Research Design, Biostatistics, and Literature Evaluation

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Chicago, Illinois
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Learning Objectives

1. Identify factors influencing the conduct of essential critical care research.
2. Justify the need for literature evaluation to apply to clinical practice.
3. Judge the appropriateness of various statistical tests for a set of data.
4. Distinguish between various types of knowledge for application to patient care.

Abbreviations in this Chapter

ARDS  Acute respiratory distress syndrome  
CDI   Clostridium difficile infection  
NMBA  Neuromuscular blocking agent  
QI    Quality improvement

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A clinical trial is being planned to determine the optimal resuscitation fluid for trauma patients. This study will seek to determine whether the administration of crystalloid fluid, lactated Ringer solution, or a transfusion strategy—packed red blood cells—in the trauma field improves survival to hospital discharge. The investigator team has consulted with various ethics scholars to identify relevant issues to be addressed in the trial design. Which issue is most relevant to the ethical conduct of this study?
   A. Treatment blinding.
   B. Uninformative study population.
   C. Consent obtained from injured subjects.
   D. Design as a noninferiority trial.

2. In recent studies of septic shock, 28-day mortality has been reported to be around 20% in the standard treatment arm. Earlier estimates of septic shock were 35%–40%, according to the results of previous trials and epidemiologic studies from the past 10 years. The investigators of a new study are seeking to identify the optimal end point or study population to test the effectiveness of a novel drug compound for the treatment of septic shock. The novel drug compound is a recombinant protein that mediates the inflammatory cascade of sepsis and has shown impressive results for all etiologies of septic shock in preclinical animal studies. Which best describes the rationale for selecting a study population or primary end point?
   A. The study should limit study inclusion to patients without a high level of comorbid conditions at baseline to limit confounders.
   B. The study should expand the target population to include patients with severe sepsis, not just septic shock, to show a 28-day mortality benefit.
   C. The study should select 90-day mortality instead of 28-day mortality as a primary end point to show the durability of the treatment effect.
   D. The study should limit study inclusion to patients with septic shock caused by pneumonia to test a relevant study population.

3. A quality improvement (QI) initiative is implemented to improve the dosing of antimicrobials for patients with septic shock presenting to the emergency department. As the pharmacy representative, you have worked with the pharmacy operations team to ensure that an appropriate selection of antibacterial agents and doses are available in the automated drug-dispensing machines. Which factor will be most important in showing the effectiveness of this QI initiative?
   A. Obtaining informed consent for participation in the QI initiative.
   B. Identifying patients with septic shock in triage.
   C. Creating a community advertising campaign to bring awareness to the initiative.
   D. Determining the social value of the QI initiative.
4. An epidemiologic study seeks to determine the impact of adverse drug events in the intensive care unit (ICU) on patient outcomes. Which would be the best approach to conducting this study?
   A. A randomized controlled trial with a test for continuous variables to determine the difference in outcomes.
   B. A retrospective case-control study with a test for proportions to determine the difference in outcomes.
   C. A prospective observational study with survival analysis to determine the difference between cohorts.
   D. A retrospective case-cohort study with a test for proportions to determine the difference in outcomes.

5. A case-control study is performed to determine whether proton pump inhibitor (PPI) use is associated with an increased risk of developing *Clostridium difficile* infection (CDI). The final analysis shows the odds ratio (OR) for the CDI with PPI exposure to be 1.3 (95% CI, 0.8–1.5). Which best describes the results?
   A. PPI exposure increases the risk of CDI by 130%.
   B. PPI exposure reduces the risk of CDI by 20%.
   C. PPI exposure increases the risk of CDI by 30%.
   D. PPI exposure is not associated with an increased risk of CDI.

6. A systematic review evaluated the effect of albumin for fluid resuscitation. A meta-analysis that evaluated the effect of albumin use compared with normal saline (NS) on 28-day mortality reported a combined OR of 0.45 (95% CI, 0.3–0.75) for the treatment of hypovolemic shock caused by trauma. For the treatment of septic shock, albumin compared with NS resulted in a combined OR of 1.1 (95% CI, 0.98–1.21) when evaluating 28-day mortality. Which best represents the findings of the review?
   A. Albumin increased mortality in trauma but did not affect survival in the treatment of septic shock.
   B. Albumin increased survival in trauma but did not affect survival in the treatment of septic shock.
   C. Albumin did not affect survival in the treatment of hypovolemic shock caused by trauma but improved survival in the treatment of septic shock.
   D. Albumin did not affect survival in the treatment of hypovolemic shock caused by trauma or septic shock.

