PROTOCOL TITLE:
Rapid diagnostic testing to guide antibiotic therapy in drug resistant pneumonia

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1.0 Objectives

1.1 The purpose of this study is to conduct an open-label randomized pilot clinical trial to compare an antibiotic strategy based on a novel rapid diagnostic test, based on polymerase chain reaction (PCR), to usual care in critically ill adults with pneumonia suspected to be caused by methicillin resistant staphylococcus aureus (MRSA).

1.2 We hypothesize that when automated PCR is used to guide antibiotic therapy, antibiotic exposure will be reduced in critically ill subjects with pneumonia.

2.0 Background

2.1 Significance.

Bacterial resistance to antibiotics is a major problem in intensive care units (ICUs). (4-6) The Centers for Disease Control (CDC) estimate drug resistant infections affect more than 2 million individuals nationwide and cause 23,000 deaths annually. (7) In a recent executive order, the President of the United States (8) called for improved antibiotic stewardship and the development of rapid diagnostic tests to identify antibiotic resistant infections. (9) In ICU patients with pneumonia, guidelines (10, 11) advocate the routine use of broad spectrum antibiotics in most patients. In large part this is because diagnostic testing for pneumonia is too insensitive and too slow to inform decision making about appropriate antibiotics. Overuse of broad spectrum antibiotics promotes drug resistance by selecting for antibiotic resistant bacterial strains. (12-14) This proposal will apply a new diagnostic test, polymerase chain reaction (PCR), to rapidly identify a drug resistant pathogen, methicillin resistant staphylococcus aureus (MRSA) to reduce inappropriate antibiotics in ICU patients with suspected pneumonia.

MRSA is an important cause of drug resistant pneumonia associated with high mortality. (15, 16) Methicillin resistance in *Staphylococcus aureus* (SA) results from acquisition of the mecA gene located in the mobile element staphylococcal cassette chromosome mec (SCCmec). (2) Risk factors for MRSA are shown in **Table 1.** MRSA pneumonia requires specific antibiotic therapy, (17) treatment guidelines recommend addition of empiric antibiotics against MRSA in patients admitted to the ICU with risk factors for DRPs. (10, 11) Our prior work demonstrates that there is significant overlap of MRSA risk factors with risk factors for other DRPs, (18) which potentially leads to the overuse of anti-MRSA antibiotics. (19, 20) Globally, MRSA pneumonia occurs in an estimated 2-6% of ICU patients. (21, 22) By contrast, empiric anti-MRSA therapy is prescribed in the

Table 1. Risk factors for drug resistant pneumonia

Nonspecific DRPs in CAP	Nonspecific DRPs in HCAP/HAP/VAP
Chronic lung disease	Hospitalization within 90 days
Immunosuppression	Antibiotics within 90 days
Wound care	Immunosuppression
Poor functional status	Non-ambulatory status
Diabetes mellitus	Tube feedings
Tobacco use	Gastric acid suppression
Gastric acid suppression	
Indwelling catheter	
MRSA specific risk factors	**MRSA specific risk factors**
Prior MRSA colonization	Prior MRSA colonization
Pulmonary necrosis	Hemodialysis
Sputum gram stain with gram positive cocci	Congestive heart failure

Adapted from (1-3))

Key: CAP: Community acquired pneumonia, HCAP: Healthcare associated pneumonia HAP: hospital acquired pneumonia, VAP: Ventilator associated pneumonia

majority of ICU patients with suspected pneumonia. (23) We have shown that at our own institution, the prevalence of MRSA is 5.5%, but empiric anti-MRSA therapy is prescribed in 89.5% of ICU patients with pneumonia. (24, 25) The large gap between empiric antibiotic therapy for MRSA pneumonia and actual cases of MRSA pneumonia is due to the lack of specificity of DRP risk factors, and the time delay of bacterial cultures. Overuse of antibiotics against MRSA has adverse consequences for patients, including new hospital acquired infections (HAIs), increased hospital length of stay (LOS), and higher cost. (26-28)
Faster and more accurate diagnostic tests for MRSA, such as PCR, have the potential to reduce antibiotic exposure and improve patient outcomes. The time delay of bacterial cultures and the lack of specificity of DRP risk factors is a major limitation to the treatment of pneumonia, particularly in ICUs where the rapid delivery of appropriate antibiotics could be life saving. PCR has the potential to change the paradigm of empiric antibiotics by increasing diagnostic certainty and reducing the time to diagnosis or exclusion of a resistant pathogen. However, molecular diagnostic tests have not yet been validated for routine clinical practice. (29)

