Study name: Antibiotic prophylaxis for critically ill patients after suspected aspiration

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Background

The clinical phenomenon of aspiration of foreign material into the lungs has been described since the 1950s, with the earliest reports primarily originating from anaesthetic or obstetric settings. Since the earliest descriptions, it has been divided into several subcategories, including chemical pneumonitis (acute lung injury related to acidity), bland aspiration (from non-irritating contents such as blood or water), and aspiration pneumonia (Marik 1995). This last phenotype results when bacteria are aspirated and grow to produce clinically-significant infectious pneumonia.

Historically, most cases of aspiration pneumonia presented with a distinct disease profile, dubbed by some sources as "anaerobic pleuropneumonia"; this classically occurred in patients with a history of alcohol use or altered mental status, was usually subacute in presentation, and frequently grew into an anaerobic pneumonia with foul secretions, cavitation, and pleural involvement (Dibardino 2015). In recent decades, this classic phenotype has decreased in incidence alongside a broader decrease in the frequency of anaerobic organisms isolated from aspiration patients, and a corresponding increase in the incidence of more subtle presentations of pneumonia (Marik 1999).

Aspiration itself is a common event in healthy humans, so progression to aspiration pneumonia depends on a variety of other factors such as host response and bacterial burden (Marik 1995). Many aspiration events never cause infectious pneumonia, and indeed it can be difficult to clearly discern which cases do have an infectious basis (Lascarrou 2017). Among those that do, pneumonia tends to develop after an interval of time from the aspiration event (i.e. after bacteria have multiplied). This raises the possibility of whether in some patients, treating as-yet benign aspiration with antibiotics before the onset of frank infectious pneumonia may prevent pneumonia from developing or limit its clinical impact if it does.

Only one retrospective study (Dragan 2018) directly addressed this question, performing a chart review of admitted inpatients who experienced witnessed aspiration events while in the hospital. They evaluated patients who initiated a course of antibiotics within 48 hours after aspiration (excluding those already receiving antibiotics at the time of aspiration), and compared their outcomes against those who did not receive antibiotics. No differences were found in 30-day mortality, transfers to critical care, or other secondary outcomes; the only difference noted was that patients who received antibiotics had a higher chance (8% vs 1%) of later needing their antibiotic regimen to be escalated for worsening clinical status. The authors concluded that "prophylactic" antibiotics for aspiration did not appear to reduce the risk of pneumonia, only to increase the risk of antibiotic resistance; however, the study was limited by its retrospective nature.

A variety of randomized studies have evaluated the role of antibiotics for ventilator-associated pneumonia (VAP) prophylaxis, on the theory that early VAP is caused by aspiration at or before the time of intubation. These studies used short courses of antibiotics beginning at the time of intubation, and monitored for the incidence of subsequent pneumonia. Most of these studies (Sirvent 1997, Acquarolo 2005, Francois 2019) showed a reduction in microbiological VAP by ~50%, but no difference in patient-centered outcomes such as mortality, ventilator time, and length of stay. One study (Valles 2013) did show a reduction in length of stay and ventilator time, but this was a non-randomized observational study.

Based on the limited evidence, best practice surrounding the use of antibiotics after aspiration is equivocal. Most clinicians would treat clear cases of pneumonia with antibiotics—i.e. those with concerning findings such as fever, leukocytosis, significant hypoxia, etc—but the role of earlier "prophylactic" antibiotics in patients without overt pneumonia is less clear. Some providers tend to use antibiotics, selecting from a wide array of reasonable regimens; some prefer to monitor initially and withhold antibiotics unless the clinical picture begins to resemble bacterial pneumonia; some follow either pathway depending on case-specific criteria, which are often personal and/or arbitrary. This variation in practice was highlighted by a member survey of the Society of Critical Care Medicine (Rebuck 2001) which demonstrated no consistency in clinician approaches to aspiration; in that diverse group of critical care clinicians, 51.9% would treat suspected aspiration without a clear infectious process with antibiotics, and 77.7% would treat confirmed aspiration with antibiotics.

