Future Research Prioritization: Comparative effectiveness of narrow-spectrum antibiotics versus broad-spectrum antibiotics in the treatment of community-acquired pneumonia in adults

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INTRODUCTION

Community-acquired pneumonia (CAP) is defined as an infection of the lung in persons who have not been hospitalized recently or exposed to other health care settings that markedly increase risk of contracting pneumonia. Health care-associated pneumonia is defined and treated differently than CAP. In 2012, 1.1 million persons were diagnosed with CAP in the United States, resulting in 327,840 hospital admissions.[1] Characteristics of individuals at increased susceptibility to CAP include older age, comorbidities, immunosuppression, non-white race, and lower education and income. In 2013, CAP was the 9th leading cause of death in the US with a mortality rate of 16.9 per 100,000 contributing to 53,000 deaths.[2] The national total cost (both direct and indirect) is estimated at $10.6 billion per year.[3,4]

Typical symptoms of CAP include fever, cough, sputum production, and shortness of breath, with leukocytosis on laboratory testing and lung consolidation or infiltrate on chest imaging. However, the diagnosis of CAP can be challenging, as some patients, especially those who are elderly or have comorbidities, may not present with these symptoms and signs. A wide range of microorganisms can cause CAP, usually bacterial (20-50%) and viral (15-23%) pathogens, and CAP is often multifactorial. Distinguishing viral from bacterial pneumonia can also be challenging based on symptoms and radiologic findings. Antibiotics are only effective for CAP with bacteria as a contributing cause, among which *Streptococcus pneumonia*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are traditionally considered to be the most common.[2,5] However, in 30-65% of CAP cases, an etiologic organism cannot be identified with current methods, even with extensive microbiologic testing. [2,5-8]

The 2007 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines[9] on the treatment of CAP are the most widely used in the US (an update is expected

Spring 2017). Most patients whose severity-of-illness score indicates eligibility for outpatient treatment respond well to therapy, and since microbiologic testing can be challenging, the guidelines recommend empiric choice of antibiotics based on risk factors for drug-resistant *S. Pneumoniae*, comorbidities, previous courses of antibiotics and other risk factors for drug-resistant *S. Pneumoniae* (Table 1).

Table 1. Antibiotic recommendations for outpatient treatment

Patient characteristics	**Antibiotics recommended**
Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection	macrolides (azithromycin, clarithromycin or erythromycin) (strong recommendation, level I evidence) doxycycline (weak recommendation, level III evidence)
Presence of comorbidities, use of antimicrobials within the previous 3 months, or other risks for DRSP infection, or in regions with a high rate of macrolide-resistant *S. pneumoniae*	fluoroquinolone (moxifloxacin, gemifloxacin or high-dose levofloxacin) (level 1 evidence) combination therapy of a beta-lactam (high-dose amoxicillin or amoxicillin–clavulanate, ceftriaxone, cefuroxime or cefpodoxime) with a macrolide (level I evidence); doxycycline (level II evidence) is an alternative to the macrolide

Broad-spectrum antibiotics are often used empirically before the formal identification of the causative bacteria or if no testing is done or no etiology is identified. They are also used for serious illness and for drug-resistant bacteria unresponsive to narrow-spectrum antibiotics. Since no consistent definition of broad-spectrum antibiotics used for CAP exists, guidelines generally use lists of antibiotics to define the two categories, although these lists differ between groups and countries. Some lists of broad-spectrum antibiotics include tetracyclines, fluoroquinolones, and third- and fourth-generation cephalosporins. Lists of narrow-spectrum antibiotics generally include penicillin, aminopenicillins, ampicillin sulbactam, and amoxicillin clavulanate. If

microbiologic testing is performed and an agent is identified that is sensitive to narrow-spectrum antibiotics, care can be tailored to use a narrow-spectrum antibiotic. Broad-spectrum antibiotic use can lead to more emergence of multidrug-resistant bacteria to these antibiotics.[10-12]

The Patient-Centered Outcomes Research Institute (PCORI) tasked the Johns Hopkins University Evidence-based Practice Center to create a prioritized agenda for research on CAP to: 1) incorporate the perspectives of relevant stakeholders; and 2) identify research questions that have a high likelihood of impacting practice patterns for CAP within 5 years of completion of a study addressing the research question.

Based on the initial brief and our literature scan we identified seven key research questions to present to the stakeholders for their feedback and modification:

- Prioritized Question 1: What is the comparative effectiveness of narrow-spectrum vs. broad-spectrum antibiotic therapy for empiric therapy and/or definitive therapy of community-acquired pneumonia in adults?
- Prioritized Question 2: What is the comparative effectiveness of shorter- vs. longer-course antibiotic therapy in the treatment of community-acquired pneumonia in adults? *(includes approaches to assess clinical response after several days of treatment to determine whether therapy should continue)*
- Prioritized Question 3: What is the comparative effectiveness of different approaches to de-escalate antibiotic therapy in the treatment of community-acquired pneumonia in adults? *(includes switch to narrow-spectrum antibiotics and from intravenous to oral agents after a microbiologic cause is identified for hospitalized patients)*

- Prioritized Question 4: What is the comparative effectiveness of different approaches to rapidly diagnose community-acquired pneumonia (*e.g.*, establishing community-acquired pneumonia diagnosis rapidly in clinical practice with respect to whether community-acquired pneumonia is present, whether hospital admission is required and establishing the type of pathogen [*e.g.*, bacteria or virus], and the causative pathogen)? *(rapid diagnosis includes methods to define the type of pathogen at point-of-care to guide initial antibiotic choice)*
- Prioritized Question 5: What are the implications of narrow-spectrum vs. broad-spectrum antibiotic therapy on antibiotic resistance?
- Prioritized Question 6: What is the comparative safety of narrow-spectrum vs. broad-spectrum antibiotic therapy for community-acquired pneumonia in adults?
- Prioritized Question 7: Is the safety and effectiveness of narrow-spectrum vs. broad-spectrum antibiotic therapy different in distinct subpopulations of adults with community-acquired pneumonia (*e.g.*, chronic conditions, immunosuppression, elderly, minorities, living in rural areas)?

METHODS

Overview of Prioritization Approach

Our methods for prioritizing future research and developing recommendations for targeted future funding by PCORI broadly follow the steps used in the Agency for Healthcare Research and Quality (AHRQ)'s Evidence-based Practice Center (EPC) Program approach to identify and prioritize future research needs.[13,14] This approach involves appraisal of recent systematic reviews and other evidence to identify important evidence gaps, transformation of evidence gaps

into potential research questions, engagement of stakeholders to identify additional gaps and prioritize research questions, and scans of recently published and ongoing studies relevant to the list of stakeholder-prioritized research questions.

Appraisal of Recent Evidence to Identify Important Evidence Gaps and Transformation of the Evidence Gaps into Potential Research Questions

In March 2015, our research group prepared a research prioritization topic brief on the comparative effectiveness of narrow-spectrum antibiotics versus broad-spectrum antibiotics in the treatment of community-acquired pneumonia. This brief described the major guidelines to treat CAP, recent research and research needs related to CAP and the population health ramifications of CAP including substantial clinical, social and economic burden in the US. The evidence gaps identified in this document were restated as seven research questions and distributed to stakeholders for comments and prioritization.

Selection and Engagement of Stakeholders

We engaged a diverse group of stakeholders, including clinical and research experts in pulmonary diseases, representatives from federal agencies, representatives from professional societies and guideline developers and health care policymakers (Table 2). Only organizations with representatives familiar with the clinical area and its current uncertainties were asked to participate in the stakeholder panel. Each organization was asked to select stakeholders to complete a feedback form delivered via email and participate in a teleconference discussion based on the feedback form.