7. A critical care pharmacist is faced with an acute drug shortage in which no furosemide is available for immediate use in patient care. During patient care rounds in the ICU, the decision is made to implement a fluid-conservative strategy for the treatment of a patient with acute respiratory distress syndrome (ARDS) (central venous pressure [CVP] goal less than 4 mm Hg). The critical care pharmacist is able to procure an allotment of bumetanide. Which statement best describes the course of action for this patient?
   A. The pharmacist uses her understanding of the medical literature and experiential knowledge to develop a titration scheme using bumetanide to achieve a CVP of less than 4 mm Hg.
   B. The pharmacist uses her understanding of research trial design and experiential knowledge to develop a titration scheme using bumetanide to achieve a CVP of less than 4 mm Hg.
   C. The pharmacists uses her friendly rapport to convince the nephrologist to treat this patient with hemodialysis to achieve a goal CVP of less than 4 mm Hg.
   D. The pharmacist uses her understanding of research ethics to obtain informed consent from the patient’s surrogate for treatment with bumetanide.
8. In a study of ARDS, patients are treated with a neuromuscular blocking agent (NMBA) or placebo to determine whether administering an NMBA within the first 48 hours of presentation improves 28- and 90-day survival. The study has an unequal distribution of patients, with a greater proportion of patients with severe ARDS compared with moderate and mild ARDS. The post hoc analysis of the results finds a survival benefit to administering NMBA to the patients with severe ARDS. Which rationale best describes why NMBAs should not be administered to patients with mild to moderate ARDS?

A. Patients with mild ARDS have a lower mortality rate and are therefore less likely to benefit from the test treatment.

B. Patients with mild and moderate ARDS are inherently different from patients with severe ARDS because of their etiology and presentation.

C. NMBAs are periodically on shortage from the manufacturer and need to be prioritized for necessary medical indications.

D. The end points selected do not carry sufficient social value to warrant treatment.
I. INTRODUCTION

A. Epidemiology of Critical Care in the United States – And why continued research is essential to improving the delivery of care to patients

B. Why Pharmacists Need to Understand the Fundamentals of Research Practice, Trial Design, and Literature Evaluation

C. The Necessity of Clinical Research in Critical Care – To optimize patient outcomes while providing the efficient stewardship of finite resources

D. Synthesizing Medical Knowledge with Experiential Knowledge and Pathophysiologic Reasoning – Essential to creating patient-specific therapy care plans

II. BIOETHICS

A. The Belmont Report – Outlines the fundamental ethical principles for the conduct of clinical research
   1. Respect for individuals dictates that each research participant be treated with respect for his or her dignity and autonomy. As such, informed consent shall be obtained from research participants or their surrogates.
   2. The principle of justice requires that investigators recruit research subjects in a manner that allows equal access to participation for all populations that may potentially benefit from the research endeavor.
   3. Beneficence requires research investigators to ensure that risks are minimized and benefits maximized for research participants.

B. A Framework for the Ethical Conduct of Clinical Research – Includes seven requirements (JAMA 2000;283:2701-11): (1) social value, (2) scientific validity, (3) fair selection of research participants, (4) a favorable risk-benefit ratio, (5) independent review, (6) informed consent, and (7) respect for enrolled participants

C. Equipoise – Must be present for the conduct of a clinical trial. Equipoise is defined as the state of uncertainty between treatments A and B for a given population of subjects with a predefined disease and/or syndrome. Once the balance of uncertainty between treatments A and B is disturbed such that one treatment is believed to be superior, the risk-benefit ratio is altered such that treatment may not be beneficial to the individual research subject.

