Trial of antibiotic restraint in presumed pneumonia: A Surgical Infection Society multicenter pilot

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BACKGROUND: Pneumonia is the most common intensive care unit–acquired infection in the trauma and emergency general surgery population. Despite guidelines urging rapid antibiotic use, data supporting immediate antibiotic initiation in cases of suspected infection are limited. Our hypothesis was that a protocol of specimen-initiated antibiotic initiation would have similar compliance and outcomes to an immediate initiation protocol.

METHODS: We devised a pragmatic cluster-randomized crossover pilot trial. Four surgical and trauma intensive care units were randomized to either an immediate initiation or specimen-initiated antibiotic protocol for intubated patients with suspected pneumonia and bronchoscopically obtained cultures who did not require vasopressors. In the immediate initiation arm, antibiotics were started immediately after the culture regardless of patient status. In the specimen-initiated arm, antibiotics were delayed until objective Gram stain or culture results suggested infection. Each site participated in both arms after a washout period and crossover. Outcomes were protocol compliance, all-cause 30-day mortality, and ventilator-free alive days at 30 days. Standard statistical techniques were applied.

RESULTS: A total of 186 patients had 244 total cultures, of which only the first was analyzed. Ninety-three patients (50%) were enrolled in each arm, and 94.6% were trauma patients (84.4% blunt trauma). The median age was 50.5 years, and 21% of the cohort was female. There were no differences in demographics, comorbidities, sequential organ failure assessment, Acute Physiology and Chronic Health Evaluation II, or Injury Severity Scores. Antibiotics were started significantly later in the specimen-initiated arm (0 vs. 9.3 hours; $p < 0.0001$) with 19.4% avoiding antibiotics completely for that episode. There were no differences in the rate of protocol adherence, 30-day mortality, or ventilator-free alive days at 30 days.

CONCLUSION: In this cluster-randomized crossover trial, we found similar compliance rates between immediate and specimen-initiated antibiotic strategies. Specimen-initiated antibiotic protocol in patients with a suspected hospital-acquired pneumonia did not result in worse clinical outcomes compared with immediate initiation. (*J Trauma Acute Care Surg.* 2023;94: 232–240. Copyright © 2022 American Association for the Surgery of Trauma.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level II.

KEY WORDS: Antibiotic timing; pneumonia; sepsis; randomized clinical trial.

Pneumonia is the most common intensive care unit (ICU)–acquired infection and carries a high associated mortality.[1] The diagnosis of pneumonia with or without sepsis can be difficult, particularly in the surgical and trauma population, where numerous noninfectious causes of fever, leukocytosis, or organ dysfunction can obscure the clinical diagnosis.[2–5]

Decisions regarding when to start antibiotics in the case of a potential pneumonia generally must balance two opposing narratives. On one side, multiple societal guidelines recommend a clinical and culture-based approach to antibiotic initiation.[6,7] On the other, the Surviving Sepsis Campaign (SSC) has historically urged for rapid initiation of antibiotics, although this stance has been softened in the most recent guidelines.[8,9] These SSC recommendations are tied to hospital reimbursement via the Centers for Medicare and Medicaid Services Severe Sepsis and Septic Shock Early Management bundle. Recently, the SSC and Severe Sepsis and Septic Shock Early Management bundle have been criticized for urging antibiotic overuse without demonstration of improved outcomes.[10–14] Despite the evidence against rapid antibiotic administration in many cases, there remain no randomized studies of antibiotic initiation strategies in the surgical and trauma population.

The purpose of this study was to compare an immediate antibiotic administration protocol contrasted to a specimen-initiated protocol based on objective evidence of infection in intubated surgical and trauma patients with suspected hospital-acquired or ventilator-associated pneumonia. We hypothesized that a protocol of specimen-initiated antibiotic initiation would have similar compliance and outcomes to an immediate initiation protocol for patients who were suspected of having a pneumonia but did not require vasopressors.

PATIENTS AND METHODS

Design

This study was designed as a pragmatic multicenter cluster-randomized crossover pilot trial.

All participating investigators received independent full institutional review board approval at their respective institutions. Each site was independently granted a minimal risk determination and waiver of informed consent by their respective institutional review boards. The study received funding from the Surgical Infection Society Foundation, which was not involved in the design or completion of the study. The trial was registered with clinicaltrials.gov (NCT04438187). The equator guideline was used to ensure proper reporting of methods, results, and discussion.