2.2 Preliminary data.

We will compare detection of MRSA in BAL samples obtained in intubated adult patients with suspected pneumonia using Cepheid Xpert® PCR to traditional microbiologic cultures.

The Cepheid Xpert® system. The Cepheid Xpert® is an automated, self-contained platform designed to detect *S. aureus* and MRSA in body fluids using PCR amplification. Two assays are available: Cepheid Xpert® SA Nasal Complete for nasopharyngeal samples and Cepheid Xpert ®MRSA/SA SSTI for use in skin and soft tissue samples. *S. aureus* (SA) is detected by the presence of the staphylococcal protein A (spa) gene, MRSA is identified by mecA gene and the SCCmec. Prior studies report detection of MRSA is possible in 58 minutes.

Three groups (30-32) have reported using Cepheid Xpert® to detect MRSA in lower respiratory tract samples. PCR exhibits a sensitivity of 80-100% and negative predictive value (NPV) of 96.3% - 100%. The range in sensitivity is likely related to variation in the prevalence of MRSA and inadequate power. One study, Leone et al (30), reported that 10.6% of the tests were not interpretable, and there was 1 false negative. All the non-interpretable results and the false negative came from a single center using the Nasal Complete assay.

Table 2. Operating characteristics of Xpert platform for detection of MRSA in respiratory samples

Study	Platform	Body fluid	MRSA prevalence	Sens	Spec	PPV	NPV
Cercenado, 2012 (31)	SSTI	ETA	High	99.0%	72.2%	90.7%	96.3%
Oh 2013 (32)	Not specified	ETA and BAL	Medium	100%	90.7%	78.0%	100%
Leone 2013 (30)	Nasal / SSTI	BAL	Low	80.0%	99.5%	66.7%	99.8%

Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value

We are currently prospectively validating automated PCR using BAL samples from intubated ICU patients with suspected pneumonia. Residual BAL samples obtained for the clinical care of ICU patients will be obtained for analysis. The methodology for this is described in our prior IRB submission: *PCR to ID MRSA in BAL,* **STU00201397**.

2.3 Innovation of the current proposal.

In this proposal, we will use automated PCR to manage antibiotics in critically ill subjects with suspected MRSA pneumonia. This is a novel approach to pneumonia diagnosis and treatment. Automated PCR has not been used previously to withhold or stop empiric antibiotics to cover MRSA in critically ill patients with suspected pneumonia.

3.0 Inclusion and Exclusion Criteria

3.1 Screening.

Patients admitted to the medical intensive care unit (MICU) with suspected pneumonia will be screened for inclusion. Screening will be conducted by the principal investigator and MICU research staff by manual review of the MICU census. Screening will be done during working hours, Monday thru Saturday, excluding holidays.

3.2 Inclusion criteria

1. Adults aged 18 years and older with known or suspected pneumonia who are endotracheally intubated and mechanically ventilated
2. Have or are planned to have bronchoalveolar lavage (BAL) for suspected pneumonia
3. Have received 48 hours or less of MRSA therapy (the antibiotics vancomycin or linezolid) prior to study enrollment but who are anticipated to continue MRSA therapy pending further workup

3.3 Exclusion criteria.

1. More than 48 hours of MRSA therapy with either vancomycin or linezolid,
2. Subjects with extra pulmonary infection requiring treatment with vancomycin or linezolid
3. Neutropenic fever
4. Chronic airway infection
5. Patient/surrogate refusal
6. Subjects in whom BAL is deemed unsafe by the treating physician
7. Treating physician refusal to discontinue antibiotics to treat MRSA if PCR negative

3.4 Special populations.

1. Adults who are unable to consent are eligible for study enrollment if a surrogate decision maker is available to provided informed consent.
2. Prisoners will be excluded.

