will likely act on the pathogenic organism. May reference only in relation to interpretation of the MIC (mean inhibitory concentration) and/or breakpoints. May mention how local resistance patterns and the strength of coverage of certain pathogens by certain antimicrobials relate to antimicrobial choice. Actual resistance information as obtained from microbiologic/culture data should be coded under "Microbiologic Data" since it pertains to an actual feature of the case rather than the therapeutic script, unless the respondent specifically discusses breakpoints for a particular antimicrobial, etc., in which case both codes would be used.

8I. Pharmacokinetics

8Ii. Pharmacokinetics Generally

Mention of the pharmacokinetics of a particular antimicrobial, without specifying which aspect.

8Iii. Bioavailability

Mention of how an antimicrobial's bioavailability (oral absorption) might influence antimicrobial choice.

8Iiii. Drug Distribution

Mention that an antimicrobial's distribution to certain areas of the body might influence antimicrobial choice. Often mentioned in relation to the organ or system being affected by the current infection.

8Iiv. Clearance/Metabolism

8Iiva. Clearance/Metabolism Generally

Mention of how an antimicrobial is cleared or metabolized generally, without specifying that it would affect treatment choice. May mention in relation to the patient's comorbidities (renal or liver failure) and the need to dose-adjust an antimicrobial. May not specifically mention the words clearance or metabolism.

8Iivb. Clearance/Metabolism Affecting Treatment Choice

Mention of how an antimicrobial is cleared might affect antimicrobial choice, rather than just dose adjustment. Likely in relation to a patient's comorbidities like renal or liver failure. May not specifically mention the words clearance or metabolism.

8J. Route of Delivery

8Ji. Route of Delivery Generally

Mention of an antimicrobial's route of delivery as part of the antimicrobial selection process. May relate specifically to the decision to use PO or IV antimicrobials, or transition between IV and PO.

8Jii. Consistency between IV and PO

Mention that consistency of coverage between IV and PO is a priority in treatment selection.

8K. Safety in Pregnancy

Mention of an antimicrobial's safety in pregnancy as related to antimicrobial choice.

8L. Spectrum

Mention of the spectrum of an antimicrobial as related to treatment selection, specifically in relation to how broad or narrow it is. May mention the spectrum being too broad or too narrow. Should be in general and not related to actual culture data or MICs.

9. OTHER (THINGS NOT RELATED TO ANTIMICROBIAL SELECTION BUT MENTIONED ANYWAY)

Mention of other factors in treatment NOT related to antimicrobial choice/selection. For instance, may call into question whether treatment (or further treatment) is warranted or may mention the possibility of non-infectious diagnoses that remain on the differential, the need for further evaluation to determine the cause of an infection, the need for patient isolation given the risk of transmission, non-antimicrobial treatments that are important in managing the patient. May mention duration of therapy in relation to the syndrome rather than the antimicrobial.