Table 2. Characteristics of the Stakeholder Organizations

Organization	Stakeholder Perspective	Purpose
American Academy of Family Physicians (AAFP)	Professional societies/researchers	AAFP and its chapters represent 120,900 family physician, resident, and medical student members. The AAFP is committed to helping family physicians improve the health of Americans by advancing the specialty of family medicine.
American Thoracic Society	Professional societies/researchers	ATS has more than 15,000 members, committed to improve health worldwide by advancing research, clinical care, and public health in respiratory disease, critical illness, and sleep disorders
American College of Chest Physicians (ACCP)	Professional societies/researchers	ACCP has more than 18,700 members with the mission to champion the prevention, diagnosis, and treatment of chest diseases through education, communication, and research
Infectious Diseases Society of America (IDSA)	Professional societies/researchers	IDSA's purpose is to improve the health of individuals, communities, and society by promoting excellence in patient care, education, research, public health, and prevention relating to infectious diseases
Center for Disease Control and Prevention (CDC)	Government/ Policy makers	The CDC conducts critical science and provides health information that protects our nation against expensive and dangerous health threats, and responds when these arise. Through the National Center for Immunization and Respiratory Diseases (NCIRD) it plays a major role in the prevention of disease, disability, and death through immunization and by control of respiratory and related diseases

Research Question Refinement and Prioritization of Future Research

The stakeholders received a feedback form (Appendix A) including the research questions derived from the Topic Development Document. Each stakeholder was asked to comment on the wording, importance, feasibility and likelihood for implementation for the seven identified research questions. They were then asked to identify any missing research questions. Finally, they were asked to assign points to prioritize the research questions. Consistent with a forced-ranking prioritization method described by the AHRQ EPC program, stakeholders were asked to distribute 3 points across the seven identified research questions, with a maximum of 3 points per item and a total of 3 points across all questions.[14] The forced ranking results were used to focus the teleconference discussion on the most highly-ranked questions and areas with lack of consensus within and across the groups. We discussed the feedback form and potential adjustments to the research questions on each teleconference with the stakeholders, in an iterative process focusing on key issues identified in the feedback forms and addressing suggested changes to the research questions in later teleconferences.

Horizon Scan of Studies Potentially Relevant to Top-Tier Research Questions

To identify the most recently published and active research addressing the research questions, we searched two databases.

We searched PubMed to identify recently indexed studies ((community acquired pneumonia) AND treatment) AND ("2014/01/01"[Date - Publication]) and ClinicalTrials.gov (community acquired pneumonia | antibiotics OR antimicrobials | Adult, Senior) for ongoing, recently completed (since January 1, 2014) and recently terminated (since January 1, 2014) studies.

We collected information on the aim, design, primary intervention, primary outcome, results (if applicable) and relevance to the research questions for each identified systematic review, trial or large cohort study and trial registration.

RESULTS

Five organizations participated from the five organizations invited (Table 1), resulting in 7 completed feedback forms (from four organizations) and four conference calls (14 stakeholder participants from four organizations).

Stakeholder Input

In response to the stakeholders' input, we modified the research questions to focus on two broad themes: diagnosis and treatment. We included sub-questions on the type of antibiotic treatments compared (*e.g.*, narrow versus broad) and duration of treatment. We incorporated safety into the comparative effectiveness of treatment question. We removed the question related to subpopulations, as stakeholders felt this issue should be incorporated into any study. The research question related to resistance was removed; although antibiotic resistance is extremely important, a specific study to examine resistance was felt to not be feasible.

Based on comments in the feedback form and the conversations during the conference call, the central themes from the stakeholders included:

The definition of narrow- and broad-spectrum antibiotics varies, a study to answer this question would be challenging to conduct, and this study might be unlikely to change practice

Stakeholders commented that there is not a consensus on the definition of narrow- and broad-spectrum antibiotics, particularly as some antibiotics may be considered narrow but cover resistant organisms, and guidelines recommend drugs in combination for some indications. Antibiotics that are considered broad-spectrum in Europe (*e.g.,* ceftriaxone) are generally viewed as narrow-spectrum in the US, and antibiotics considered narrow-spectrum in Europe (*e.g.,* amoxicillin) are generally not used in the US for pneumonia. One stakeholder commented that an important issue is the effectiveness of broad-spectrum treatment with pseudomonas/ methicillin-resistant coverage, resulting in part from definitions of health care-acquired pneumonia and some suggestions of worse outcomes, and that evaluating and defining this broad-spectrum issue would be of high importance.

There was also a concern that enrolling patients and changing practice would not be feasible, as practitioners would be concerned about putting their patients at risk with narrow-spectrum antibiotics and would not use them, and that the likelihood of results convincing enough to change practice from such a study would be low. Stakeholders also commented that such a study might be challenging to conduct since multiple study arms might be needed, depending on which regimens are included, and adequate follow up of treated outpatients would be challenging.

Finally, if the study is not randomized, careful evaluation of patient factors would be needed to evaluate the reasons behind the initial choice of antibiotics.

Studies of outpatient, emergency department, hospitalized and intensive care unit patients with CAP are needed, but outpatient is the top priority for these research questions

Multiple stakeholders agreed that defining the population is critical for any study of CAP. The treatment decisions and outcomes of interest differ for outpatients (including those seen in the emergency department), inpatients on standard units and inpatients in intensive care units (ICUs). Issues of narrow- vs broad-spectrum and duration of therapy apply most directly to outpatients. Recruiting outpatients with CAP may be difficult, although patients presenting to the emergency department with CAP are likely to be generally representative of the outpatient population. Inpatient studies of CAP should take into account those individuals treated in an ICU, those at high risk of ICU and those not at high risk of ICU in the study designs.

Some stakeholders commented that studies should consider patients at high risk of CAP, including those with pre-existing respiratory diseases and immunocompromised individuals, in their design and analysis. Studies of a single group of high-risk patients would lack generalizability given the prevalence of CAP and may have recruitment issues compared with studying CAP by treatment setting and performing subgroup analyses of the high-risk groups. Treatment effectiveness by common effect modifiers such as age, sex and race should be considered in the design and analyses.

When asked if studies comparing the different prognostication tools are needed to determine which patients require hospitalization or intensive care unit support, stakeholders felt that standard prognostic tools have been well-tested and are available, but are not used in routine

practice because clinicians prefer to use subjective judgment to determine whether patients should be hospitalized.

The duration of antibiotics to treat CAP may be as important as the choice of antibiotic, and these issues could potentially be combined in one comparative effectiveness trial

Stakeholders commented that long duration of antibiotics for CAP has already been well-covered by a recent systematic review, and 14-day courses are no longer used. However, multiple stakeholders commented that the duration of antibiotic treatment could possibly be shortened even further than current 7-day recommendations. Defining the shortest effective duration of therapy could have benefits to patients (*e.g.,* fewer side effects) and to ecology (*e.g.,* resistance). Multiple stakeholders agreed that comparing treatment of 3, 5 or 7 days duration for effectiveness is reasonable, and these specific durations should be noted in the research question. The stakeholders noted that providers may not be comfortable with randomizing patients to single-day treatment at present. Others stated that the duration of treatment should be determined by clinical response. The stakeholders commented that examining de-escalation strategies are unnecessary if treatment can be shortened to a period where de-escalation is no longer needed.

Multiple stakeholders agreed that combining both antibiotic choice and duration of treatment as study questions would be desirable, although such a study might not be feasible due to the need for multiple study arms.

Patient-centered outcomes are needed in CAP studies

Outcomes should include patient-centered outcomes such as time to return to work or activities of daily living. Inpatient studies should include need for readmissions. Outpatient and

emergency department-based studies should include need for admission to the hospital and unplanned additional emergency department visits. Mortality should not be the primary outcome. Stakeholders noted that safety should not be an independent research question but is a component of comparative effectiveness, and should include rates of *Clostridium difficile* infection.

There is general consensus that a comparative effectiveness study on diagnostics to identify causative pathogens for CAP could improve care

Some stakeholders stated that a study addressing timely, point-of-care diagnosis of the specific pathogen may have greater impact than a study comparing narrow to broad spectrum antibiotics. If the pathogen is rapidly identified, the initial treatment can be matched accordingly. Of importance, stakeholders noted that simply identifying a viral cause is not sufficient, because CAP is often multifactorial. Proposed diagnostic tests need to identify a bacteria, to ensure that antibiotics are needed. Stakeholders also noted that current diagnostic testing does not identify a causative pathogen in the majority of cases, and that better diagnostic approaches are needed.

One group of stakeholders suggested comparing pathogen-matched treatment to empiric treatment and comparing the patient-centered outcomes as well as the increased resource utilization and potential delay in treatment associated with identifying the pathogen prior to initiating treatment. If diagnostic tests are examined, some stakeholders noted that procalcitonin has not been studied in a non-industry-funded trial setting, but others stated that biomarkers such as procalcitonin and C-reactive protein are likely too nonspecific to guide individual patient antibiotic choices. They also suggested comparing clinical decision tools based on information

contained within the medical record to biologic tests like extended spectrum viral panels or procalcitonin.

One group of stakeholders noted that even before determining the pathogen, establishing the diagnosis of pneumonia is needed. For patients with comorbidities, such as congestive heart failure, it can be difficult to determine a diagnosis based on imaging.

Antibiotic resistance is a concern, but studies designed to examine antibiotic resistance as an outcome would not be feasible

Multiple stakeholders commented that studies of resistance would likely not be feasible due to the need for a longer-term study with follow up testing and cultures (which might be of low yield, regardless).

