National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases

Improving CarE for Community Acquired Pneumonia (ICE-CAP)

Antibiotic Decision Support (Phase 1)
Prognostic Decision Support (Phase 2)

Two Prospective, Randomized Clinical Trials to Assess the Effectiveness of the EHR-based Antibiotic Decision Support Application and Prognostic Tool for Promoting Guideline-Concordant Antibiotic Prescribing and the Appropriate Site of Care Disposition in Children Aged 0.6 - 17 Years With Emergency Care

Short Title: ICE-CAP

Statistical Analysis Plan

Version 1.1

February 1, 2020

1 INTRODUCTION

This document describes the statistical procedures that will be utilized for the ICE-CAP protocol. This statistical analysis plan (SAP) describes the methods of statistical analysis. The initial draft SAP (Version 0.1) was written prior to any data being analyzed in order to avoid bias. Any subsequent changes that occur to the study protocol warranting changes to the analysis procedures will be documented in the SAP. Table 1 below will be used for tracking changes to the SAP.

Table 1. Statistical Analysis Plan Versions

Version	Date of Approval	Major Changes from Prior Version
1.0	Jul 30, 2018	-
1.1	Feb 1, 2020	Update study site; clarification for concordance definitions; minor edits for clarity

2 PROTOCOL OBJECTIVES FOR PHASE 1

2.1 Primary

a) PO 1: To compare proportions of participants exclusively receiving guideline-concordant antibiotic therapy during the first 24 hours of care with or without EHR-based decision support in children 0.5-17 years of age presenting for emergency care.

2.2 Secondary

a) SO 1: To compare proportions of participants exclusively receiving guideline-concordant antibiotic therapy for the entire episode, by EHR-based decision support or usual care.

b) SO 2: To compare proportions of participants receiving any guideline-concordant antibiotic therapy during the first 24 hours of care, by EHR-based decision support or usual care.

c) SO 3: To compare proportions of participants receiving any guideline-concordant antibiotic therapy for the entire episode, by EHR-based decision support or usual care.

d) SO 4: To compare proportions of participants having ED revisits and hospitalizations within 72 hours of the index discharge, by EHR-based decision support or usual care.

e) SO 5: To compare proportions of participants having ED revisits and hospitalizations within 7 days of the index discharge, by EHR-based decision support or usual care.

2.3 Exploratory

a) EO 1: To compare time to first antibiotic, by EHR-based decision support or usual care.

b) EO 2: To compare the proportion of participants not receiving antibiotics during the first 24 hours of care, by EHR-based decision support or usual care.

c) EO 3: To compare the proportion of participants not receiving antibiotics for the entire episode, by EHR-based decision support or usual care.

d) EO 4: To compare the changes in antibiotics, used as a proxy for treatment failure, after 72 hours, by EHR-based decision support or usual care.

e) EO 5: To compare the proportion of death, by EHR-based decision support or usual care.

f) EO 6: To compare the proportion of delayed ICU transfer among hospitalized children, by EHR-based decision support or usual care.

3 PROTOCOL OBJECTIVES FOR PHASE 2

3.1 Primary

a) PO 1: To compare proportions of appropriate overall site of care disposition with or without EHR-based prognostic decision support in children with emergency care aged 0.6-17 years.

3.2 Secondary

a) SO 1: To compare proportions of appropriate site of care disposition, by EHR-based prognostic decision support or usual care.

b) SO 2: To compare proportions of participants having ED revisits and hospitalizations within 72 hours of the index discharge, by EHR-based prognostic decision support or usual care.

c) SO 3: To compare proportions of participants having ED revisits and hospitalizations within 7 days of the index discharge, by EHR-based prognostic decision support or usual care.

3.3 Exploratory

a) EO 1: To compare the proportion of death, by EHR-based prognostic decision support or usual care.

b) EO 2: To compare hospital length of stay among hospitalized children, by EHR-based prognostic decision support or usual care.