Overall, there is equipoise around the clinical question of whether critically ill patients with apparent aspiration but without systemic signs of pneumonia benefit from receiving early antibiotics.

Hypotheses or Research Question, Aims and Objectives

Hypothesis/Question

Does the early administration of antibiotics to ICU patients with suspected aspiration improve their clinical course compared to supportive care alone?

Aims/Objectives

We propose to perform the first randomized trial investigating the use of early antibiotics after aspiration. Our objective is to provide initial single-center pilot data regarding the impact of antibiotics on ICU length-of-stay in a pragmatic cohort of critically ill patients, as well as to demonstrate the safety and feasibility of such a trial.

Study Design

Study design

This will be a prospective, randomized, non-blinded trial of antibiotics versus supportive care in ICU patients. Patients will be candidates if they have radiographic findings suggestive of aspiration, plus a clinical history consistent with aspiration (including a witnessed aspiration event). Both intubated and non-intubated patients are eligible. Both new ICU admissions admitted with aspiration and previously-admitted patients later witnessed to aspirate in the ICU are eligible.

Importantly, patients will be excluded from our study if they are positive for 2 or more of a constellation of pneumonia markers: leukocytosis, fever, purulent secretions, and hypoxia. Hypoxia is defined by the SpO2 to FiO2 (S/F) ratio, a validated surrogate for P/F ratio that does

not require measuring a blood gas (Rice 2007), with a cutoff for significant hypoxia established as S/F <215. Excluding this group leaves a cohort of patients with apparent aspiration but without overt signs of pneumonia. Also excluded are patients who have already received antibiotics (e.g. in the ED, ICU, or undergoing an active course of therapy as an outpatient) or who will require antibiotics for other reasons. However, for pragmatic reasons, patients who have received up to 2 doses of antibiotics after hospital presentation will be eligible, as a significant number of study candidates may receive this dosing before they can be consented and randomized. For patients already admitted, the exclusion rule will be greater than 2 doses of antibiotics since hospital admission, unless the last dose was more than 1 week prior to screening.

At the time of enrollment, the advanced practice provider (APP) in the ICU will screen patients for eligibility, obtain consent from either the patient or their legal representative, and perform randomization via sealed envelope. At that time the patient may either be under the care of the APP, or may be cared for by a different ICU team. Patients will be randomized to receive either prophylactic antibiotics or supportive care. In the former group, treating clinicians can select from a regimen of antibiotics based upon current community-acquired pneumonia guidelines of the Infectious Disease Society of America and American Thoracic Society (Metlay 2019). In this pragmatic trial, there is flexibility in the choice of agent to accommodate for individual patient risk factors and clinician judgment; consequently the intervention being evaluated is "early antibiotics" as a class effect, not one specific antibiotic agent or bundle. A standard course of 5 days will be used, after which the treatment pathways ends and further treatment is at clinician discretion.

In the supportive care group, no antibiotics will be given initially. In both groups, supportive measures such as oxygen can be offered *ad libitum* per clinician discretion, in accordance with usual care. In the Epic EMR, all patients will be flagged as study patients, and antibiotic orders will be entered via a standardized orderset.

In both groups, antibiotics can subsequently be escalated (or in the supportive care group, initiated) if the treating team deems it necessary due to clinical deterioration or other factors. Such patients who are escalated or crossed-over will be tracked as an expected sub-group.

All patients will be followed for 30 days, or until hospital discharge or death, whichever comes first. Their ICU length-of-stay will be the primary outcome, and a variety of secondary outcomes will be tracked, including mortality, frequency of escalation of antibiotics, and frequency of developing positivity of the 4-part "pneumonia" criteria.

Sample size and justification

$n = 100$. A power analysis was performed using the primary outcome of ICU length-of-stay (LOS) and powered to detect a LOS difference of 4–5 days. Preliminary data indicate a standard deviation for LOS in our general ICU of approximately 6. A sample size of 50 in each group would have 91% power to detect a difference in means of 4 days, assuming that the common standard deviation is 6, and using a two group t-test with a 5% two-sided significance level. A difference of 3.5 days could be detected with 82 percent power using the same set of assumptions.