III. PRACTICAL CHALLENGES TO CRITICAL CARE RESEARCH

A. Research Subject Recruitment. To maximize external validity, research subjects recruited for participation in a clinical trial should be representative of the general population of patients afflicted with the disease or syndrome.
   1. Critical care is exemplified by the provision of supportive care for the treatment of diseases and syndromes.
      a. Diseases are characterized by the specific test to identify the pathophysiologic process.
      b. Syndromes are often identified by the presence of a constellation of signs and symptoms that suggest the presence of a disease.
2. Recognition of the attendant syndrome is critical for the timely provision of therapy and, in research, subject recruitment.
   a. Heterogeneity in syndromes challenges the ability to identify subjects for participation in clinical research.
   b. In addition, heterogeneity challenges the ability to interpret the results from dissimilar populations, even though they have a single syndrome in common.
3. Unique to critical care clinical research is the need to enroll subjects similar in acuity or at a similar stage in the process of their syndrome to allow meaningful comparisons (e.g., N Engl J Med 2010;363:1107-16).
4. Selection of end points should be based, in part, on the ethical values outlined previously. End points should provide social value and possess scientifically validity. A growing area of emphasis in research is on the need to design studies that are patient-centered (JAMA 2012;307:1583-4).

B. Informed Consent
1. Because of the acute nature of critical illness, it may be singularly difficult to obtain informed consent within a short time.
2. Obtaining informed consent is particularly challenging in the case of critically ill patients, primarily because many critically ill patients lack decisional capacity due the acute nature of their illness and the effect of their medications.
3. Usually not required in studies that are deemed quality initiatives because the intent of these studies is to improve the delivery of care
4. Surrogates and family members are recognized as having authority to provide consent on the behalf of patients, despite the ambiguous legal standing on this issue in several states. Underlying motives for proxy consent may include the belief that participation in the research protocol will lead to improved care.
   a. Important to acknowledge that patients and surrogates entrust clinical researchers to act in their best interests
   b. Research supports the notion that surrogate consent and patient preferences agree a majority of the time (Chest 2001;119:603-12).

C. Waiver of Consent
1. In select circumstances, informed consent may be waived by the IRB.
2. Of note, differences exist in the guidance between the Department of Health and Human Services and the FDA for waiver of informed consent. In many circumstances, local IRBs will follow the Common Rule as the minimum standard.
3. Waiver of informed consent is typically granted for any of the following circumstances:
   a. Research that is deemed of minimal risk to the participant, does not adversely affect the welfare of the subject, and could not otherwise be practically carried out.
   b. Research that is carried out to evaluate public benefits or service programs.
   c. Research in emergency settings where consent would be impractical to obtain. An example is a study testing the hypothesis of whether drug A is non-inferior to drug B for the treatment of status epilepticus (N Engl J Med 2012;366:591-600).
4. Controversy exists as to how quality improvement projects should be evaluated. Currently, quality improvement research is subject to the interpretation of local IRBs.
D. Community Consent
1. Occasionally, critical care research will need to be conducted in the general community. Obtaining consent in this scenario would impossible given the medical condition of the research subject. Example: (N Engl J Med 2012;366:591-600).
2. Guidance exists for investigators to inform the community and community leaders prior to undertaking the research endeavor.
3. Approval for this type of research is required from local/national IRBs.

IV. RESEARCH DESIGN

A. Figure 1 (Crit Care Med 2010;38:1882-9)

B. Randomized Controlled Trial
1. Hallmark of clinical research
2. Experimental design to test the effects of an intervention compared with either placebo or the established standard of care (treatment or process of care); allows for description and causality
3. Preliminary research should exist to suggest that the intervention is based on an existing scientific foundation sufficient to warrant the proposed testing on patients.
4. Examples:
   b. JAMA 2012;308:1985-92
   c. JAMA 2011;305:363-72

C. Observational
1. Observation of clinical practice; no intervention is tested
2. Describes associations between phenomena
3. Hypothesis-generating: Case-control study – Retrospective design
   a. Case-control
      i. Retrospective design
         (a) Provides an efficient means to determine the association between the risk factor and the outcome of interest
         (b) Two groups (with and without the outcome) are compared to identify the differences and risk factors for developing the outcome of interest
         (c) Potential for selection bias and confounding

4. Cases and controls are representative of the population afflicted with the disease and are chosen to minimize selection bias.

5. The process for handling missing data should be defined a priori. Significant amounts of missing data may introduce bias.