4 STUDY OUTCOME MEASURES FOR PHASE 1

4.1 Primary

a) POM 1.1: Proportions of participants exclusively receiving guideline-concordant 1st line antibiotic therapy during the first 24 hours of care, by EHR-based decision support. Please see Appendix 1 for the concordant use definitions for 1st line antibiotics.

4.2 Secondary

a) SOM 1.1: Proportions of participants exclusively using of concordant antibiotic therapy for the entire episode, by EHR-based decision support or usual care.

b) SOM 2.1: Proportions of participants using any of concordant antibiotic therapy during the first 24 hours of care, by EHR-based decision support or usual care.

c) SOM 3.1: Proportions of participants using any of concordant antibiotic therapy for the entire episode, by EHR-based decision support or usual care.

d) SOM 4.1: Proportions of participants having ED revisits within 72 hours of the index discharge (the enrollment ED visit or hospitalization through discharge), by EHR-based decision support or usual care.
SOM 4.2: Proportions of participants having hospitalizations within 72 hours of the index discharge, by EHR-based decision support or usual care.

e) SOM 5.1: Proportions of participants having ED revisits within 7 days of the index discharge, by EHR-based decision support or usual care.
SOM 5.2: Proportions of participants having hospitalizations within 7 days of the index discharge, by EHR-based decision support or usual care.

4.3 Exploratory

a) EOM 1.1: Time to first antibiotic, by EHR-based decision support or usual care.

b) EOM 2.1: Proportion of participants lacking of antibiotics during the first 24 hours of care, by EHR-based decision support or usual care.

c) EOM 3.1: Proportion of participants lacking of antibiotics for the entire episode, by EHR-based decision support or usual care.

d) EOM 4.1: Proportion of participants with different antibiotic(s) or changing treatments from no-antibiotic(s) to antibiotic(s), used as a proxy for treatment failure, after 72 hours, by EHR-based decision support or usual care.

e) EOM 5.1: Proportion of death, by EHR-based decision support or usual care.

f) EOM 6.1: Proportion of delayed ICU transfer (>24 hours following hospitalization) among hospitalized children, by EHR-based decision support or usual care.

5 STUDY OUTCOME MEASURES FOR PHASE 2

5.1 Primary

a) POM 1.1: Proportions of appropriate overall site of care disposition with or without EHR-based prognostic decision support in children 0.6-17 years presenting for emergency care. Please see Appendix 2 for the definition of appropriate site of care disposition (an investigator in both Nashville and Pittsburgh will be in charge of review, blinded to intervention assignment).

5.2 Secondary

a) SOM 1.1: Proportions of appropriate site of care disposition, by EHR-based prognostic decision support or usual care.

b) SOM 2.1: Proportions of participants having ED revisits within 72 hours of the index discharge, by EHR-based prognostic decision support or usual care.
SOM 2.2: Proportions of participants having hospitalizations within 72 hours of the index discharge, by EHR-based prognostic decision support or usual care.

c) SOM 3.1: Proportions of participants having ED revisits within 7 days of the index discharge, by EHR-based prognostic decision support or usual care.
SOM 3.2: Proportions of participants having hospitalizations within 7 days of the index discharge, by EHR-based prognostic decision support or usual care

5.3 Exploratory

a) EOM 1.1: Proportion of death, by EHR-based prognostic decision support or usual care.

b) EOM 2.1: Hospital length of stay among hospitalized children, by EHR-based prognostic decision support or usual care.

6 STUDY DESIGN

6.1 Study Description

Extensive variation in both antibiotic use and hospitalization decisions is evident among clinicians caring for children with pneumonia, with high potential for avoidable harm. In our prior study, one-third of children were hospitalized for less than 48 hours and nearly 10% less than 24 hours. Some of these hospitalizations were likely unnecessary. Most of these children also received broad-spectrum antibiotic therapy instead of the narrow-spectrum agents recommended by the national guideline. Conversely, one-third of children admitted to intensive care were initially managed on a general ward—earlier transfer for more intensive therapy may have improved outcomes for some of these children. New strategies to inform decision making are needed, and the combination of risk stratification using objective tools and clinical decision support in the ED setting are innovative and promising approaches to achieve this goal.