3. Vulnerable populations (pregnant women and children) will not be eligible for inclusion.

4.0 Study-Wide Number of Subjects

The study will be a time-limited study but will aim to recruit at least 44 subjects in about a 12-month period of time from a single site, the medical intensive care unit (MICU) at Northwestern Memorial Hospital (NMH).

5.0 Study-Wide Recruitment Methods

Not applicable

6.0 Multi-Site Research

Not applicable

7.0 Study Timelines

7.1 Timeline for subject recruitment

Subjects will be followed by the research staff from the time of screening (order or notification of a planned BAL in the MICU) until discharge from the hospital. The study intervention, randomization to PCR strategy versus usual care, will occur at the time of consent. Subjects who are randomized to PCR strategy will have BAL soon after enrollment if not already obtained, and PCR will be conducted within 1 hour of study enrollment and or receipt of sample. Subject in both the PCR arm and usual care arm will be followed until discharge from the hospital. Clinical data will be gathered using the Northwestern University Electronic Data Warehouse (NU-EDW)

7.2 Timeline for subject enrollment

The anticipated duration of the clinical trial to enroll subjects is January 2016 to January 2017

7.3 Timeline for study completion

The estimated date for the investigators to complete the study, including the primary analysis, is targeted for April 2017

8.0 Study Endpoints

8.1 Study outcomes

The primary outcome measure is **antibiotic-days of vancomycin or linezolid,** defined as days on which at least one dose of antibiotic is given. For antibiotics dosed at > 24 hour intervals, any interval day will be included as an antibiotic day. Secondary outcomes are cost, subsequent hospital acquired infections (HAIs), ICU and hospital length of stay (LOS), and mortality.

8.2 Safety outcomes

The primary safety endpoint is concordance of MRSA PCR result to the results of respiratory cultures. In addition, clinical response subsequent to withdrawing/withholding MRSA drugs and subsequent documentation of MRSA infection(s) at other sites will be recorded.

9.0 Procedures Involved

9.1 Study goals

Whether rapid automated PCR can safely replace the traditional approach that relies on DRP risk factors and bacterial cultures to choose appropriate antimicrobial therapy in the ICU is unknown. Therefore we will conduct a clinical trial to compare a PCR guided approach to MRSA therapy to usual care.

Goals of the clinical trial are:

1) To determine if an antibiotic strategy that utilizes rapid automated PCR reduces antibiotic-days in ICU subject with suspected pneumonia,

2) To compare the safety of an antibiotic strategy that relies on rapid automated PCR to usual care,

3) To compare costs of the rapid automated PCR based strategy to routine microbiologic cultures,

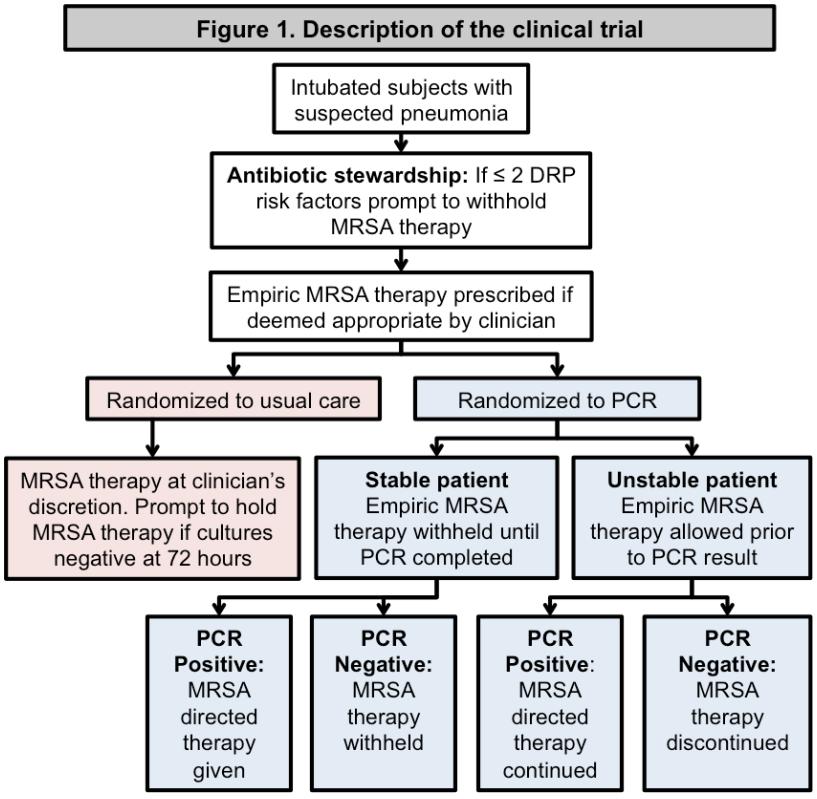
4) To determine if an antibiotic strategy based on rapid automated PCR will reduce subsequent HAIs.