A reduction in LOS of less than 4 days may still be meaningful. However, a study with a larger sample size and a longer enrollment period was not felt to be feasible in our center. Therefore, this study was designed as a pilot, intended to demonstrate the safety and feasibility of such a trial, produce initial data for this data-poor topic, and generate interest in a larger, more definitive trial. The sample size is therefore primarily the product of balancing size and feasibility.

Explain on what basis it is reasonable to assume that the sample size will be obtained

A surveillance period was conducted prospectively in early 2021 on a random 4-week sample of ICU patients. All patients with suspected aspiration were screened using similar eligibility rules to the study criteria. In 4 weeks, 15 patients were screened, and 5 found eligible. Extrapolated over time, this equals 65 patients per year. 100 patients would require approximately 18 months to enroll, which was thought to be achievable. Although a small number of patients are expected to be missed by screening or drop out, this was felt to be balanced by the patients likely missed during the surveillance process.

Method(s) of data analysis

With a sample size of 100, a linear regression model will be used to assess the treatment difference in the presence of covariates and demographic variables. LOS would be the numerical outcome variable and the main predictor would be treatment group. This would provide an assessment of the treatment (i.e. the p-value for treatment in the model) adjusted for covariates. The p-value from the t-test would be unadjusted.

All data will be analyzed according to intention-to-treat groups, regardless of eventual antibiotic exposure. Data fields that are not recorded in all patients (such as laboratory studies that were not obtained) will be analyzed only among the patients in which they are available; i.e. the denominator will be the patients in each group with data recorded for that field.

The data to be collected are as follows:

<u>Baseline characteristics:</u>

- Age (#)
- Sex (m/f/other)
- Admitting diagnosis (free text)
- APACHE IV (#)
- Intubated prior to enrollment (y/n)
- Chronic tracheostomy (y/n)
- Current steroid use at time of enrollment (y/n)

- Admitted from health care facility (y/n)
- Witnessed aspiration event, prior to admission (y/n)
- Days between hospital admission and aspiration (#) *
- Pneumonia diagnosed this admission, prior to enrollment (y/n) [a]
- Positive serum ethanol at time of admission (y/n)
- Positive sputum culture with presumed pathogen [prior to antibiotics] (y/n/no culture)
- Reason for intubation (options)
    - Altered mental status
    - Respiratory failure
    - Expected clinical course
    - Other

* Zero for patients admitted with aspiration.

[a] Only applies to patients who have an aspiration event after hospital admission.

Outcomes

Primary:

- ICU-free days (#)

Secondary:

- Ventilator-free days (#)
- Hospital-free days (#)
- Antibiotic-free days (#)
- Intubated after enrollment (y/n)
- Tracheostomy after enrollment (y/n)
- Developed pneumonia criteria after enrollment (y/n)
    - 2 or more of fever, leukocytosis, purulent secretions, hypoxia (defined below)
- Days before pneumonia criteria (#)
- Mortality (y/n)
- Additional antibiotics prescribed (y/n)
    - Excluding prophylactic antibiotics, and excluding any peri-operative antibiotics for patients undergoing surgery
- Positive sputum culture with presumed pathogen [after enrollment] (y/n) **
- Any positive culture with organism resistant to prophylactic antibiotics (y/n)
- Positive C. Difficile stool toxin assay after enrollment (y/n)
- Temperature >38c on day 3
- WBC >11k on day 3 **
- S/F <215 on day 3
- Purulent secretions on day 3 **

** These studies are performed at discretion of the treating team, and hence will not always be obtained; the denominator for these data will be variable.

Subject Characteristics

Age: ≥18

Ethnicity: Any

Gender: Any

Other characteristics (e.g. pregnant women, prisoners, children, decisionally impaired): Excluding pregnant patients and prisoners

Inclusion Criteria:

- Admitted to the ICU
- **with** radiographic findings on chest x-ray or CT deemed by the treating ICU provider to be consistent with aspiration (e.g. dependent infiltrates or intraluminal airway debris)
- **and** with a clinical history consistent with possible aspiration (e.g. cardiac arrest, found unconscious, or with a witnessed aspiration event).