6.1.1 Phase 1

To test the hypothesis that electronic antibiotic decision support increases guideline-concordant antibiotic use compared with usual care in the ED.

The primary outcome is the proportion of children exclusively receiving guideline-concordant 1st line antibiotic therapy during the first 24 hours of care (Table 1). Secondary outcomes include exclusive use of guideline-concordant antibiotic therapy for the entire episode, any use of concordant antibiotic therapy during the first 24 hours of care and for the entire episode, and ED revisits and hospitalizations within 72 hours and 7 days of the index discharge.

6.1.2 Phase 2

To test the hypothesis that the delivery of severity information generated by our prognostic tool leads to more appropriate site of care disposition compared to usual care.

The primary outcome is appropriate site of care disposition (Table 2). Surveillance for subsequent ED visits and hospitalizations to our institutions as well as escalation to higher levels of care will be captured within the EHR data extracted by the decision support application. Secondary efficacy and safety outcomes include the overall site of care disposition (ED discharge, ward, ICU), and ED revisits and hospitalizations within 72 hours and 7 days of the index discharge.

6.2 Sample Size and Power

6.2.1 Phase 1

Based on ED and hospitalization data from our hospitals during the conduct of the EPIC study, we anticipate nearly 2000 total children with pneumonia will be evaluated annually during the conduct of these studies. Assuming conservatively that data for 750 children are enrolled in each arm, and 30% guideline-concordant antibiotic use in the usual care arm (based on our prior study of antibiotic use in the EPIC cohort), we will be able to detect an absolute difference of $\geq$6.8% in guideline-concordant prescribing at an alpha level of 0.05 with 80% power. Effective sample size may be reduced due to the cluster randomized nature of the study (a conservative estimate for effective sample size would be around 500 children in each arm).

6.2.2 Phase2

As outlined in P1, we anticipate nearly 2000 children with pneumonia will be evaluated annually during the conduct of these studies. Assuming conservatively that data for 2000 children (1000 in each arm) are captured during the two-year study period, and 90% appropriate site of care disposition in the usual care arm (based on data from the EPIC cohort), we will be able to detect an absolute difference of $\geq$3.4% in appropriate care disposition at an alpha level of 0.05 with 80% power.

6.3 Randomization

6.3.1 Phase 1

During the 18-month study period, EHR-based antibiotic decision support will be active monthly (4-week blocks) based on the cluster randomized scheme at each hospital. To ensure balanced representation of each arm in periods of both low and high pneumonia prevalence, randomization will occur in 3 permuted blocks (size=6). The antibiotic decision support application will be provided to those randomized to the intervention arm, whereas the control arm will receive usual care. Participants enrolled during the month with antibiotic decision support will be assigned to the intervention arm, and participants receiving usual care will be in the control arm. Participants will be blinded to the treatment assignments and study staff and providers will not be blinded to treatment arm assignments due to the nature of the interventions.

6.3.2 Phase 2

During the 24-month study period, randomization will occur at the patient level. Allocation to intervention or control will be based on medical record number (even vs. odd) and will be assigned automatically once the treating provider confirms the diagnosis of pneumonia and eligibility. We expect participants will be randomized (1:1). The providers of intervention subjects will receive prognostic information derived using our previously validated and best performing model. Providers of control arm subjects will not receive this information but will have access to all clinical data. Participants will be blinded to the treatment assignments and study staff and providers will not be blinded to treatment arm assignments due to the nature of the interventions.