6. Confounding variables must be handled in a manner that can be controlled for in the analytical process.
   a. Odds ratio (OR)
      i. Describes the odds of being exposed to a risk factor and the occurrence of the outcome of interest compared with those who are not exposed to the risk factor.
      ii. The OR is interpreted in relation to a reference point (1.0). If the 95% confidence interval (CI) includes 1, the odds of the event occurring are equally likely in either group.
   b. Case-cohort study
      i. Prospective or retrospective design
         (a) Observational study of a given population over a given time to determine the association between risk factors and the outcome of interest. Identifies the relationship between exposure and outcome
         (b) Describes the natural progression of a disease or syndrome
         (c) Example: JAMA 2004;291:1753-62
      ii. Incidence versus prevalence

7. Incidence – Measures the occurrence of a disease (or event) over a period

8. Prevalence – Measures the occurrence of a disease (or event) at a fixed point in time
   a. Case reports/case series: Describes the experience in the treatment of a singular patient or the cumulative experience in the treatment of a series of patients
   b. Validity
      i. Internal
         (a) Does the study design adequately test the hypothesis?
         (b) Are the study methods sound?
      ii. External
         (a) Is the study population representative of the clinical setting?
         (b) Are the study findings generalizable outside the study setting?
         (c) Can the study be replicated in clinical practice?
      iii. Bias – Systematic error
         (a) Selection bias: Systematic selection of subjects that leads to an imbalance, or an advantage, in favor of one cohort over the other
         (b) Observation bias: Observers (research team) are aware of the research purpose and allow this knowledge to influence interpretation of results.
         (c) Recall bias: Methodological error that is introduced in survey research when the participant is asked to provide recall of a past event.
iv. Bias can be accounted for with sufficient planning for design, data collection, and analysis and can potentially be minimized.

v. Confounding variables – Extraneous variables that influence both the dependent and the independent variable, affecting how the overall result can be interpreted. Controlling for confounding variables
(a) Study design: Randomization, matching

9. Analysis: Multivariate analysis, propensity score matching

V. STATISTICAL ANALYSIS

A. Hypothesis Testing – To determine whether the observation was caused by chance
   1. Null hypothesis (H₀): No difference exists between groups. Accepting the null hypothesis means accepting that no difference exists between groups.
   2. Alternative hypothesis (H₁): There is a difference between group A and group B.
      a. Type I error (alpha [α] error): To reject the H₀ when, in fact, it is true. Decisional threshold to accept/reject the H₀ is conventionally set at α = 0.05. The α value represents the likelihood that a type I error will be made (i.e., rejecting the H₀ when the H₀ should be accepted). An α set at 0.05 means that the H₁ will be erroneously accepted 1 in 20 times.
      b. Type II error (beta [β] error): To accept the H₀ when, in fact, there is a difference between groups (i.e., the H₁ should be accepted). Decisional threshold to set β at 0.20
         i. What does “power” really mean? The ability to detect a difference if one truly exists. Contingent on sample size. However, this is an estimate and may be inaccurate (usually based on previous literature).

B. Types of Data
   1. Continuous
      a. Counting, chronological order (e.g., 7.0, 7.1, 7.2, 7.3)
      b. Sample tests: t-test, Wilcoxon rank sum/Mann-Whitney U
   2. Categorical
      a. Categories or groups for data to be designated to (e.g., race, sex, hypertension, heart failure)
      b. Sample tests: Chi-square, Fisher exact test
   3. Descriptive statistics
      a. Measures of central tendency
         i. Mean: Used for continuous and normally distributed data, sensitive to outliers
         ii. Median: 50th percentile, used for ordinal data or nonparametric continuous data
         iii. Mode: Value occurring most frequently in a distribution
      b. Standard deviation
         i. Used for continuous, parametric data
         ii. Describes variability around the mean
      c. Range: Describes spread of data, minimum to maximum values
      d. Percentiles
         i. The value where the percentage of values fall below. Example: The 75th percentile is where 75% of values are smaller.
         ii. IQR (interquartile range): Describes the values between the 25th and 75th percentile
C. Parametric Data
   1. Student t-test: Comparison of means between two independent groups
   2. Analysis of variance: Comparison of means between three or more groups

D. Nonparametric Data
   1. Two groups: Wilcoxon rank sum or Mann-Whitney U test
   2. Three or more groups: Kruskal-Wallis

E. Nominal Data
   1. Chi-square test
   2. Fisher exact test: Unique to small data sets (fewer than five observations)

F. Confidence Interval
   1. A method to describe a point estimate within the study population
   2. CIs offer a more descriptive interpretation of the data.
      a. Magnitude of difference between groups
      b. Range of values (possible spread of point estimates)
      c. A 95% CI has a 0.95 probability of containing the true mean.