9.2. Study site.

This study will be conducted in the medical ICU (MICU) at NMH, a 33-bed unit staffed by critical care physicians, trainees, and respiratory therapists (RTs). In intubated patients with suspected pneumonia, BALs are obtained by the MICU physician or qualified trainee for bronchoscopic BALs, or trained RTs for nonbronchoscopic BALs (NBBALs). About 60 total BALs are collected monthly in the MICU.

9.3. Study design.

An overview of the clinical trial is shown in **Figure 1**. Patients admitted to the MICU with suspected pneumonia will be screened for inclusion. Subjects with suspected pneumonia will be randomized to antibiotic management with automated PCR compared to usual care in a 1:1 fashion. In the usual care arm, MRSA therapy will be given at the discretion of the care team. If bacterial cultures are negative for MRSA at 72 hours, the care team will be prompted to discontinue MRSA therapy. In subjects randomized to the automated PCR arm who are clinically stable, results from the PCR must be available prior to the administration of MRSA therapy. Subjects with a positive MRSA PCR will be administered MRSA therapy. In subjects with a negative MRSA PCR, MRSA therapy will be withheld. In subjects randomized to the automated PCR arm who are clinically unstable, as defined by hypotension requiring vasopressors, lactic acidosis, or intubation within the previous 12 hours, empiric MRSA therapy will be allowed until the PCR is completed. In these cases of unstable subjects, empiric MRSA therapy will be discontinued if the PCR is negative.



9.4 Bronchoalveolar lavage (BAL)

Bronchoalveolar lavage specimens will be gathered from all study subjects by a respiratory therapist (RT) nonbronchoscopically (NB-BAL) or by a qualified physician bronchoscopically (B-BAL). BAL is routinely preformed for clinical care of patients with pneumonia in ICU settings, and all subjects enrolled in this study will have had a BAL done for clinical care rather than for the study. The most common risk is transient hypoxia which typically resolves within 15 minutes of the procedure without the need for any specific intervention other than an increase in the fraction of inspired oxygen. There is a very small risk of other procedural complications including bronchospasm, airway bleeding, and pneumothorax. These are seen rarely and occur in <1% of all non-bronchoscopic BALs performed.

9.5 Sample processing and Study device

Following collection, BAL samples gathered from subjects in the PCR arm will be transferred immediately to the molecular epidemiology laboratory at NMH where the BAL will tested for the presence of MRSA using PCR by a qualified laboratory technician. Testing will be done using the Cepheid Xpert® Assay, performed on the GeneXpert® Instrument Systems, a qualitative in vitro diagnostic test designed for rapid detection and differentiation of *Staphylococcus aureus (SA)* and methicillin resistant *Staphylococcus aureus* MRSA in body fluids using the Cepheid Xpert ® MRSA/SA SSTI developed for use in skin and soft tissue samples. SA is detected by the presence of the staphylococcal protein A (spa) gene, MRSA is identified by the mecA gene and staphylococcal cassette chromosome mec (SCCmec). Prior studies report detection of MRSA is possible in 58 minutes. (30) the GeneXpert® Instrument is already available in the NMH Microbiology laboratory.