7 7. PARAMETERS OF ANALYSIS

7.1 Data Collection and Storage

Data collection will be triggered by the pneumonia BPA and will be acquired directly from the EHR and stored securely for later analysis. Prior to study initiation, support analysts will conduct detailed requirement explorations to identify necessary data elements and associated data flows, validate accuracy, and evaluate for missing data. Data to be collected includes decision support usage statistics, visit details (e.g., admission and discharge date and time, site of care, ED revisits or hospital readmissions), patient demographics (e.g., age, sex, race, insurance), medication orders and prescriptions (dose, frequency, route, and duration), laboratory testing and results, radiologic studies, and data elements from the decision support applications. Manual review of the EHR will also be conducted where necessary. All data will be stored in REDCap.

7.2 Analytic Issues

There are two sites participating in the study and analysis of the primary objective will be stratified by site to account for site variation. There will be one primary objective per aim evaluated at the alpha 0.05 level. There will be no adjustments to the alpha level for all secondary and exploratory analyses.

8 ANALYSIS POPULATIONS

8.1 Intent-to-Treat (ITT) Population:

The ITT Population includes any participant that is enrolled, randomized into the study. The ITT Population is the primary population for analysis unless otherwise stated.

9 BASELINE DATA AND FLOW CHART

9.1 Presentation of Baseline Data

The following baseline data will be presented by site, season, and intervention group: age, gender, ethnicity, race, comorbidities, clinical presentation, laboratory findings, and radiographic features.

9.2 Flow Chart

The number of enrolled participants will be presented in a flow chart by site and intervention group.

10 ANALYSIS OF STUDY OBJECTIVES FOR PHASE 1

Descriptive analyses will be summarized for continuous variables with mean, standard deviation, median, and interquartile range. Categorical variables will be summarized with frequencies and percentages. Explanatory figures will be generated to evaluate the data distribution. Comparisons of demographic characteristics between intervention groups will be conducted using Pearson Chi-square and Wilcoxon tests appropriately.

All analyses will be performed using R 3.5.0 (r-project.org), SAS version 9.4, or STATA version 15, or updated software from these programs.

10.1 Primary Objective

The primary objective (PO 1) of the study is to compare proportions of participants exclusively receiving guideline-concordant 1st line antibiotic therapy during the first 24 hours of care with or without EHR-based decision support in children 0.6-17 years of age presenting for emergency care. The hypothesis for this primary objective is that the proportion of participants exclusively receiving guideline-concordant 1st line antibiotic therapy during the first 24 hours of care is higher in the group receiving EHR-based decision support vs. the group receiving usual care. This information is captured through chart review and entered in the REDCap database. The antibiotics received by a participant is concordant yes (1) or no (0) based on Appendix 1 table, for this analysis.

The proportions will be compared between the intervention arm versus the control arm using a Cochran-Mantel-Haenszel method in a stratified analysis by site to control for two sites at the alpha 0.05 level. The proportion difference and corresponding 95% confidence interval for concordance of antibiotics with or without adjusting for sites will also be calculated.

We will use a hierarchical and mixed effects logistic regression model, a complex analytic approach which offers flexibility regarding model assumptions and incorporation of cluster-level and individual-level covariates. The outcome is proportions of participants exclusively receiving guideline-concordant 1st line antibiotic therapy during the first 24 hours of care and the main exposure variable is intervention vs. usual care. The month of each participant enrolled will be treated as a random effect. We will also use a weighted, cluster-level logistic regression to compare guideline-concordant antibiotic prescribing between groups. In this analysis, data for each cluster are collapsed into a single summary measure, and the summary measures are then analyzed as if they were raw data, facilitating simple data reporting and interpretation. Important baseline covariates (e.g., age, sex, race, site, season, frequency of bacteremia and other pneumonia-related complications) will also be assessed and included as model covariates.

10.2 Secondary Objectives

There are five secondary objectives for this study.

a) The first secondary objective (SO 1) is to compare proportions of participants exclusively receiving guideline-concordant antibiotic therapy for the entire episode, by EHR-based decision support or usual care.

   The analysis is similar to primary objective 1 though the proportion of participants exclusively receiving guideline-concordant antibiotic therapy for the entire episode is the outcome.

b) The second secondary objective (SO 2) is to compare proportions of participants receiving any guideline-concordant antibiotic therapy during the first 24 hours of care, by EHR-based decision support or usual care.