CAP treatments could be studied with innovative designs given the variety of treatment options available and prevalence of the condition

Some stakeholders recommended combining multiple treatment modalities (*e.g.,* different diagnostic tests, types of antibiotics and durations of treatment) into a single study. The novel study designs described by PCORI such as Bayesian adaptive trials could be appropriate. The novel trial designs examined by PCORI-funded methods research could be tested in CAP diagnosis and treatment studies. However, some stakeholders thought that the complexity of CAP diagnosis and treatment could make the design of such a trial impractical. The findings of a complex study may not change practice patterns if the complexity of the design and its merit is not obvious to the practitioners currently caring for the majority of CAP patients. However, one stakeholder stated that diagnosis-treatment bundles have been tested for sepsis and are currently

being implemented into practice. The sepsis bundle precedent may make implementation of effective CAP bundles easier to disseminate.

Additional areas of research

Several additional areas were noted by one or two stakeholders. One noted that the dose of antibiotics is also an important issue, in addition to duration. Others noted that the area of pneumonia vaccination is also critical in the area prevention, but since the CDC will be revising its guidelines in 2018, it would be challenging for a PCORI study to provide relevant evidence in time. Another area suggested was the prognosis of patients for factors that predispose to mortality or long duration of illness.

Stakeholder Ranking of Research Questions

Based on the prioritization in the feedback forms, we arranged the prioritized research questions according to the number of points assigned (Table 3).

Table 3. Prioritized Research Question Rating

Question	Points	Stakeholders, n
Prioritized Research Question 1: What is the comparative effectiveness of different approaches to rapidly diagnose community-acquired pneumonia (*e.g.*, establishing community-acquired pneumonia diagnosis rapidly in clinical practice with respect to whether community-acquired pneumonia is present, whether hospital admission is required and establishing the type of pathogen [*e.g.*, bacteria or virus], and the causative pathogen)	7	5
Prioritized Research Question 2: What is the comparative effectiveness of narrow spectrum vs. broad spectrum antibiotic therapy for empiric therapy and/or definitive therapy of community-acquired pneumonia in adults?	6	5
Prioritized Research Question 3: What is the comparative effectiveness of shorter- vs. longer-course antibiotic therapy in the treatment of community-acquired pneumonia in adults?	4	4
Prioritized Research Question 4: What is the comparative safety of narrow spectrum vs. broad spectrum antibiotic therapy for community-acquired pneumonia in adults?	2	2
Prioritized Research Question 5: Is the safety and effectiveness of narrow spectrum vs. broad spectrum antibiotic therapy different in distinct subpopulations of adults with community-acquired pneumonia (*e.g.*, chronic conditions, immunosuppression, elderly, minorities, living in rural areas)?	2	2
Prioritized Research Question 6: What is the comparative effectiveness of different approaches to de-escalate antibiotic therapy in the treatment of community-acquired pneumonia in adults?	0	0
Prioritized Research Question 7: What are the implications of narrow spectrum vs. broad spectrum antibiotic therapy on antibiotic resistance?	0	0

Revised research questions

As a result of the stakeholder input, we revised the research questions.

- Revised Research Question 1: What is the comparative effectiveness and safety of different approaches for rapid, point-of-care diagnosis of the etiology of community-acquired pneumonia in adults (whether there is a bacterial contributing cause, the specific etiologic agent, and strain/ antibiotic sensitivity)?
- Revised Research Question 2: What is the comparative effectiveness and safety of different antibiotic regimens in the empiric treatment of community-acquired pneumonia in adults?
    - Revised Research Question 2a: What is the comparative effectiveness of empiric narrow- versus broad-spectrum antibiotics for community-acquired pneumonia?
    - Revised Research Question 2b: What is the comparative effectiveness of different durations of antibiotic treatment for CAP (3 versus 5 versus 7 days) for community-acquired pneumonia?

Horizon Scan of Studies Potentially Relevant to Prioritized Research Questions

a. PubMed results

Our PubMed search identified 683 articles. Of these, 48 met our inclusion criteria including (8 RCTs, 1 study plan for a published RCT), 12 prospective studies (including 3 pre-post), 17 retrospective cohorts, 2 case-control studies, 2 cross-sectional studies and 4 reviews. Fifteen studies aimed to compare diagnostic tests, 13 focused on resistance and the remainder of the studies compared antibiotic treatment strategies. One study focused on safety and 3 on specific subpopulations. None of the RCTs were conducted in the US. The Tables in Appendix C detail

key characteristics of the included PubMed articles separately for each of the prioritized research questions.

Two systematic reviews also addressed critical areas for the research questions of most interest. A 2014 Cochrane systematic review evaluated the efficacy and safety of different antibiotic treatments for CAP in patients >12 years of age treated in outpatient settings. This review included 11 randomized controlled trials (RCTs) (3352 participants) with 15 different antibiotic comparisons. The authors concluded that there is insufficient evidence to recommend a single best choice of antibiotics.[7] Another meta-analysis published in 2008 found no difference in effectiveness between short- and long-term courses of antibiotics (defined as short- (< or = 7 days) versus long- (> or = 2 days difference)).[15]

b. Clinical Trials.gov results

Our search of ClinicalTrials.gov yielded 85 studies; of these, 13 met our inclusion criteria. Three studies were potentially applicable to prioritized questions 1 and 6 (although none addressed narrow vs broad spectrum antibiotics), 7 studies were applicable to prioritized question 2, only 1 study was applicable to prioritized question 3, and 2 were applicable for prioritized question 4. We did not identify any studies applicable to prioritized questions 5 or 7.

For prioritized question 1, no studies directly addressed prioritized question 1 (narrow- vs. broad-spectrum). One study (not yet recruiting) is designed to compare 2 similar beta-lactams to evaluate a drug (faropenem) not yet available in the United States, 1 study (recruiting) is evaluating a specific drug, pristinamycin, which is similar to a narrow-spectrum but has activity against resistant strains, and 1 is comparing different broad spectrum regimens to each other. All studies are evaluating both effectiveness and safety outcomes (Prioritized Question 6).

For prioritized question 2, 3 trials (2 recruiting, 1 recently completed) are comparing different duration of antibiotic treatment, and 4 (2 recruiting, 1 recently completed, 1 not yet recruiting) are evaluating the role of using biomarker testing (procalcitonin, C-reactive protein) in shortening the duration of antibiotic treatment.

For prioritized question 3, 1 trial (not yet recruiting) likely addresses this question, although details were not specified.

For prioritized question 4, 1 trial (not yet recruiting) is evaluating point-of-care testing for identification of microbial etiology for targeted narrow-spectrum antibiotics, and 1 trial (recruiting) is evaluating procalcitonin biomarker for determination of likely bacterial vs viral etiology. (One of the studies identified for prioritized question 2 also includes a similar study question).

No studies were identified for prioritized question 5 or 7.

The Tables in Appendix D detail key characteristics of the included ClinicalTrials.gov articles separately for each of the prioritized research questions.

LIMITATIONS OF APPROACH AND SUPPORTING LITERATURE

Although our stakeholder group comprised key researchers, guideline developers, epidemiologists, experienced clinicians, and representatives of five stakeholder groups, there was no patient stakeholder group represented. The ability to identify a stakeholder or stakeholder group is more difficult for acute conditions, like CAP, compared with chronic conditions. One limitation to the available literature was the lack of recent US guidelines. The most recent guidelines for the diagnosis and treatment of CAP in the United States were published in 2007;

updated guidelines are expected in late 2016 or early 2017, and leaders of this current guideline effort were represented on the stakeholder teleconferences.

APPENDIX A

ISSUES WITH DIAGNOSIS AND TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA (CAP) IN THE UNITED STATES.

There is agreement that treatment is best when it is pathogen-directed, but controversies exist on how to achieve this. The prevalent contemporary assumption regarding CAP in the United States has been that the microbial pathogen is rarely identified, the major causes are Streptococcus pneumoniae and the "atypical agents" and that antimicrobial therapy should be directed against these pathogens, based on decades of work.[16] The 2007 IDSA/ATS guidelines state that diagnostic tests are optional for outpatients and describe indications for testing in hospitalized patients, and guidelines are available for specific testing.[17]

However, in 2015, a report in the New England Journal of Medicine by Jain et al[8] reporting extensive prospective microbiology studies on > 2000 adults with CAP challenged underlying assumptions of the microbiology of CAP in the United States. This report used a vast menu of diagnostic studies including standard cultures, urinary antigen tests and extensive use of molecular diagnostics. This showed a pathogen could be detected in only 38% of cases, with bacteria in 14% (the pneumococcus accounted for only 5% and atypical agents for 4%) and viruses were the most commonly detected agents with 23%. In brief, this report confounds contemporary concepts regarding CAP and its pathogens which obviously influence therapeutic decisions. Three facets of CAP are relevant:

- What causes CAP? The history of microbiology of CAP in the US has undergone substantial

change in the past 50 years. The assumption has been that S. pneumoniae was the most common pathogen based on historical studies including transthoracic needle aspiration reported to yield S. pneumoniae in 81% in 1937. During the subsequent 60 years the yield of S. pneumoniae gradually decreased to 10 – 20% from reports published in 1987 – 92.[16] During that period there was an often aggressive effort to recover pathogens in CAP using some novel and aggressive techniques including the bronchial brush catheter with quantitation and trans-tracheal aspiration.