Exclusion criteria:

- Already received 3 or more doses of any antibiotic since hospital presentation, unless the last dose was greater than 1 week before enrollment.
- Requires antibiotic therapy for the treatment of other infections
- Patient "comfort measures only" at time of screening
- Currently participating in other trials using investigational drugs or interventions
- Currently pregnant
- Currently a prisoner
- The consenting party (patient or their legally authorized representative) is unable to understand or read English at a fifth-grade level.
- 2 or more of the following are present at the time of screening:
  - White blood cell count: ≥ 11.0
  - Temperature ≥ 38.0C (100.4F)
  - Purulent secretions
  - S/F (pulse oximetry saturation to FiO2) ratio ≤ 215

Study Procedures

Screening Procedures, who will perform them, where

Coverage of the John Dempsey Hospital ICU is by two teams that are separate, although they mutually assist with care of each other's patients as needed: a "Navy team" staffed primarily by APPs, and a "White team" staffed primarily by residents. Screening and consent will be performed by the ICU APPs on service at the time of admission. Consequently, patients admitted to the Navy team will be screened by members of their primary treating team, while patients on the White team will not.

Patients can become eligible by either of two qualifying events:

1. Admission to the ICU (from the emergency department, floor, or outside hospital) with signs of aspiration as part of the initial presentation.
2. Witnessed aspiration event in the ICU.

#1 will be the most common. For these patients, at the time when an ICU admission is found to be a potential candidate, either the admitting APP will perform eligibility screening using the criteria described above, or the admitting provider (if different) will notify the APP of a potential study candidate, at which time the APP will perform said screening. If no APP is available, which can occur overnight up to several nights per week, the admitting resident will communicate potential eligibility to the oncoming day-shift APP, and screening will be performed then.

If eligibility is confirmed, the patient will enter the consent process. Patients who are not enrolled within 24 hours of their qualifying event, are screened but found to be ineligible, or decline consent will be noted on a separate list ("Screen Failures") without protected health information.

"Time zero" for purposes of screening and the enrollment window will be the time of admission, e.g. using initial vital signs and admitting labs and imaging.

Group #2 will be less frequent and will involve aspiration after admission to ICU. In those cases, the same process would occur. In that case, "time zero" is considered the time that aspiration is recognized by ICU staff.

Study Procedures, who will perform them, where:

A random number generator service will be used to produce a series of sealed envelopes via simple randomization strategy and 1:1 allocation. At the time of enrollment, an envelope will be opened, assigning patients to either:

- Supportive care alone

or

- Supportive care *plus* a regimen of antibiotics (based upon 2019 IDSA/ATS guidelines for care of community-acquired pneumonia), as follows:

1. If there is low risk for *P. aeruginosa* and/or methicillin-resistant staphylococcus aureus (MRSA), as deemed by the treating team:

   Ceftriaxone 2 g IV, every 24 hours for 5 days

   At any point after 24 hours, clinicians may (but are not required to) transition stable patients to:

   Amoxicillin + clavulanate (Augmentin) 875 mg PO or per feeding tube, twice daily for the remainder of 5 days

2. If there is significant risk of *P. aeruginosa* and/or MRSA (i.e. the former category of "HCAP"), as deemed by the treating team:

   Cefepime 2 g IV, every 8 hours for 5 days

   In addition, use:

   Vancomycin IV, dosed by pharmacy protocol (trough or AUC/MIC monitoring) **for 5 days**

   and order:

   Nasal MRSA swab

   At any point after 24 hours, clinicians may (but are not required to) transition stable patients from cefepime to:

   Levofloxacin PO or per feeding tube, 750 mg every 24 hours for the remainder of 5 days

   Vancomycin is recommended (although not required) to be discontinued if MRSA swab is negative.