G. Correlation: Describes the association between two variables
   1. Correlation value (r) contains a range of values from -1 to +1. An r value of -1 or +1 indicates a perfect negative or positive relationship. The closer the values to 1, the closer the correlation between the two variables.
   2. Pearson: Parametric continuous data
   3. Spearman rank: Nonparametric continuous data or ordinal data

H. Regression Analysis: Describes whether an independent variable can predict the dependent outcome. Can be used to describe the strength of the association between a predictor variable and a dependent variable

I. Linear Regression
   1. Used when the dependent variable is a continuous variable (e.g., length of stay)
   2. A single predictor variable (continuous or categorical) can be tested in a simple linear regression model.
   3. More than one predictor variable (continuous or categorical) can be tested at a time in a multiple linear regression model.

J. Logistic Regression
   1. Used when the dependent variable is a categorical variable (e.g., mortality)
   2. A single predictor variable (continuous or categorical) can be tested in a simple logistic regression model.
   3. More than one predictor variable (continuous or categorical) can be tested at a time in a multiple logistic regression model.

K. Survival Analysis (time-to-event analysis)
   1. Censoring: Adjusts data so that patients are not included (i.e., “censored”) in the analysis if they did not experience, or, were not observed for, the event
2. Kaplan-Meier method
   a. Describes the impact of a single predictor variable on the time-to-event between cohorts
   b. Compares the survival times between two cohorts while controlling for a singular predictor variable
   c. Survival curves are typically analyzed using the log-rank test.
   d. Results reported as OR with 95% CI

3. Cox proportional hazards model
   a. Describes the impact of several predictor variables on the time-to-event
   b. Compares the survival times between two cohorts while controlling for several predictor variables
   c. Results reported as HR (hazard ratio) with 95% CI

Table 1. Statistical Tests According to Type of Data

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>Independent Variables</th>
<th>Test(s)</th>
</tr>
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<tbody>
<tr>
<td>Continuous, parametric</td>
<td>Categorical</td>
<td>Two-sample t-test</td>
</tr>
<tr>
<td>Continuous, nonparametric</td>
<td>Categorical</td>
<td>Mann-Whitney U test</td>
</tr>
<tr>
<td>Categorical</td>
<td>Categorical</td>
<td>Chi-square test</td>
</tr>
<tr>
<td>Continuous</td>
<td>Continuous</td>
<td>Linear regression</td>
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<tr>
<td>Continuous</td>
<td>Categorical</td>
<td>Linear regression</td>
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<tr>
<td>Categorical</td>
<td>Continuous</td>
<td>Logistic regression</td>
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<tr>
<td>Categorical</td>
<td>Categorical</td>
<td>Logistic regression</td>
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VI. APPLICATION OF KNOWLEDGE TO PATIENT CARE