- Decrease in diagnostic studies for CAP: Current guidelines for antibiotic treatment of CAP have been based on mortality outcome and led to the "6 hour rule", meaning that hospitals receiving Medicare funding reported how frequently they were able to deliver antibiotics to patients within 6 hours of arrival in the emergency room ("door to needle time").[18,19] This requirement essentially precluded microbiology studies and also provided guidance for antibiotic choices. The result was essentially no studies of the microbiology in the US.
- Pneumococcal vaccines: The United States has been justifiably aggressive in the use of pneumococcal vaccine, initially PPCV23 and more recently Prevnar 7 & 13. This has had an extraordinary impact on the frequency of invasive pneumococcal infections, especially with vaccine use in pediatrics since they appear to be the vectors of adult pneumococcal infections, which is prevented by "herd immunity". Of importance here is that microbiology data for CAP in other countries, especially European countries, cannot be extrapolated to the US due to variations in national pneumococcal vaccine policies.

In summary, we don't currently know what causes CAP in the US because the most definitive study done using modern technology including virtually all valid diagnostic studies failed to

show any pathogen in 62% of cases and found pneumococcal infections in just 5%. Guidelines based on pneumococcal infections may no longer be appropriate in the US.

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Appendix B. Feedback Form for Stakeholders

Key Informant Feedback Form for Topic Refinement & Future Research Prioritization

Topic:

Comparative Effectiveness of Narrow-Spectrum Antibiotics versus Broad-Spectrum Antibiotics in the Treatment of Community-Acquired Pneumonia in Adults

Johns Hopkins Evidence-based Practice Center

Responses due to Catalina Suarez-Cuervo

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We are conducting a review to prioritize the research questions on the treatment of community-acquired pneumonia. The goal of the topic refinement is to better assess the

- Importance
  - *Is the issue important for clinical practice and patient outcomes?*
- Feasibility
  - *Can research be practically conducted to answer this question?*
- Likelihood for implementation
  - *How well can the results be translated into practice?*
  - *How well can the results help patients make better informed treatment decisions?*
  - *Likelihood that the results of research conducted to address the research questions will be used by the stakeholders that you represent*
  - *Can results be used to select treatment, translation into guidelines or standards?*

We are asking for your input to identify the questions that are most important to patients, clinicians, policy makers and the stakeholder group that you represent.

We will ask you to comment on each of the 7 Research Questions suggest any missing key questions and assign points to identify the most important questions that need to be addressed by research right now.

Which stakeholder group do you represent? *Check all that apply*

Patient Provider Payer Researcher Other

For each of the 7 proposed key questions, comment on the wording, importance, feasibility and likelihood for implementation in the table below.

QUESTION 1: **What is the comparative effectiveness of narrow spectrum vs. broad spectrum antibiotic therapy for empiric therapy and/or definitive therapy of community-acquired pneumonia in adults?**		
Is question1 clearly worded?	YES	NO
Comments on question wording or content of question *1*		
Is question 1 important?	YES	NO
Comments on importance of question *1*		
Is it feasible for a single study to address question 1?	YES	NO
Comments on feasibility of question*1*		
Will the results of a study addressing question 1 be used by your stakeholder group?	YES	NO
Comments on likelihood for implementation of question *1*		
Other comments on question 1		
QUESTION 2: **What is the comparative effectiveness of shorter- vs. longer-course antibiotic therapy in the treatment of community-acquired pneumonia in adults?**		
Is question 2 clearly worded?	YES	NO
Comments on question wording or content of question *2*		
Is question 2 important?	YES	NO
Comments on importance of question *2*		
Is it feasible for a single study to address question 2?	YES	NO
Comments on feasibility of question *2*		
Will the results of a study addressing question 2 be used by your stakeholder group?	YES	NO
Comments on likelihood for implementation of question *2*		
Other comments on question 2		

QUESTION 3: **What is the comparative effectiveness of different approaches to de-escalate antibiotic therapy in the treatment of community-acquired pneumonia in adults?**		
Is question 3 clearly worded?	YES	NO
Comments on question wording or content of question *3*		
Is question 3 important?	YES	NO
Comments on importance of question *3*		
Is it feasible for a single study to address question 3?	YES	NO
Comments on feasibility of question *3*		
Will the results of a study addressing question 3 be used by your stakeholder group?	YES	NO
Comments on likelihood for implementation of question *3*		
Other comments on question 3		
QUESTION 4: **What is the comparative effectiveness of different approaches to rapidly diagnose community-acquired pneumonia** (*e.g.*, establishing community-acquired pneumonia diagnosis rapidly in clinical practice with respect to whether community-acquired pneumonia is present, whether hospital admission is required and establishing the type of pathogen [*e.g.*, bacteria or virus], and the causative pathogen)		
Is question 4 clearly worded?	YES	NO
Comments on question wording or content of question *4*		
Is question 4 important?	YES	NO
Comments on importance of question *4*		
Is it feasible for a single study to address question 4?	YES	NO
Comments on feasibility of question *4*		
Will the results of a study addressing question 4 be used by your stakeholder group?	YES	NO
Comments on likelihood for implementation of question *4*		
Other comments on question 4		

QUESTION 5: What are the implications of narrow spectrum vs. broad spectrum antibiotic therapy on antibiotic resistance?		
Is question 5 clearly worded?	YES	NO
Comments on question wording or content of question *5*		
Is question 5 important?	YES	NO
Comments on importance of question *5*		
Is it feasible for a single study to address question 5?	YES	NO
Comments on feasibility of question *5*		
Will the results of a study addressing question 5 be used by your stakeholder group?	YES	NO
Comments on likelihood for implementation of question *5*		
Other comments on question 5		
QUESTION 6: What is the comparative safety of narrow spectrum vs. broad spectrum antibiotic therapy for community-acquired pneumonia in adults?		
Is question 6 clearly worded?	YES	NO
Comments on question wording or content of question *6*		
Is question 6 important?	YES	NO
Comments on importance of question *6*		
Is it feasible for a single study to address question 6?	YES	NO
Comments on feasibility of question *6*		
Will the results of a study addressing question 6 be used by your stakeholder group?	YES	NO
Comments on likelihood for implementation of question *6*		
Other comments on question 6		

QUESTION 7: Is the safety and effectiveness of narrow spectrum vs. broad spectrum antibiotic therapy different in distinct subpopulations of adults with community-acquired pneumonia (*e.g.*, chronic conditions, immunosuppression, elderly, minorities, living in rural areas)?		
Is question 7 clearly worded?	YES	NO
Comments on question wording or content of question *7*		
Is question 7 important?	YES	NO
Comments on importance of question *7*		
Is it feasible for a single study to address question 7?	YES	NO
Comments on feasibility of question *7*		
Will the results of a study addressing question 7 be used by your stakeholder group?	YES	NO
Comments on likelihood for implementation of question *7*		
Other comments on question 7		
Are there important key questions not addressed in the list above?	YES	NO
Describe the missing key questions		

Which Key Questions are in greatest need of an answer right now using a patient-centered research design? Assign up to 3 points to identify the most important Key Question(s). You can give all 3 points to 1 question or distribute the points across the questions.

Key Question	**Points given**
QUESTION 1 – Narrow vs Broad therapy	
QUESTION 2 – Short vs Long therapy	
QUESTION 3 – Antibiotic de-escalation	
QUESTION 4 – Relevance of diagnosis improvement	
QUESTION 5 – Antibiotic resistance	
QUESTION 6 – Safety	
QUESTION 7 – Subpopulations	
Missing question (written-in above)	
Total points	3

Thank you for your time and attention!