   Proportions of participants with any concordant antibiotic therapy during the first 24 hours of care (yes or no) will be compared between intervention and control arms using a Chi-square test. Proportions and difference of proportions between intervention and control arms will be reported along with their 95%CIs.

   A mixed effects logistic regression model will be conducted. The outcome is any concordant antibiotic therapy (yes or no) and covariates under the consideration will be similar to the ones listed in the primary objective analysis 10.1.

c) The third secondary objective (SO 3) is to compare proportions of participants receiving guideline-concordant for the entire episode, by EHR-based decision support or usual care.

   The analysis is similar to secondary objective 2 though the proportion of participants using any of concordant antibiotic therapy for the entire episode is the outcome.

d) The fourth secondary objective (SO 4) is to compare proportions of participants having ED revisits and hospitalizations within 72 hours of the index discharge, by EHR-based decision support or usual care.

   Proportions of participants having ED revisits or hospitalizations within 72 hours of the index discharge will be compared between intervention and control arms using Chi-square tests. Proportions and difference of proportions between intervention and control arms will be reported along with their 95%CIs.

   Two mixed effects logistic regression models will be conducted. The outcomes are ED revisits (yes or no) and hospitalizations (yes or no) within 72 hours of the index discharge and covariates under the consideration will be similar to the ones listed in the primary objective analysis 10.1.

e) The fifth secondary objective (SO 5) is to compare proportions of participants having ED revisits and hospitalizations within 7 days of the index discharge, by EHR-based decision support or usual care

   The analysis is similar to secondary objective 4 though proportions of having ED revisits and hospitalizations within 7 days of the index discharge are the outcomes.

10.3 Exploratory Objectives

There are six exploratory objectives for this study.

a) The first exploratory objective (EO 1) is to compare time to first antibiotic, by EHR-based decision support or usual care.

   The Wilcoxon rank-sum test will be used to compare time to first antibiotic between intervention and control arms.

   A frailty regression model will be conducted. The outcome is time to first antibiotic and participants not receiving antibiotics shall be censored at discharge. The covariates under the consideration will be similar to the ones listed in the primary objective analysis 10.1.

b) The second exploratory objective (EO 2) is to compare the proportion of participants not receiving antibiotics during the first 24 hours of care, by EHR-based decision support or usual care.

   Proportions of participants not receiving antibiotics during the first 24 hours of care (yes or no) will be compared between intervention and control arms using a Chi-square test. Proportions and difference of proportions between intervention and control arms will be reported along with their 95%CIs.

   A mixed effects logistic regression model will be conducted. The outcome is lacking of antibiotics during the first 24 hours of care (yes or no) and covariates under the consideration will be similar to the ones listed in the primary objective analysis 10.1.

c) The third exploratory objective (EO 3) is to compare the proportion of participants not receiving antibiotics for the entire episode, by EHR-based decision support or usual care.

   The analysis is similar to exploratory objective 2 though the proportion of lacking of antibiotics for the entire episode is the outcome.

d) The fourth exploratory objective (EO 4) is to compare the changes in antibiotics, used as a proxy for treatment failure, after 72 hours, by EHR-based decision support or usual care.

   The analysis is similar to exploratory objective 2 though the proportion of participants with different antibiotic(s) or changing treatments from no-antibiotic(s) to antibiotic(s) after 72 hours is the outcome.

e) The fifth exploratory objective (EO 5) is to compare the proportion of death, by EHR-based decision support or usual care.

   The analysis is similar to exploratory objective 2 though the proportion of death is the outcome.

f) The sixth exploratory objective (EO 6) is to compare the proportion of delayed ICU transfer among hospitalized children, by EHR-based decision support or usual care.

The analysis is similar to exploratory objective 2 though the proportion of delayed ICU transfer among hospitalized children is the outcome.