Once the PCR is completed, the results will be relayed to the study physician who will communicate with the treating physician regarding whether MRSA antibiotic therapy (vancomycin or linezolid) will be started or stopped based on the study protocol. All BAL samples will be sent for routine bacterial cultures based on routine clinical care. If there bacterial culture result and the PCR result are discordant, the treating physician will be notified immediately.

9.6 Safety

The major safety concern is a false negative PCR result, which would result in withholding MRSA therapy in a subject with MRSA pneumonia. However, PCR is a sensitive diagnostic test, and based on prior work the rate of false negative is approximately 0.1%. In subjects who are clinically unstable, as defined above, MRSA coverage will be provided until the results of the PCR are available. Our prior study, PCR to ID MRSA in BAL, **STU00201397**, is designed to confirm there is high concordance of the two tests. In the unlikely event that the PCR yields a false negative test for MRSA, the treating team will be informed immediately and appropriate antibiotic therapy will be started.

9.7 Patient data collection

All relevant patient data will be collected using the Northwestern University Enterprise Data Warehouse (NU-EDW) from Cerner Powerchart and EPIC electronic health records. A program will be written using NU-EDW to extract clinical variables (see Appendix for data collection form and coded identifier list). Patient data will be removed and subjects will be identified based a unique study identifier. A separate password protected file will map the study identifier to the subject's medical record number. All patient data will be kept on a password

protected computer. Only the study personnel will be allowed to access patient data.

10.0 Data and Specimen Banking

10.1 Data storage

Patient data will be kept on a single, encrypted, Northwestern University issued password protected computer. Only the study investigators will have access to the data. In the event that the data has to be transported to another computer, it will be done using a password protected USB drive. Patient data will be available for the duration of the study and publication of the manuscript, which is anticipated to be 1 year from study completion.

10.2 Specimen storage

BAL specimens will be stored in a refrigerator contained in a locked room only accessible to the study staff and microbiology lab personnel. The specimens will be stored at 2-8°C for up to 96 hours. Following testing, the specimens will be disposed of in accordance to NMH policies.

10.3 Optional Sample Banking

Subject and/or LAR will have the option of participating to have any left over BAL speciman and their collected clinical information stored in a de-identied manner for use in other not directly related research. These samples will be stored in a -80°C freezer in the Wunderink lab for up to 1 year from study completion.

11.0 Data and Specimen Management

11.1 Data analysis plan.

Main Outcomes. The primary outcome measure is antibiotic-days of vancomycin or linezolid, defined as days on which at least one dose of antibiotic is given. (37, 38) For antibiotics dosed at > 24 hour intervals, any interval day will be included as an antibiotic day. Secondary outcomes are cost, subsequent hospital acquired infections (HAIs), ICU and hospital LOS, and mortality. Disease adjusted mortality will be calculated using the Acute Physiology and Chronic Health Evaluate (APACHE) IV score. (39, 40) Patient information will be collected using the NU-EDW. Categorical outcomes will be analyzed using logistic regression, continuous outcomes will be analyzed using linear regression. Statistical analysis will be conducted with SPSS (IBM corporation) and STATA. We have budgeted statistical support to conduct the analyses for this Aim.

11.2 Power calculation.

Based on our prior work, 89.5% of intubated subjects with suspected pneumonia in the MICU will receive empiric vancomycin or linezolid therapy; however the prevalence MRSA pneumonia is approximately 5.5%. In patients with no evidence of MRSA, only 32.1% had antibiotics discontinued appropriately (24, 25) Therefore the potential reduction in antibiotics-days of vancomycin or linezolid with a rapid diagnostic test based on current practices is 65.7%. With a conservative estimate that all subjects will have received up to 3 doses of vancomycin or linezolid prior to randomization, and that up to 94% of vancomycin or linezolid therapy can be discontinued at 72 hours in the usual care arm, we anticipate PCR will be able to

Table 4. Power calculation for clinical trial

Usual care group anti-MRSA antibiotic utilization (% antibiotic days)	Effect size of intervention	N (for each group)
94%	88.5%	3
57.1%	**33.6%**	**22**
46%	25%	35
36%	15%	109
26%	5%	861

reduce antibiotic exposure by 33.6%. Based on these estimates, 22 subjects in each group would be needed to detect a clinically relevant difference in antibiotic days between the intervention and control groups, with 80% power (β=0.20) and two-sided α=0.05, see also **Table 3**. The average cost per dose of vancomycin is $43.45, whereas the cost of PCR is $72.75; 33.6% reduction in empiric antibiotic use would result in an average cost savings of $121.75 per subject.