Appendix C. – Studies Characteristics – PubMed Search

Studies included for Question 1 - narrow- vs broad-spectrum antibiotics

	Title	Purpose	Interventions	Type of study	Conclusions
1	Increasing use of third-generation cephalosporins for pneumonia in the emergency department: may some prescriptions be avoided?	Third-generation cephalosporins are used to treat inpatients with community-acquired pneumonia. Some of these prescriptions may be avoided, i.e. replaced by agents less likely to promote ESBL-mediated resistance. Our objectives were to assess the recent trend of third-generation cephalosporins use for pneumonia in the emergency department, and the proportion of avoidable prescriptions	third-generation cephalosporins	retrospective study	The proportion of patients treated with a third generation cephalosporin increased significantly from 13.9 % (6.9-24.1 %) in 2002 to 29.5 % (18.5-42.6 %) in 2012 (OR = 1.07 [1.01-1.14] , P = 0.02) Antibiotic stewardship programs should be implemented to restrict the third-generation cephalosporins use for pneumonia in the emergency department.
2	Antibiotics for community-acquired pneumonia in adult outpatients	To compare the efficacy and safety of different antibiotic treatments for CAP in participants older than 12 years treated in outpatient settings with respect to clinical, radiological and bacteriological outcomes	10 RCTs - nine antibiotic pairs (n=3321) 1 RCT - four antibiotics (n=31)	Systematic review	Individual study results do not reveal significant differences in efficacy between various antibiotics and antibiotic groups. 2 studies showed significantly more adverse events with use of cethromycin as compared to clarithromycin and nemonoxacin when compared to levofloxacin. Multi-drug comparisons using similar administration schedules are needed to provide the evidence necessary for practice recommendations. There is a need for more research on diagnosis, management, cost-effectiveness and misuse of antibiotics in CAP and LRTI
3	Improvement in clinical and economic outcomes with empiric antibiotic therapy covering atypical pathogens for community-acquired pneumonia patients: a multicenter cohort study	To determine the effectiveness of empiric antibiotic regimens covering atypical pathogens with respect to detailed clinical and economic outcomes in community-acquired pneumonia (CAP)	Patients with a diagnosis of CAP were enrolled and categorized into two groups according to the initial antibiotic strategy used - covering or not covering atypical pathogens	population-based, multicenter, retrospective cohort	Antimicrobial treatment covering atypical pathogens for hospitalized CAP patients is associated with reduced mortality and economic burden

Studies included for Question 2 - Short vs Long treatment

	Title	Purpose	Interventions	Phase, n, Status	Outcomes assessed
1	A randomized controlled clinical trial of levofloxacin 750 mg versus 500 mg intravenous infusion in the treatment of community-acquired pneumonia	to compare the efficacy and safety of levofloxacin 750 mg for 5 days versus 500 mg for 7-14 days intravenous (IV) in the treatment of community-acquired pneumonia (CAP)	levofloxacin 5 days versus 7-14 days	Randomized controlled trial	levofloxacin for 5 days was at least as effective and well tolerated as for 7-14 days for the treatment of CAP
2	Early versus later response to treatment in patients with community-acquired pneumonia: analysis of the REACH study	Retrospective Study to Assess the Clinical Management of Patients With Moderate-to-Severe Complicated Skin and Soft Tissue Infections [cSSTI] or CAP in the Hospital Setting)	Short lasting antibiotic (3 days) compared to long lasting (8 days)	retrospective observational study	Achieving early clinical stabilization in CAP (</=4 days) is associated with improved outcomes, lower requirement for initial treatment modification or readmission and lower resource use, compared with a later response
3	Can an antimicrobial stewardship program reduce length of stay of immune-competent adult patients admitted to hospital with diagnosis of community-acquired pneumonia? Study protocol for pragmatic controlled non-randomized clinical study	In immune-competent adult patients admitted to a hospital ward with a diagnosis of community-acquired pneumonia, does a multi-faceted ASP utilizing prospective chart audit and feedback reduce the length of stay, compared with usual care, without increasing the risk of death or readmission 30 days after discharge from hospital?	Antimicrobial stewardship programs (ASPs)	Randomized controlled trial NCT 02264756	Study Protocol: outcomes are Primary: hospital length of stay; secondary days and duration of antibiotic therapy, inadvertent adverse outcomes of 30 day post-discharge mortality and hospital readmission rates

4	A tailored implementation strategy to reduce the duration of intravenous antibiotic treatment in community-acquired pneumonia: a controlled before-and-after study	To implement a novel protocol, tailored to previously identified barriers, to switched to oral therapy in a timely fashion	No comparator	multi-centre controlled before-and-after study	
5	Early response to antibiotic treatment in European patients hospitalized with complicated skin and soft tissue infections: analysis of the REACH study	Retrospective Study to Assess the Clinical Management of Patients With Moderate-to-Severe Complicated Skin and Soft Tissue Infections [cSSTI] or CAP in the Hospital Setting)	we review characteristics and outcomes of patients with an early response (</=72 hours) compared with those without an early response to treatment	descriptive analysis NCT 01293435	patients without early response had a higher rate of adverse clinical outcomes (e.g. septic shock) and higher use of healthcare resources
6	Improvement of antibiotic therapy and ICU survival in severe non-pneumococcal community-acquired pneumonia: a matched case-control study	to compare intensive care unit mortality due to non-pneumococcal severe community-acquired pneumonia between the periods 2000-2002 and 2008-2014, and the impact of the improvement in antibiotic strategies on outcomes	matched by the following variables: microorganism, shock at admission, invasive mechanical ventilation, immunocompromised, chronic obstructive pulmonary disease, and age over 65 years	matched case-control study	Early antibiotic administration and use of combined antibiotic therapy were both associated with increased intensive care unit survival during the study period.
7	Impact of macrolide therapy in patients hospitalized with Pseudomonas aeruginosa community-acquired pneumonia	to assess the effect of macrolide therapy on mortality in patients hospitalized for Pseudomonas aeruginosa community-acquired pneumonia (CAP)	Macrolide within the first 48 h of admission	retrospective population-based study	Macrolide therapy in the first 48 h of admission is not associated with decreased 30-day mortality, ICU admission, need for mechanical ventilation, and LOS in hospitalized patients with P aeruginosa CAP

8	Patient Outcomes on Day 4 of Intravenous Antibiotic Therapy in Non-Intensive Care Unit Hospitalized Adults With Community-Acquired Bacterial Pneumonia	to assess health outcomes (length of stay [LOS] and hospital charges) between responders and non-responders at day4 of hospitalization	Chart review	Retrospective n=666	In this real-world chart study, less than half of hospitalized patients with CABP achieved clinical response at day 4 of initial intravenous antibiotic therapy. The observed clinical response was associated with a significantly shorter hospital stay and trended toward lower total hospital charges. These findings corroborate the Food and Drug Administration guidance for assessing antimicrobial therapy at day 4 because responder is associated with improved health outcomes.

Studies included for Question 4- Diagnostic strategies

	Title	Purpose	Interventions	Phase, n, Status	Outcomes assessed
1	Rapid diagnostic tests for defining the cause of community-acquired pneumonia	review the potential new diagnostic tools for determining the cause of pneumonia in the setting of community-acquired infection after outlining the limitation of currently available tests		Review	empiric therapy based on knowledge of local epidemiological data is likely to remain the standard of care until the hurdles of proven accuracy, physician acceptance and cost-effectiveness are successfully negotiated
2	Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis	To assess the diagnostic utility of PCT in critically ill patients with pneumonia and suspected H1N1 influenza	PCT levels, measured within 24 hours of ICU admission	individual patient data meta-analysis by combining data with data from five other studies	In critically ill patients with pneumonia during the influenza season, PCT is a reasonably accurate marker for detection of bacterial pneumonia, particularly in patients with community-acquired disease and without immune-compromising disorders, but it might not be sufficient as a stand-alone marker for withholding antibiotic treatment
3	Procalcitonin, a valuable biomarker assisting clinical decision-making in the management of community-acquired pneumonia	To assess the sensitivity and specificity of this test in the largest series of cases to date and used logistic regression models to determine predictors of positivity in patients hospitalized with community-acquired pneumonia.	Detection of the C-polysaccharide of Streptococcus pneumoniae in urine by an immune-chromatographic test	prospective observational n=4,374	The urinary antigen sensitivity and specificity were 60% and 99.7% in diagnosing pneumococcal pneumonia Predictors of urinary antigen positivity were: female sex; heart rate ≥ 125 bpm, systolic blood pressure ≤30 mmHg