Table 2. Assessment of Primary Literature for Clinical Application

<table>
<thead>
<tr>
<th>Assessment</th>
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<tbody>
<tr>
<td>Study design</td>
</tr>
<tr>
<td>• Were the hypothesis and study purpose clearly stated?</td>
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<tr>
<td>• Is the study sample representative of the population with the disease/syndrome?</td>
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<tr>
<td>― Are the inclusion/exclusion criteria too restrictive?</td>
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<tr>
<td>• Did the study meet power? Was a sample size calculation described?</td>
</tr>
<tr>
<td>• How were blinding and randomization conducted?</td>
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<tr>
<td>• Is the study design translatable to clinical practice?</td>
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<tr>
<td>― How were the primary and secondary end points defined?</td>
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<tr>
<td>― Have those definitions been validated in the critically ill?</td>
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<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>• Is the primary outcome scientifically valid and meaningful?</td>
</tr>
<tr>
<td>• Are the secondary outcomes clearly described?</td>
</tr>
<tr>
<td>• How were adverse effects defined and analyzed?</td>
</tr>
<tr>
<td>Analysis</td>
</tr>
<tr>
<td>• Were the statistical tests appropriate?</td>
</tr>
<tr>
<td>• How were the data analyzed (intention-to-treat, per-protocol, as-treated)?</td>
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<tr>
<td>• How large was the treatment effect?</td>
</tr>
<tr>
<td>• Will the effect size be duplicated in clinical practice?</td>
</tr>
<tr>
<td>• Did the author(s) provide an interpretation of the study findings and describe them in the context of the available knowledge?</td>
</tr>
</tbody>
</table>
A. Integration of Various Types of Knowledge
   1. Medical literature
      a. Remaining current with evolving literature is a necessary skill for the critical care clinician.
      b. Knowledge gained from the primary literature can be objective, can limit bias, and may be
         translatable compared with experiential knowledge.
      c. The findings of clinical research can be limited to the conditions of the study and may not easily
         confer the same benefit in clinical practice.
      d. The study results limit the findings attributable to chance but may not fully exclude chance.
   2. Experiential knowledge
      a. Knowledge accumulated through clinical experience and for a sustained period is valuable.
      b. Valuable when determining how an individual patient differs from a study population in a
         clinical trial.
      c. When possible, this type of knowledge should be reinforced with scientific evidence.
   3. Pathophysiologic reasoning
      a. Application of physiologic concepts to drive therapeutic choices.
      b. Can aid in determining short-term goals. Example: Selecting an initial dose of loop diuretic
         according to the home medication dose and current therapeutic goal of urine output greater than
         1 L in 24 hours.
      c. Primary literature on which to base treatment decisions for all clinical scenarios may not exist;
         therefore, use of pathophysiologic reasoning is key to the sound provision of pharmaceutical care
         for critically ill patients.

B. Negotiating Between Various Kinds of Medical Knowledge for Direct Application to Patient Care
   1. Applying the knowledge gained from the primary literature that is based exclusively on the hierarchy
      of study design may not be practical for all patient interactions.
   2. Integrating the various types of knowledge can lead to systematic problem solving rather than arbitrary
      judgments. This becomes necessary when making systems-based treatment decisions (i.e., treatment
      protocols) and understanding when to modify existing protocols to fit the needs of individual patients.

C. Synthesizing the Available Evidence to Develop Treatment Protocols
   1. Protocols are intended to synthesize the best available evidence and standardize a series of treatment
      options to reduce variability and error while maximizing treatment effect. Examples: Sterile technique
      for central line placement, heparin infusion, and aPTT (activated partial thromboplastin time)
      monitoring, the mnemonic FASTHUG.
   2. Determining which literature to incorporate and its applicability to the local practice environment
      is key.

D. Unique Factors That Promote/Impede the Application of Treatment Protocols
   1. Resource use
      a. Personnel (e.g., Lancet 2010;375:475-80)
      b. Drug shortage
      c. Fiscal
   2. Ease of protocols
      a. Complexity
      b. Familiarity
   3. Lack of consensus
REFERENCES

Bioethics

Practical Challenges to Critical Care Research

Research Design

Statistical Analysis

Application of Knowledge to Patient Care

1. **Answer: C**
   This study seeks to compare two viable treatments of hypovolemic shock in trauma patients. Because subject identification would be trauma patients from the community and treatment would be initiated in the field, there is potential harm associated with each treatment, and it is expected that many potential patients would lack decisional capacity at the time of informed consent. Although treatment blinding is an essential component to trial design to limit investigator and clinician bias, it is not an ethical consideration (Answer A is incorrect). Given the incidence of trauma in the general population and its burden on society, treatments to improve the outcomes of trauma patients are necessary and informative (Answer B is incorrect). Acknowledging the limited supply of blood products, a superiority trial is essential to help steward the use of a finite resource (Answer D is incorrect). The issue of informed consent in this study is challenging but the issue needs to be addressed for the ethical conduct of this study. There is precedent for this trial to receive an exception for informed consent requirements under the U.S. Food and Drug Administration code of regulations.