We do not anticipate that statistical significance will be obtained for any secondary endpoint. This pilot is designed to provide preliminary data for a larger multicenter trial which would address these more difficult endpoints. However, the preliminary data will be important for powering that study.

11.3 Data storage

Patient data will be kept on a single, encrypted, Northwestern University issued password protected computer. Only the study investigators will have access to the data. In the event that the data has to be transported to another computer, it will be done using a password protected USB drive. Patient data will be available for the duration of the study and publication of the manuscript, which is anticipated to be 1 year.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Patients will be monitored daily for evidence of adverse events, particularly in the first 72 hours when results of BAL cultures become available. Safety data collection will begin at the start of the clinical trial. Safety data will be collected with case report forms.

The principle investigator and other members of the research team will meet on a bi-monthly basis to review the interim data including main outcome measures. Safety information will be collected by review of the medical record and maintained by the MICU research staff.

Untoward events will be defined as mortality of subjects and discordant results between the PCR test and routine bacterial cultures. Standardized mortality rate using APACHE IV disease adjusted mortality and Chi-square tests will be used to determine difference in mortality and discordance between the two diagnostic tests of pneumonia. An interim analysis will be conducted when half of the target subjects are enrolled. If a significant trend in increased mortality in the PCR arm ($P < 0.10$) is seen, the study will be immediately suspended. If a greater than 5% false negative rate with PCR compared to routine bacterial cultures for the detection of MRSA, the study will be immediately terminated.

13.0 Withdrawal of Subjects*

13.1 Subjects who withdraw consent

Subjects who withdraw their consent at any time for any reason will be allowed to exit the study. In that event, antibiotic prescription will be left up to the treating physician. If a subject or his/her surrogate withdraws consent after randomization, the subject will continue to be followed by the MICU research team and their results will be included in the final analysis.

13.2 Subjects with indeterminate PCR results

Subjects in whom PCR test on BAL yields an indeterminate result will be allowed to start empiric antibiotic therapy with either vancomycin or linezolid while the PCR is repeated. If the PCR on BAL is indeterminate a second time, the subject will be withdrawn from the study. Any subject

withdrawn from the study will be followed by the research team, but outcomes will not be included in the final analysis.

13.3 Subjects with a new indication for vancomycin or linezolid

Subjects who develop a new or suspected extrapulmonary infection due to MRSA following randomization will be allowed to start vancomycin or linezolid per the treating physician's discretion. Outcomes of subjects who start vancomycin or linezolid for an extrapulmonary indication following randomization will be included in the final analysis.

14.0 Risks to Subjects*

14.1 Risks to subjects

The main intervention of this clinical trial is the decision to start or stop specific antibiotic therapy for MRSA pneumonia (the antibiotics vancomycin or linezolid) based on the results of the PCR. All PCR results will be followed up with bacterial culture, the current gold standard test. The primary risk to subjects is an inaccurate PCR test. The time delay between the PCR test and bacterial cultures is between 48 to 72 hours.

14.1a In the case of a false positive PCR test, the risk to subjects is continuing antibiotic therapy for MRSA (either vancomycin or linezolid per the treating physician's discretion) until the results of the bacterial culture. This is consistent with usual care of ICU patients of pneumonia, and therefore adds no added risk to subjects.

14.1b In the case of the false negative PCR test, the risk to subjects is stopping appropriate antibiotic therapy. The probability of this occurring is extremely low based on weighted average of the negative predictive value (NPV) of prior work listed in Table 1: approximately 0.3%. The duration of stopping appropriate antibiotic therapy would last approximately 48 to 72 hours, until bacterial cultures result. The physical risk of withholding appropriate antibiotic therapy includes worsening infection, sepsis, and death.