11 ANALYSIS OF STUDY OBJECTIVES FOR PHASE 2

Descriptive analyses will be summarized for continuous variables with mean, standard deviation, median, and interquartile range. Categorical variables will be summarized with frequencies and percentages. Explanatory figures will be generated to evaluate the data distribution. Comparisons of demographic characteristics between intervention groups will be conducted using Pearson Chi-square and Wilcoxon tests appropriately.

All analyses will be performed using R 3.5.0 (r-project.org), SAS version 9.4, or STATA version 15, or updated software from these programs.

11.1 Primary Objective

The primary objective (PO 1) of the study is to compare proportions of appropriate overall site of care disposition with or without EHR-based prognostic decision support in children 0.6-17 years of age presenting for emergency care. The hypothesis for this primary objective is that the proportion of appropriate site of care disposition is higher in the group receiving EHR-based prognostic decision support vs. the group receiving usual care. This information is captured through chart review and entered in the REDCap database. An investigator in both Nashville and Pittsburgh will be in charge of outcome assessment review, blinded to intervention assignment, and will decide whether site of care disposition is appropriate, yes (1) or no (0), based on Appendix 2 table for this analysis.

The proportions will be compared between the intervention arm versus the control arm using a Cochran-Mantel-Haenszel method in a stratified analysis by site to control for two sites at the alpha 0.05 level. The proportion difference and corresponding 95% confidence interval for concordance of antibiotics with or without adjusting for sites will also be calculated.

We will conduct a multivariable logistic regression model to compare appropriate site of care disposition between the two study arms, controlling for important baseline covariates. Important baseline covariates (e.g., age, sex, race, site, season, month, frequency of bacteremia and other pneumonia-related complications) will also be assessed and included as model covariates. Robust standard errors will be calculated to account for hospital clustering effects. We will also perform analyses to assess for interactions between two study arms and predicted risk for severe outcomes, age, provider type, and initial site of care, to identify subgroups in whom decision support may be most useful.

11.2 Secondary Objectives

There are three secondary objectives for this study.

a) The first secondary objective (SO 1) is to compare proportions of appropriate site of care disposition, by EHR-based prognostic decision support or usual care.

   The analysis is similar to primary objective 1 though proportions of appropriate site of care disposition is the outcome.

b) The second secondary objective (SO 2) is to compare proportions of participants having ED revisits and hospitalizations within 72 hours of the index discharge, by EHR-based prognostic decision support or usual care.

Proportions of participants having ED revisits or hospitalizations within 72 hours of the index discharge will be compared between intervention and control arms using Chi-square tests. Proportions and difference of proportions between intervention and control arms will be reported along with their 95%CIs.

Two multivariable logistic regression models clustering by hospitals will be conducted. The outcomes are ED revisits (yes or no) and hospitalizations (yes or no) within 72 hours of the index discharge and covariates under the consideration will be similar to the ones listed in the primary objective analysis 11.1.

c) The third secondary objective (SO 3) is to compare proportions of participants having ED revisits and hospitalizations within 7 days of the index discharge, by EHR-based prognostic decision support or usual care.

The analysis is similar to secondary objective 2 though proportions of having ED revisits and hospitalizations within 7 days of the index discharge are the outcomes.

11.3 Exploratory Objectives

There are two exploratory objectives for this study.

a) The first exploratory objective (EO 1) is to compare the proportion of death, by EHR-based prognostic decision support or usual care.

The analysis is similar to secondary objective 2 though the proportion of death is the outcome.

b) The second exploratory objective (EO 2) is to compare hospital length of stay among hospitalized children, by EHR-based prognostic decision support or usual care.

The Wilcoxon rank-sum test will be used to compare length of stay between intervention and control arms.

A cox regression model will be conducted. The outcome is length of stay. The covariates under the consideration will be similar to the ones listed in the primary objective analysis 11.1.