2. **Answer: C**
   The study seeks to establish the effectiveness of a novel drug compound for the treatment of septic shock. This is challenging because of the dramatic improvements made in 28-day mortality during the past decade. To demonstrate the effectiveness of a novel drug compound, the drug should be tested in a representative population of patients with the disease. Excluding patients because of baseline comorbidity would limit external validity (Answer A is incorrect). Including patients with severe sepsis, which has a lower 28-day mortality rate than septic shock, would not address the issue of an appropriate end point (Answer B is incorrect). Limiting study inclusion to patients with a pneumonia etiology would be inappropriate unless the pharmacology of the novel drug specifically targeted pneumonia pathophysiology (Answer D is incorrect). Answer C is correct because the study should maximize external validity and provide survival benefit in a heterogeneous population of patients with the syndrome. However, if 28-day survival is increasingly difficult to show, a more appropriate end point might be 90-day survival to show the durability of the treatment beyond intensive care.

3. **Answer: B**
   A QI study would likely show effectiveness using a pre-/postintervention cohort design. In this type of study, informed consent is generally not required because the treatment is provided to all patients as a standard of care (Answer A is incorrect). A community advertising campaign may improve the delivery of care and improve patient adherence, but it is unnecessary to measure the effectiveness of the QI initiative (Answer C is incorrect). The QI initiative is believed necessary and has therefore been deemed to possess intrinsic social value (Answer D is incorrect). To show the effectiveness of the intervention, it is critical to recognize the syndrome before initiating treatment (Answer B is correct).

4. **Answer: C**
   To effectively determine the incidence and clinical impact of adverse drug events on clinical outcomes in the ICU, it would be unethical to randomize patients to experience the event (Answer A is incorrect). A retrospective design would not be ideal because of the limitations in data extraction, assignment of events, and interpretation of causality (Answers B and D are incorrect). A prospective observational design would allow the investigator team to identify the incidence of events and sequential events and determine causality (Answer C is correct).

5. **Answer: D**
   A correct interpretation of the results is recognition that even though the OR suggests an associated increase of 30% in the risk of being exposed to CDI, the 95% CI crosses 1, meaning that the odds of exposure to CDI are as likely to increase the risk as to decrease that risk (Answers A, B, and C are incorrect).

6. **Answer: B**
   Use of albumin reduced the odds of mortality (and conversely, increased the odds of survival) with an OR of 0.45, and the 95% CIs were all less than 1 in the treatment of hypovolemic shock in trauma. In addition, the OR was 1.1 for septic shock, whereas the 95% CI crossed 1, showing that the odds were as likely that albumin increased mortality as that it reduced it (Answer B is correct). Because the OR and the 95% CI for the treatment of hypovolemic shock are both less than 1, mortality was decreased with albumin use (Answers A, C, and D are incorrect).
7. **Answer: A**
   This patient case provides a practical example of a critical care pharmacist’s integration of various types of knowledge to optimize patient care. The FACT trial showed that a fluid-conservative strategy improves ventilator-free days for patients with acute lung injury and ARDS. The drug used in the study to show the outcome benefit was furosemide. However, the study was testing a treatment strategy, not specifically a drug strategy. Therefore, it can be reasoned that similar treatment outcomes can be shown with similar drugs if the study drug is unavailable—in this case, because of drug shortage. Knowledge of trial design is helpful but not critical to optimizing this patient’s therapy with bumetanide (Answer B is incorrect). Hemodialysis is invasive, requires finite resource use, and has an associated morbidity risk (Answer C is incorrect). Because this patient case does not include a broader hypothesis test in a systematic design, this is not a research activity, and informed consent is not required (Answer D is incorrect). A critical care pharmacist, using her knowledge of the FACT trial (medical knowledge) together with her understanding and experience with bumetanide therapy (experiential knowledge), can develop a treatment plan (Answer A is correct).

8. **Answer: A**
   Acute respiratory distress syndrome is a clinical syndrome with an associated mortality with each progressing phase (mild, moderate, and severe). While the syndrome is also a constellation of findings and pathologic observations, patients who have ARDS present with a similar finding of severe, refractory hypoxia from a common etiology (Answer B is incorrect). Given the associated mortality of about 45% for severe ARDS, a finite resource should be prioritized for it (in this case, an NMB) (Answer C is incorrect). Mortality/survival is readily identified as an end point of social value for research design (Answer D is incorrect). Given the relatively low mortality associated with mild ARDS (around 20%) compared with severe ARDS (around 45%), administration of NMBAs would be less likely to improve survival and more likely to increase harm if systematically administered to patients with mild ARDS.