4	Lung inflammatory pattern and antibiotic treatment in pneumonia	To assess inflammatory response against the causative microorganism	Cytokine profiles (IL-6, IL-8, IL-10), + tumour necrosis factor alpha in blood and bronchoalveolar lavage of Responders vs non-responders	prospective study n=52	After 72 hours of antibiotic effect, patients who received macrolide had lower inflammatory cytokine levels in pulmonary and systemic compartments along with faster stabilization of infectious parameters.
5	Impact of pre-hospital antibiotic use on community-acquired pneumonia	To test the influence of pre-hospital antibiotic, clinical features and outcomes of patients with community-acquired pneumonia (CAP)	Patients were divided into two groups: those who had received pre-hospital antibiotic treatment for the same episode of CAP and those who had not	observational study of a prospective cohort	The frequency of positive sputum culture and the sensitivity and specificity of the pneumococcal urinary antigen test for diagnosing pneumococcal pneumonia were similar in the two groups No significant differences were found in prognosis between study groups.
6	Predictive value of methicillin-resistant Staphylococcus aureus (MRSA) nasal swab PCR assay for MRSA pneumonia	All patients with confirmed pneumonia who had both a nasal swab MRSA PCR test and a bacterial culture within predefined time intervals were included in the study.	Calculated sensitivity, specificity, positive predictive value, negative predictive value for clinically confirmed MRSA pneumonia	retrospective cohort n=435	In pneumonia: The MRSA PCR assay Sensitivity 88.0% Specificity 90.1%, positive predictive value 35.4% negative predictive value 99.2%. MRSA PCR nasal swab Poor positive predictive - excellent negative predictive value in populations with low MRSA pneumonia incidence. In cases of culture-negative pneumonia where initial empirical antibiotics include an MRSA-active agent, a negative MRSA PCR swab can be reasonably used to guide antibiotic de-escalation.
7	Community acquired bacterial pneumonia: aetiology, laboratory detection and antibiotic susceptibility pattern	to identify the common bacterial causes of community acquired pneumonia (CAP) from sputum and blood by culture and polymerase chain reaction (PCR) and to evaluate the effectiveness of these tests	sputum and blood samples were collected from patients with pneumonia on clinical suspicion PCR	cross sectional study n-105	Considering culture as a gold standard, the sensitivity of PCR was 96.55% and specificity was 88.15%. More than 80% of Streptococcus pneumoniae isolates were sensitive to ampicillin, amoxicillin/clavulanate, and ceftriaxone.

					Susceptibilities to other antimicrobials ranged from 65% for azithromycin to 70% for levofloxacin. Gram negative organisms were more sensitive to meropenem, ceftriaxone, amoxycillin-clavulanate and amikacin
8	Bacterial and viral etiology in hospitalized community acquired pneumonia with molecular methods and clinical evaluation	to evaluate the bacterial and viral etiology of hospitalized CAP cases and compare clinical and laboratory findings of patients with pure bacterial and bacterial and viral (mixed) infections	Deep tracheal aspiration samples were examined for bacterial and viral pathogens by multiplex PCR, and standard bacteriological culture method	prospective study n=55	The etiological identification rate in 50 patients for bacteria, viruses and mixed virus-bacteria combination by PCR were 62%, 4%, 32%, respectively and 60% in 55 patients by bacterial culture method. Concomitance of bacterial and viral agents is frequent and resemble with bacterial infections alone
9	The urinary antigen tests have high sensitivity in diagnosis of Pneumococcus caused community-acquired pneumonia posterior to antimicrobial therapy	To evaluate the impact of antimicrobial therapy on sensitivity of the immunochromatographic test (ICT) test	specimens were collected before or after antibiotic treatment and compared to blood and sputum	prospective study n=487	The positive rate of blood and pleural fluid was declined from 5.7 to 2.7 % and sputum, from 9.9 to 4.7 % after the antibiotic treatment, while in the ICT positive rates were not different 10.9 % and 13.2 % ($P > 0.05$)
10	Detection and serotyping of pneumococci in community acquired pneumonia patients without culture using blood and urine samples	To investigate methods to detect pneumococcal CAP using non-culture based techniques	quantitative PCR (qPCR) capsular sequence typing (CST) Inhibition multiplex immunoassay (IMIA)	prospective study n=487	This study indicates the usefulness of additional molecular methods to conventional laboratory methods for the detection of pneumococcal pneumonia. Direct detection and subsequent serotyping on clinical samples will improve the accuracy of pneumococcal surveillance to monitor vaccine effectiveness.
11	Diagnostic value of serum procalcitonin in identifying the etiology of non-responding community-acquired pneumonia after initial antibiotic therapy	to investigate the diagnostic value of serum procalcitonin(PCT) in identifying the etiology of non-responding community-acquired pneumonia (CAP) after initial antibiotic therapy	PCT if treatment failure after 72hours of treatment.	retrospective analysis n=232	Serum PCT level fails to predict non-responsiveness, but is suggestive of bacterial infections in hospitalized CAP patients with early treatment failure

12	Validation of sputum Gram stain for treatment of community-acquired pneumonia and healthcare-associated pneumonia: a prospective observational study	to evaluate the usefulness of sputum Gram stain in etiological diagnosis and pathogen-targeted antibiotic treatment of CAP and HCAP	Gram stain on sputum samples	prospective observational study n=670 (2010-2012)	Sputum Gram stain is highly specific for the etiologic diagnosis and useful in guiding pathogen-targeted antibiotic treatment of CAP and HCAP.
13	Ruling out Legionella in community-acquired pneumonia	Currently used antigen tests and culture have limited sensitivity with important time delays, making empirical broad-spectrum coverage necessary. We sought to validate these parameters	a score with 6 variables: fever, cough, hyponatremia, lactate dehydrogenase, C-reactive protein, and platelet count	multinational database (Community Acquired Pneumonia Organization)	A logistic regression with all predictors: AUC of 0.91 (95% CI, 0.87-0.94). Original dichotomized score AUC, 0.73; 95%CI, 0.65-0.81) NPV 99% for patients with less than 2 parameters present
14	The value of signs and symptoms in differentiating between bacterial, viral and mixed aetiology in patients with community-acquired pneumonia	To compare clinical and laboratory parameters of patients with CAP caused by different groups of pathogens to evaluate the potential for targeted diagnostics and directed treatment	adult patients with CAP were tested for the presence of a broad range of possible respiratory pathogens using bacterial cultures, PCR, urinary antigen testing and serology	Prospective study N=263	Although several variables were independently associated with the detection of a pathogen group, substantial overlap meant there were no reliable clinical predictors to distinguish aetiologies. Therefore, testing for common respiratory pathogens is still necessary to optimize treatment.
15	Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia	Clinical data and microbiological tests were assessed; blood cultures, serums, nasopharyngeal swabs and lower tracheal specimens via intubation tube	Urine pneumococcal and legionella antigens, Mycoplasma pneumoniae and Chlamydia pneumoniae antibodies respiratory virus by multiplex, real-time polymerase chain reaction (PCR)	Prospective study N=49 mechanically ventilated SCAP patients	Viral findings were demonstrated in almost half of the SCAP patients. Clinical characteristics were similar between the pure bacterial and mixed bacterial-viral infections groups. The frequency of viral detection depends on the availability of PCR techniques and lower respiratory specimens.

Studies included for Question 5- Antibiotic resistance

	Title	Purpose	Interventions	Phase, n, Status	Outcomes assessed
1	Microbiological Profile and Drug Sensitivity Pattern among Community Acquired Pneumonia Patients in Tertiary Care Centre in Mangalore, Coastal Karnataka, India	To study the microbiological profile of patients with community acquired pneumonia and to study drug sensitivity pattern	Sputum culture	Hospital based cross sectional study N=100	Most of the organisms were found to be sensitive to monotherapy with extended spectrum beta lactamases, third generation cephalosporins, fluoroquinolones, macrolides.
2	Molecular characterizations of PCR-positive Mycoplasma pneumoniae specimens collected from Australia and China	to compare genotype distribution and macrolide resistance rates between locations	PCR analysis and sequencing of domain to compare genotype distribution and macrolide resistance rates	Specimen collections N=30	3.3% macrolide resistance in Australia vs 85.5% in China; which may reflect differences in antibiotic use and/or measures in resistance control
3	The Effect of Macrolide Resistance on the Presentation and Outcome of Patients Hospitalized for Streptococcus pneumoniae Pneumonia	to determine the effect of macrolide resistance on the presentation and outcomes of patients with pneumococcal pneumonia	Evaluate outcomes in adult patients hospitalized with pneumonia who had positive cultures for S. pneumoniae	retrospective, observational study n=643	Of 643 patients hospitalized for S. pneumoniae pneumonia, 139 (22%) were macrolide resistant. no evidence suggesting that patients hospitalized for macrolide-resistant S. pneumoniae pneumonia were more severely ill on presentation or had worse clinical outcomes if they were treated with guideline-compliant versus noncompliant regimens
4	Overview of antimicrobial options for Mycoplasma pneumoniae pneumonia: Focus on macrolide resistance			Review	
5	Investigations of Mycoplasma pneumoniae infections in the United States: trends in molecular typing and macrolide resistance from 2006 to 2013	Data from 17 investigations of cases, small clusters, and outbreaks of M. pneumoniae infections that were supported by the Centers for Disease Control and Prevention (CDC) between 2006 and 2013.	199 M. pneumoniae-positive specimens collected during this time period in order to identify trends in antimicrobial resistance and circulating types	Prospective study n=199	Overall, macrolide resistance was identified in approximately 10% of M. pneumoniae infections occurring during this time period. A systematic surveillance program is necessary to understand the burden of M. pneumoniae disease in the United States, facilitate case and outbreak identification, and inform appropriate therapeutic and infection control strategies.