Appendix 1

Prior B-lactam	Severe PCN allergy	Moderate to large PPE	Necrotizing or severe pneumonia	Aspiration	Outpatient	Inpatient	ICU withOUT invasive mechanical ventilation or shock	ICU WITH invasive mechanical ventilation and withOUT shock	ICU WITH invasive mechanical ventilation AND shock
NO	NO	NO	NO	NO	Amoxicillin	Ampicillin	Ampicillin or Ceftriaxone	Ceftriaxone	Ceftriaxone plus Vancomycin
NO	NO	NO	NO	YES	Amoxicillin/Clavulanate	Ampicillin/Sulbactam	Ampicillin/Sulbactam or Clindamycin	Ampicillin/Sulbactam or Clindamycin	Ceftriaxone plus Vancomycin
NO	NO	NO	YES	NO	n/a	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin	Ceftriaxone plus Vancomycin
NO	NO	NO	YES	YES	n/a	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin	Ceftriaxone plus Vancomycin
NO	NO	YES	NO	NO	n/a	Ampicillin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin
NO	NO	YES	NO	YES	n/a	Ampicillin/Sulbactam	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin
NO	NO	YES	YES	NO	n/a	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin	Ceftriaxone plus Vancomycin
NO	NO	YES	YES	YES	n/a	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin	Ceftriaxone plus Vancomycin

NO	YES	NO	NO	NO	Clindamycin	Clindamycin	Clindamycin or Levofloxacin	Levofloxacin	Levofloxacin plus Vancomycin
NO	YES	NO	NO	YES	Clindamycin	Clindamycin	Clindamycin or Levofloxacin	Levofloxacin	Levofloxacin plus Vancomycin
NO	YES	NO	YES	NO	n/a	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Vancomycin	Levofloxacin plus Vancomycin
NO	YES	NO	YES	YES	n/a	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Vancomycin	Levofloxacin plus Vancomycin
NO	YES	YES	NO	NO	n/a	Clindamycin	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Vancomycin
NO	YES	YES	NO	YES	n/a	Clindamycin	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Vancomycin
NO	YES	YES	YES	NO	n/a	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Vancomycin	Levofloxacin plus Vancomycin
NO	YES	YES	YES	YES	n/a	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Clindamycin or Vancomycin	Levofloxacin plus Vancomycin	Levofloxacin plus Vancomycin
YES	NO	NO	NO	NO	Amoxicillin or Amoxicillin/Clavulanate	Ampicillin or Ceftriaxone	Ampicillin or Ceftriaxone	Ceftriaxone	Ceftriaxone plus Vancomycin
YES	NO	NO	NO	YES	Amoxicillin/Clavulanate or Clindamycin	Ampicillin/Sulbactam or Clindamycin	Ampicillin/Sulbactam or Clindamycin	Ampicillin/Sulbactam or Clindamycin	Ceftriaxone plus Vancomycin

YES	NO	NO	YES	NO	n/a	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin	Ceftriaxone plus Vancomycin
YES	NO	NO	YES	YES	n/a	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin	Ceftriaxone plus Vancomycin
YES	NO	YES	NO	NO	n/a	Ampicillin or Ceftriaxone	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin
YES	NO	YES	NO	YES	n/a	Ampicillin/Sulbactam or Clindamycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin
YES	NO	YES	YES	NO	n/a	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin	Ceftriaxone plus Vancomycin
YES	NO	YES	YES	YES	n/a	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Clindamycin or Vancomycin	Ceftriaxone plus Vancomycin	Ceftriaxone plus Vancomycin

Appendix 2

Appropriate Site of Care Definitions

Disposition	Appropriate if:
Home care	No subsequent hospitalization within 24h
Inpatient, ward	Hospital length of stay ≥ 24h; or hospital length of stay < 24h but objective criteria for admission present (eg, need for supplemental oxygen); and no subsequent transfer to ICU within 24h
Inpatient, ICU	ICU length of stay ≥ 24h; or ICU length of stay < 24h but objective criteria for ICU admission present (eg, respiratory failure)