14.2 There are no unforeseeable risks to subjects.

14.3 This trial does not include pregnant women.

14.4 There are no foreseeable risk to others who are not subjects, e.g., risks to ethnic or cultural groups, risks to sexual partners of subjects, etc.

15.0 Potential Benefits to Subjects

Subjects who are randomized to the PCR arm who have MRSA pneumonia may benefit due to early recognition and treatment of the infection. Subjects who are randomized the PCR arm who do not have MRSA pneumonia may benefit from earlier tailored antibiotic therapy and therefore reduced antibiotic exposure; however, the impact of these benefits are not known. Otherwise, we not anticipate any direct benefit to subjects for participation in the trial.

16.0 Vulnerable Populations

This study will not involve pregnant women.

This study will be enrolling critically ill subjects. Many of the individuals will lack decision-making capacity. In addition, the critical condition of these subjects limits their autonomy. Thus, all of these subjects must be considered vulnerable

research subjects. This study cannot be accomplished without enrollment of these subjects.

17.0 Community-Based Participatory Research

Not applicable.

18.0 Sharing of Results with Subjects

The results of the PCR test will be shared with the subject or surrogate decision maker verbally by the research team. Results of the study will not be shared with subjects.

19.0 Setting

19.1 Clinical trial

Patients who was admitted to the medical ICU (MICU) at Northwestern Memorial Hospital (NMH) will be screened for inclusion in this trial. The NMH MICU is a 33-bed unit staffed by critical care physicians, trainees, and respiratory therapists (RTs). In intubated patients with suspected pneumonia, BALs are obtained by the MICU physician, qualified trainee, or RT. About 60 BALs are collected monthly.

19.2 Research procedure

PCR will be conducted in the molecular epidemiology laboratory at NMH under the direction of Chao Qi, PhD. PCR will be conducted using the GeneXpert® Instrument Systems (Cephaid Inc, Sunnyvale, CA). using the The Cepheid Xpert® Skin and Soft Tissue (SSTI) Assay. The PCR is a is a qualitative in vitro diagnostic test designed for rapid detection and differentiation of Staphylococcus aureus (SA) and methicillin resistant Staphylococcus aureus (MRSA) in body fluids using PCR amplification. SA is detected by the presence of the staphylococcal protein A (spa) gene, MRSA is identified by the mecA gene and staphylococcal cassette chromosome mec (SCCmec). Prior studies report detection of MRSA is possible in 58 minutes. PCR analysis will be conducted by the investigators or a qualified laboratory technician.

20.0 Resources Available

20.1 Clinical research team

Screening and enrollment will be conducted by research team already in place in the MICU at NMH. This group is made up of physicians, a registered nurse, a pharmacist, and two research assistants. This group will screen all intubated patients who are receiving antibiotics therapy admitted to the MICU for enrollment into the clinical trial. Screening will be done using the daily census data of the MICU. Our research group has extensive experience conducting clinically oriented research in drug resistant pneumonia and critical care. BAL is routinely done at our ICU in patients with suspected pneumonia, which will provide us with patient samples and potential research subjects. We have scheduled monthly in person team meetings to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

20.2 Laboratory research team

The analysis of BAL using PCR will be conducted in the clinical epidemiology laboratory at NMH using the research instrument described above. BAL will be received by the laboratory within 1 hour of collection

by physician or RT. The PCR assay will be conducted by a qualified laboratory technician once the sample is received. The GeneXpert® Instrument is designed to require minimal laboratory expertise and laboratory technician qualified to perform the assay will be routinely available**.**

20.3 Feasibility and time frame

Approximately 60 to 80 patients monthly had a BAL collected in the MICU due to suspicion for pneumonia. We estimate approximately 50 patients per month will be eligible to enroll this study. Our goal is to enroll at least 44 subjects over 12 months, or 3-4 subjects per month. The principal investigator devotes 75% of time to clinical research, and the MICU research team devotes 75-100% of effort to clinical research.

21.0 Prior Approvals

Not applicable.

22.0 Recruitment Methods

Patients will be recruited from the Medical Intensive Care Unit at NMH. Potentially eligible patients will be identified during a daily screen of admissions to the medical intensive care unit and/or RT orders for NBBAL by authorized study personnel.