Patients randomized to the antibiotic arm who are not eligible for any regimen within the listed options—for instance, due to multiple drug allergies—can still be enrolled at discretion of the treating team using another appropriate regimen, typically with guidance from the Infectious Disease service. All study regimens will last 5 days, after which the intervention period ends, and further treatment is at discretion of the treating team.

These antibiotic orders will appear in the chart and will be labeled as being part of a research study; no blinding will occur. Patients in either group can receive chest physiotherapy, oxygen, non-invasive ventilation, intubation, mucolytics, or other measures as determined by the treating team and in accordance with usual care.

If elected by the treating team, patients in the antibiotic group can have their antibiotics changed or escalated due to deteriorating clinical status or new culture results; these patients will continue to be tracked, but their subsequent treatment will not be determined by the study protocol.

Similarly, patients in the supportive care group can have antibiotics initiated for deteriorating clinical status; new development of the "pneumonia" features (2 or more of the findings of fever, leukocytosis, purulent secretions, and hypoxia) will be recommended as a potential indication to initiate antibiotics. These instances of antibiotic "crossover" will be tracked, but such therapy will be determined by the treating team.

Subsequent to the initial 5-day course of treatment, all patients will be followed until the earlier of 30 total days, death, or hospital discharge. Outcomes such as mortality and ICU length-of-stay will be collected by chart review. Outcomes such as cultures and laboratory studies will be available only if ordered as part of routine care; no tests will be performed solely for the purposes of the study

Any unexpected adverse events will be tracked by the ICU APPs and reported to the study investigators, who will follow up to determine if there are unexpected risks associated with study participation.

Describe length of subject's participation in the study including number of visits, frequency of visits, and length of visits:

The intervention period will last 5 days. The data collection will continue until hospital discharge, 30 days from enrollment, or death, whichever occurs first. Patient care after the intervention period will not be determined by the study.

Recruitment

All Recruitment Methods and Materials

Patients will be screened by the ICU providers. At a time not later than 24 hours after their qualifying event (ICU admission or witnessed inpatient aspiration), an APP will perform consent as described below; this may or may not be the provider treating the patient primarily. Patients accepting will be enrolled immediately; patients declining will be noted on the "Screen Failures" list kept by the ICU APP team. Eligible patients where a consent process was not attempted within 24 hours of their qualifying event will also be tracked on "Screen Failures" list.

Consent Process

Process for Obtaining Consent (timing, location, length of discussion, time for consideration)

Three pathways for consent will be available. In either case, patients who have previously consented can withdraw from the study at any time. In such cases, subsequent treatment will be determined by the treating team and no further data will be collected, but data already collected may still be analyzed.

Consent will be performed by the ICU APP at the time of enrollment; this may either be a member of the primary treating team or may be from a different ICU team and not be the primary provider.

Pathway #1: In-person paper consent

This is the optimal pathway and will be used when possible. It will require either a patient with capacity to consent, or an LAR who is physically present at the time of enrollment, or who is able to be present within 24 hours, and is free from untoward duress induced by the stress of the situation.

In such cases, the APP will engage them by reading a pre-written description of the study. (This can occur over the telephone if they are not present.) If they are agreeable to participating, a written consent form will be provided to them; if they are not present at the time they will be asked to come to the hospital within the 24 hour window. The APP will then review the consent form with them, as well as the HIPAA authorization and study feedback form. If they request, it will be read aloud to them; in either case the APP will be available to answer questions. This will typically happen either at the patient bedside or in a quiet, empty room.

If requested, patients or their LAR may take time to consider their participation, and may keep the consent form to review during that period. They will be informed they have up to 24 hours from the qualifying event to make a decision. Signed forms will be returned to the APP who will file them securely, open a randomization envelope, enter the patient onto the confidential list, and use the Epic orderset to enter the appropriate orders. A copy of the signed consent form will be provided to the consenting party.

Pathway #2: Remote electronic consent

This option will be used when the patient cannot consent, and the LAR can be reached but cannot become physically available to sign a consent form within the 24-hour window. It can also be used if they are initially present, but request time to consider their decision, and will not be able to return to the hospital within the 24-hour window.