6	No Development of Imipenem Resistance in Pneumonia Caused by Escherichia coli	To examine antibiotic resistance in patients with community- and nosocomial-acquired pneumonia caused by E coli	Hospital charts of patients with pneumonia caused by E coli.	Retrospective	E coli was resistant to many of the typically used antibiotics. high resistance ampicillin (60.7%), piperacillin (56.3%), a ampicillin-sulbactam (44.4%) co-trimoxazole (25.9%). No resistance toward imipenem
7	The comparative development of elevated resistance to macrolides in community-acquired pneumonia caused by Streptococcus pneumoniae	To examines the possible development of resistance to antibiotics in S. pneumoniae in recent years	Hospital charts of patients with pneumonia caused by S. pneumoniae in Germany	Retrospective	Increased resistance was found for macrolides and tetracycline in patients with CAP by S. pneumoniae.
8	Predicting risk of drug-resistant organisms in pneumonia: moving beyond the HCAP model			Review	In addition to the five risk factors incorporated in HCAP, at least 13 other factors have been identified. The independent predictive value of any single factor is low, but accumulating factors results in increased risk of CAP-DRP. The performance characteristics of 9 clinical prediction scores are reviewed
9	Epidemiology and predictors of multidrug-resistant community-acquired and health care-associated pneumonia	to ascertain the rate of pneumonia caused by multidrug-resistant organism (MDROs) and to evaluate whether HCAP is a risk factor for MDRO pneumonia	Chart reviews	retrospective study n=521	MDROs were isolated in 20 (3.8%) patients MDROs were uncommon. Local etiology of community onset pneumonia and specific MDRO risk factors should be integrated into therapeutic decisions to prevent empirical overprescribing of antibiotics for methicillin-resistant Staphylococcus aureus (MRSA) and P. aeruginosa.
10	Clinical evaluation of the need for carbapenems to treat community-acquired and healthcare-associated pneumonia	Carbapenems have an overall broad antibacterial spectrum and should be protected against from the acquisition of drug resistance	Chart reviews pneumonia cases that did not require intensive care unit management, mechanical ventilation or treatment with vasopressor agents	retrospective study n=591	Carbapenem use can be avoided in cases of CAP or HCAP that are not in a critical condition The frequent use of antipseudomonal beta-lactams does not improve the clinical outcomes of HCAP
11	Targeting antimicrobial-resistant bacterial respiratory tract pathogens: it is time to 'get smart'			review	Pathogen-directed therapy guided by in-vitro microbiological data is a safe approach for the treatment of respiratory infections due to antibacterial-resistant bacteria. Further research should focus on the

					role of rapid diagnostic tools, new antibiotics, and novel immunotherapy for respiratory infection.
12	Third-generation cephalosporin resistance of community-onset Escherichia coli and Klebsiella pneumoniae bacteremia in a secondary hospital	To enable appropriate antimicrobial treatment for community-onset infections in emergency departments (EDs), data are needed on the resistance profiles of Escherichia coli and Klebsiella pneumoniae, which are the main pathogens of community-onset bacteremia	Chart reviews patients with E. coli and K. pneumoniae bacteremia Korea	Retrospective n=734	the rate of resistance (10.6%) was significantly higher, compared to the annual averages of 2003 to 2008 (6.1%; p = 0.03) Previous exposure to antibiotics was an independent risk factor for third-generation cephalosporin resistance in multivariate logistic regression analysis
13	Comparison of sputum and nasopharyngeal aspirate samples and of the PCR gene targets lytA and Spn9802 for quantitative PCR for rapid detection of pneumococcal pneumonia	to compare sputum and nasopharyngeal aspirate (NpA) samples and the PCR gene targets lytA and Spn9802 in quantitative PCR (qPCR) assays for rapid detection of pneumococcal etiology in community-acquired pneumonia (CAP)	PCR gene targets lytA and Spn9802 in quantitative PCR (qPCR) assays in sputum and nasopharyngeal aspirate (NpA)	Prospective n=78	The best-performing test, the sputum lytA qPCR assay, showed high sensitivity (94%) and specificity (96%) with a cutoff value of 10(5) DNA copies/ml. In CAP patients with good sputum production, this test has great potential to be used for the rapid detection of pneumococcal etiology and to target penicillin therapy.

Studies included for Question 6 - Safety

	Title	Purpose	Interventions	Phase, n, Status	Outcomes assessed
1	Azithromycin is not associated with QT prolongation in hospitalized patients with community-acquired pneumonia	to examine the association of azithromycin treatment on QT prolongation in a cohort of patients hospitalized with community-acquired pneumonia (CAP)	90 (73.8%) - azithromycin 32 (26.2%) other antibiotics (ampicillin-clavulanate, chloramphenicol doxycycline, or ceftriaxone)	Cohort N=122	Azithromycin treatment was not associated with QT prolongation in patients with severe CAP

Studies included for Question 7- Subpopulations

	Title	Purpose	Interventions	Phase, n, Status	Outcomes assessed
1	Pneumonia in solid organ transplant recipients: a prospective multicenter study	to investigate epidemiology, diagnosis, therapy, and outcome of pneumonia in an unselected solid organ transplant recipients population	to report on all SOT recipients with pneumonia treated during 2 separate weeks (1 each in February and June 2012)	point prevalence 35 centers 54 cases	Causative agents included bacteria (87.1%), virus (29%), and fungi (6.4%). Pneumonia remains a frequent problem in SOT recipients, although it occurs later in patients who are in better physical health. Therefore, harmful pathogens and worse outcome are less common than previously thought.
2	Decrease in mortality in severe community-acquired pneumococcal pneumonia: impact of improving antibiotic strategies (2000-2013)	to compare intensive care unit mortality due to non-pneumococcal severe community-acquired pneumonia between the periods 2000-2002 and 2008-2014, and the impact of the improvement in antibiotic strategies on outcomes	matched by the following variables: microorganism, shock at admission, invasive mechanical ventilation, immunocompromised, chronic obstructive pulmonary disease, and age over 65 years	matched case-control study	Early antibiotic administration and use of combined antibiotic therapy were both associated with increased intensive care unit survival during the study period.
3	Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis	Some studies suggest better outcomes with macrolide therapy for critically ill patients with community-acquired pneumonia.	28 observational studies 9,850 patients	Systematic review	In observational studies of almost 10,000 critically ill patients with community-acquired pneumonia, macrolide use was associated with a significant 18% relative (3% absolute) reduction in mortality compared with nonmacrolide therapies. After pooling data from studies that provided adjusted risk estimates, an even larger mortality reduction was observed. These results suggest that macrolides be considered first-line combination treatment in critically ill patients with community-acquired pneumonia and support current guidelines.

Appendix D. – Studies Characteristics – ClinicalTrials.gov Search

Clinical trials included for Question 1 and 6 - narrow- vs broad-spectrum antibiotics *

	NCT identifier	Title	Purpose	Interventions	Phase, n, status	Outcomes assessed
1	NCT01937832 QUESTION 1 QUESTION 6	A Phase III Study of Faropenem in the Treatment of Adult Community-acquired Bacterial Pneumonia	The purpose of this study is to evaluate the safety and efficacy of Faropenem in community-acquired pneumonia (CAP) subjects	Faropenem vs Ertapenem	Phase 3 540 Not yet recruiting	Primary: Per subject clinical cure rate
2	NCT02332577 QUESTION 1 QUESTION 6	Study to Compare the Efficacy of Pristinamycin (Pyostacine) Versus Amoxicillin in the Treatment of Acute Community Acquired Pneumonia	To evaluate the clinical efficacy of pristinamycin at a dose of 2g x 2/day for 2 days then 1g x 3/day for 5 to 7 days versus amoxicillin 1g x3 /day for 7 to 9 days, 5 to 9 days after the end of treatment. (Pristinamycin would generally be considered narrow-spectrum but has some activity against resistant strains)	Pristinamycin vs. Amoxicillin	Phase 4 500 Recruiting	Primary: Percentage of patients cured (clinical course -pulmonary radiological course) Secondary: Percentage of patients cured (bacteriological - procalcitonin levels –pneumococcus documentation) Percentage of relapse Mortality rate Documented failures Adverse events
3	NCT01660204 QUESTION 1 QUESTION 6	Community-Acquired Pneumonia - Study on the Initial Treatment With Antibiotics of Lower Respiratory Tract Infections (CAP-START)	To compare the cost and effectiveness of three existing antibiotic strategies for patients with community-acquired pneumonia admitted to the hospital, but not the intensive care unit	Beta-lactam monotherapy (eg, ceftriaxone) vs. Beta-lactam combination + macrolide (eg, erythromycin) vs. Quinolone monotherapy (eg, levofloxacin)	NR 2283 Completed January 2014	Primary: Day 90 Mortality Secondary: Length of intravenous antibiotic treatment Length of hospital stay Tolerability Complications Health care costs Non-health care costs