No materials will be used to recruit subjects and no payments will be made to subjects.

23.0 Local Number of Subjects

As noted above, we anticipate enrolling at least 44 patients during the first year. Our minimum enrollment goal is 44 patients which we anticipate will take anywhere from 6 to 12 months.

24.0 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPPA). Those regulations require a signed subject authorization (included in the informed consent document) informing the subject of the following

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for user of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization

As noted above*,* patient data will be kept on a single, encrypted, Northwestern University issued password protected computer on servers maintained by Feinberg Information Technology in compliance with NUFSM policies outlined in

their “Data Security Plans for Identifiable Information Used in Clinical Research.” Only the study investigators will have access to the data. In the event that the data has to be transported to another computer, it will be done using a password protected USB drive. Patient data will be available for the duration of the study.

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Once informed consent has been obtained, subjects will be given a study number. This number will be used to link the subject to the data. The subject name and number will be kept separate. Only the study team will have access to this information

25.2 The study team will access the subject’s eMR to obtain study specific information. This data will be directly input into a secure database

26.0 Compensation for Research-Related Injury

In the event the subject becomes ill or injured as a result of this study (medications or procedures), the hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from participation.

27.0 Economic Burden to Subjects

The subjects will not accrue costs related to participation in this research

28.0 Consent Process

28.1 We anticipate that the majority, if not all, subjects in this trial will not be able to provide informed consent because of their critical illness. Therefor, after identification, a member of the study team will discuss participation in the study with the patient’s legally authorized representative (LAR). The LAR will be identified in the subject’s eMR via the advanced directives tab in accordance to the hospital and Illinois law

28.2 Informed consent will be administered and the patient’s LAR will be asked to sign and date the approved informed consent document. The subject is not obligated to take part in research, and this will be made clear to their LAR. Furthermore, LARs are not obligated to sign an informed consent document the same day in which they learn about the study. If the patient’s surrogate decision maker does decide to take part in the study and reads, understands, and decides to sign the informed consent, all of his/her questions must be answered prior to the consent being signed. Once the consenting form is signed and dated, it will be copied and the volunteer will receive a copy. If at any point during the course of the study, a subject who was previously dependent on a LAR for consent regains the ability to provide informed consent, the study will be reviewed with the subject and consent obtained. A signature block at the end of the consent document is available for appropriate documentation should this situation arise. In situations where the LAR is not immediately available in person a copy of the informed consent will be faxed or emailed for their review. A member of the study team will review the consent with signee over the telephone. The LAR may fax back and/or scan email back the signed consent. They will be instructed to return the original signed document at their next visit to the hospital.

29.0 Process to Document Consent in Writing

Written consent will be obtained following the procedures for documentation of informed consent outlined in HRP-091. A consent documented is attached in this application.

30.0 Drugs or Devices

30.1 PCR will be conducted in the molecular epidemiology laboratory at NMH under the direction of Chao Qi, PhD. PCR will be conducted using the GeneXpert® Instrument Systems (Cephaid Inc, Sunnyvale, CA). using the The Cepheid Xpert® Skin and Soft Tissue (SSTI) Assay. The PCR is a is a qualitative in vitro diagnostic test designed for rapid detection and differentiation of Staphylococcus aureus (SA) and methicillin resistant Staphylococcus aureus (MRSA) in body fluids using PCR amplification. SA is detected by the presence of the staphylococcal protein A (spa) gene, MRSA is identified by the mecA gene and staphylococcal cassette chromosome mec (SCCmec). Prior studies report detection of MRSA is possible in 58 minutes..

30.2 After obtaining informed consent, the study team will obtain the study sample from leftover BAL fluid collected as standard of care. For subjects randomized to PCR analysis this sample tested will be conducted by the investigators or a qualified laboratory technician.

31.0 Publication plan

It is anticipated that the investigators will submit abstracts and research articles to major journals based on the data from this study. In addition, the results of this study may also be used for teaching, publications, and/or presentations at scientific meetings. If a subject's individual results are discussed, their identity and all personal information will be protected.