LARs will be contacted via telephone and the study discussed as in the other consent pathways. If agreeable, they will be asked to provide an email address which they vouch to be private and secure. Via this mailbox, they will be emailed access to the REDCap (Research Electronic Data Capture) eConsent system at UConn, a secure system validated for research purposes. This will directly link them to a combined electronic version of the consent form and HIPAA authorization form, identical to the paper versions except for: (1) Formatting changes, (3) Removal of the date/time fields (since the system automatically, permanently timestamps the signature once completed), and (3) Removal of the patient signature field (since the eConsent will only be used for LAR-based consents). The LAR will sign the consent electronically using touchscreen or mouse, at which point it will be automatically time-stamped. The study personnel performing consent will counter-sign it using a similarly time-stamped module within the REDCap interface, after which the two completed portions will be downloaded as a merged PDF and emailed to the LAR. The study feedback form will be emailed separately, or provided in person at a later date.

The merged, completed consent will be printed and stored physically using the same system as other paper consents. The archived PDF will remain on the REDCap system as an electronic backup.

Pathway #3: Remote telephone consent

This option will be used in the same circumstances as electronic consent if eConsent platform is not available, or if the patient's LAR is unable to adequately use the eConsent platform.

The LAR will be contacted by telephone, and if agreeable to study participation, will be provided with a digital copy of the consent identical to the paper version in all respects. This will be sent by email or fax at their preference. After adequate time for review, the LAR will be called back to discuss the consent and answer questions. If they agree to consent, they will sign and date the document at that time with a witness on the line documenting the subject/LAR agreeing to consent the participation in the clinical trial, and email or fax it back to the study screener. The screener will sign and date a paper copy at the same time. After receipt of the LAR copy, the two copies will be joined together.

The HIPAA form will also be sent to the LAR via fax or email, and returned in similar fashion. The study feedback form will be provided to them by fax, email, or in person later after consent is complete.

Who will Provide Consent (e.g. subject, legally authorized representative)

As above.

Assessment of Capacity

Determined by clinical evaluation and provider judgment, in accordance with usual standards of capacity for procedural consent in the hospital setting.

Request for Waiver/Alteration of Consent:

None.

Privacy of Subjects

Privacy of subject

Consent will be performed using standard considerations for patient privacy, with consent and other discussions held either at the patient bedside (all ICU rooms are private), the APP office, or an empty conference room.

Confidentiality of Data

Confidentiality of Data

The patient list will be tracked automatically using Epic. Patients will also be simultaneously logged in two tracking sheets.

The first (the "Data Sheet") will be digitally maintained on a secure, encrypted network account on the UConn SharePoint system. This is a hospital-approved resource for encrypted data storage and the account will only be accessible by the ICU provider team. The Data Sheet will include patient information such as treatment group (Antibiotic vs. Supportive care) and the baseline and outcome fields, but will be identified only by a serial number (#0-9999).

The second sheet (the "Master Key") will be on paper. It will include the serial numbers of enrolled patients, alongside their full name and medical record number. It will be stored in a binder in a locked filing cabinet in the ICU APP office. Both the cabinet and the office will be locked at all times, and only the ICU APP staff have these keys. Signed consent forms will also be kept in this locked cabinet.

A final sheet ("Screen Failures") will be kept in the same locked cabinet, listing patients screened but unable to be enrolled (due to exclusions, failure to consent, or late screening out of the enrollment window); this will be anonymous, listing the date of screening and the reason for failure but no patient information.

After completion of the study, the Data Sheet alone will be used for analysis by the study team. The Master Key will be kept in the locked drawer or a similar locked location for 3 years after study completion, then destroyed. All data will be available only to the study team and the IRB.

Budget / resources: Investigator time is donated, or part of other duties. All patient care is considered routine care and costs are not paid by the study. The only expected expense is the potential cost of hiring statistical support in the analysis phase, which will be paid by the investigators.

Dissemination: Peer-reviewed journal article.

Additional Information: None.

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