*While all of these are comparing different antibiotic regimens, none are comparing narrow- vs broad-spectrum antibiotics

Clinical trials included for Question 2- Short vs Long treatment

	NCT identifier	Title	Purpose	Interventions	Phase, n, Status	Outcomes assessed
1	NCT01661920 QUESTION 2	Suitability of Antibiotic Treatment for CAP	To evaluate the last North American guideline for CAP, which recommends using clinical stability criteria as a reference to establish the duration of antibiotic treatment, which would result in about 5 days of antibiotic use for the majority of pneumonia cases	Intervention group (antibiotic treatment for at least 5 days), vs Control group (routine treatment, which generally lasts 9-10 days)	NR 602 Completed April 2014	Primary: Duration of antibiotic treatment Mortality Clinical cure Secondary: In-hospital mortality for any cause Readmission Days needed to reach clinical stability Recurrence Duration of hospital stay Days to return to normal activity
2	NCT01963442 QUESTION 2	Short Duration Treatment of Non-severe Community Acquired Pneumonia	To investigate the non-inferiority of a short lasting (3 days) compared to a long lasting(8 days) antibiotic treatment at Day 15, in terms of clinical efficacy, in adults admitted to emergency services for a non-severe Community Acquired Pneumonia (CAP), who responded well to 3 days of beta-lactam treatment	Short lasting antibiotic (3 days) compared to long lasting (8 days)	Phase 2 310 Recruiting	Primary: Clinical evaluation at Day 15 Secondary: Clinical evaluation at Day 30 Other: mortality
3	NCT01492387 QUESTION 2	Duration of Antibiotic Therapy in Community - Acquired Pneumonia	To assess the efficacy of an individualized approach to duration of antibiotic therapy based on each subject's clinical response compared to a local standard approach in patients coming from the community and who are hospitalized because of a pneumonia	Individualized approach (therapy will be discontinued 48 hours after patient reaches clinical stability, with at least 5 days antibiotic treatment) vs local standard approach (duration determined by physician)	Phase 4 892 Recruiting	Primary: Composite outcome including adverse events at 30-60 and 90 Days Other complications Need for new antibiotic Secondary: Antibiotic exposure (days) Adverse effects Length of hospitalization Costs

4	NCT01723644 QUESTION 2	Clinical Reassessment Versus Procalcitonin in Order to Shorten Antibiotic Duration in Community-acquired Pneumonia	To compare two strategies: clinical reassessment and procalcitonin guided diagnostic and therapeutic strategy in patients with community-acquired pneumonia	Clinical reassessment arm vs the procalcitonin arm.*	NR 286 Completed June 2015	Primary: duration of antibiotic therapy expressed in days of therapy Secondary: clinical success at Day 30
5	NCT01964495 QUESTION 2	Reduction of Antibiotic Therapy by Biomarkers in Patients With Community-acquired Pneumonia Episodes (REDUCE Study)	To evaluate two different treatment strategies in patients admitted to hospital with Community Acquired Pneumonia. The investigators hypothesize both procalcitonin (PCT) and C-reactive protein (CRP) will be effective in reducing the length of antibiotic treatment.	Discontinuation of treatment according to CRP (C-reactive protein) levels vs. Discontinuation of treatment according to procalcitonin levels Treatment according to current guidelines	NR 468 Recruiting	Primary: Length of antibiotic treatment Secondary: Length of stay Clinical response 30-day mortality Time to clinical stability Relapse rate
6	NCT01018199 QUESTION 2	Procalcitonin Versus C-reactive Protein to Guide Therapy in Community Acquired Pneumonia	To test if C-reactive protein (CRP) or procalcitonin (PCT) - guided strategy allows to reduce the antibiotic use in patients with community-acquired pneumonia.	C-reactive protein vs. Procalcitonin to guide the duration of antibiotic therapy. Stopping antibiotics will be recommended based on the levels.	NR 120 Not yet recruiting	Primary: Duration of antibiotic therapy for the first episode of infection Total antibiotic exposure days per 1,000 days Days alive without antibiotics Secondary: All cause mortality Clinical cure rate Infection relapse Length of hospitalization stay In-hospital mortality Nosocomial infection rate Nosocomial superinfection Isolation of resistant bacteria Costs of hospitalization
7	NCT01723644 QUESTION 2	Clinical Reassessment Versus Procalcitonin in Order to Shorten Antibiotic Duration in Community-acquired Pneumonia	To compare two strategies: clinical reassessment and procalcitonin guided diagnostic and therapeutic strategy in patients with community-acquired pneumonia	Clinical reassessment vs. Procalcitonin arm	NR 286 Completed	Primary: Duration of antibiotic therapy expressed in days of therapy Secondary: clinical success at Day 30

* On Day 1, the aim of the clinical reassessment is diagnosis reassessment: to confirm or not the diagnosis of community-acquired pneumonia and to confirm or not the antibiotherapy. On Day 5, the aim of the clinical reassessment is to evaluate the possibility to stop the current antibiotherapy based on criteria for clinical stability defined by the Infectious Diseases Society of America. In the procalcitonin arm, initiation and discontinuation of the antibiotherapy is based on the antibiotic stewardship based on procalcitonin (PCT) cut-off ranges previously published. Also potentially relevant for QUESTION4.

Clinical trials included for Question 3 – De-escalation

	NCT identifier	Title	Purpose	Interventions	Phase, n, Status	Outcomes assessed
1*	NCT02276092 QUESTION 3	Impact of a Regional Antimicrobial Stewardship on the Length of Stay of Patients Admitted to Hospital With Pneumonia	To evaluate the effectiveness of an antimicrobial stewardship program to reduce the length of stay of patients admitted to hospital with a diagnosis of pneumonia	Antimicrobial stewardship: identify patients with pneumonia, review their charts and make recommendations to their attending physicians about antibiotic management.	NR 2000 Not yet recruiting	Primary: Length of hospital stay Secondary: Days of antibiotic therapy Mortality rate Readmission to hospital

* Could potentially also be relevant for other QUESTION, depending on content of intervention –not specified

Clinical trials included for Question 4 - Diagnostic strategies

	NCT identifier	Title	Purpose	Interventions	Phase, n, Status	Outcomes assessed
1	NCT01662258 QUESTION 4	Microbiology Testing With the Aim Of Directed Antimicrobial Therapy For CAP	To determine if Targeted strategy is non-inferior to Empiric therapy with respect to outcome endpoints, and assess if the use of innovative POC (point-of-care) tests allows targeted narrow-spectrum antimicrobial therapy.	Targeted therapy with Point-of-Care diagnostic laboratory test for microbial etiology vs. empiric therapy	NR 5500 Not yet recruiting	Primary: Improvement or resolution of symptoms of CAP AND absence of objective signs of deterioration Secondary: Identification of microbial etiology by laboratory testing Other: Receipt of narrow spectrum antimicrobial agent targeted toward a specific microbe (as opposed to empiric antimicrobial therapy that is broad-spectrum)

						Length of stay for hospitalized patients
2	NCT02130986 QUESTION 4	Procalcitonin Antibiotic Consensus Trial (ProACT)	To test the effect of implementation of a novel procalcitonin guideline on antibiotic use and adverse outcomes in emergency department (ED) patients with lower respiratory tract infection (LRTI)	Usual care vs Procalcitonin level with results of procalcitonin (PCT) level to treating clinician, provide procalcitonin guideline to treating clinician (guidance for whether likely to be bacterial and if antibiotics are encouraged)	NR 1514 Recruiting	Primary: Total antibiotic exposure Combined endpoint of adverse outcomes that could be attributable to withholding antibiotics Secondary: Rate of antibiotic initiation by the initial ED clinician

No clinical trials included for QUESTION 5
No clinical trials included for QUESTION 7