As a pilot trial, no sample size calculation was conducted. Since this is a study of patients with suspected but not yet confirmed pneumonia, we estimated a roughly 50% rate of pneumonia among all patients receiving a culture.[15,16] We limited the duration of each arm of the study to 4 months or 100 patients

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This study was presented at the 81st Annual Meeting of the American Association for the Surgery of Trauma and Clinical Congress for Acute Care Surgery, September 21–24, 2022 in Chicago, Illinois.

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(whichever occurred first), allowing for a maximum enrollment of 200 patients with suspected pneumonia.

Inclusion / Exclusion Criteria

Adult patients 18 to 88 years of age who were suspected of having pneumonia were included in this study. All patients needed to be admitted to a surgical intensive care unit (SICU) or trauma intensive care unit (TICU) for at least 48 hours for a primary surgical diagnosis before collecting a culture. Patients needed to be intubated, but not necessarily for 48 hours, at the time of culture, ensuring that our population included health care–associated but not necessarily ventilator-associated pneumonia. As a pragmatic study, we did not control the clinical parameters used by each intensivist to determine which patient should receive a culture.[17] For study purposes, suspicion for pneumonia was defined as collection of a respiratory culture based on the assessment of the clinical care team. Cultures were obtained via bronchoscopy or mini-bronchoalveolar lavage (BAL). If patients had multiple cultures obtained, then only the initial culture was considered for this analysis.

Patients were excluded if they were not admitted to a SICU or TICU or did not have concern for pneumonia requiring culture. Patients who were pregnant, incarcerated, had a primary diagnosis of burns, had an absolute neutrophil count of <500 cells/mL, or were immunosuppressed were also excluded from the study.

Immediate Initiation Protocol

In the immediate initiation protocol, patients were started on broad spectrum antibiotics immediately after collection of an appropriate respiratory culture regardless of clinical status. Antibiotics were to be stopped after 72 hours if cultures were negative and no other source of infection was identified. Choice of antibiotics was left to intensivist discretion. If a patient in the immediate initiation protocol was already on antibiotics for another indication, antibiotics were immediately broadened.

Specimen-Initiated Protocol

In the specimen-initiated protocol, if the patient did not require vasopressors, antibiotics were held until there was objective evidence of infection. Patients who were considered by the intensivist to be in septic shock or required vasopressors were started on antibiotics immediately. For the purposes of this analysis, vasopressor use served as a surrogate for shock as is common in the literature on this subject.[18,19] Objective evidence of potential pneumonia was defined by a Gram stain listing "2+," "moderate," or "many" bacteria, or >10,000 colony-forming units/mL of bacteria on a BAL specimen, mini-BAL specimen, or quantitative endotracheal suction specimen. If a Gram stain reported bacteria but did not report either quantitative or qualitative findings, then it was considered adequate evidence of potential infection.[20,21] If a patient in the specimen-initiated protocol was already receiving antibiotics for another indication, no changes in the antibiotic regimen were made unless there was some objective evidence of pneumonia. If there was objective evidence, then antibiotics were broadened as indicated. Choice of antibiotics was left to intensivist discretion.

The intensivist could override the study to start or stop antibiotics as deemed necessary if it was felt that further participation in the study was harmful to the patient, although this would be listed as noncompliance.

Microbiology

The result of each culture and any antibiotic resistance was recorded. Patients whose final culture grew contaminants, "normal oropharyngeal flora," or a pathogen below the colony-forming units threshold were considered to have had growth on culture ("positive" culture) but were not considered a clinical pneumonia. For patients in the specimen-initiated arm, this may result in initiation of antibiotics for what is ultimately normal flora. Antibiotics would be expected to stop in both protocols if the final cultures did not demonstrate a clinical pneumonia.

Randomization and Crossover

Randomization was conducted by the primary investigator. Each site was randomly assigned a number between 0 and 100 using the RANDBETWEEN function in Microsoft Excel (Microsoft Corporation, Redmond, WA). The sites receiving the lowest two random numbers were assigned to begin with the immediate initiation protocol, while the others were assigned to the specimen-initiated protocol. Enrollment for the first phase of the study ran from February 1, 2021, to May 31, 2021. During the washout period, an interim data analysis was conducted and reviewed by the Data Safety and Monitoring Board. After approval from the Data Safety and Monitoring Board, each site crossed over to the opposite arm of the study and continued enrollment from September 6, 2021, to January 5, 2022.

Outcomes

The primary outcome of the study was protocol compliance. Compliance education was provided to the ICU teams by each site investigator. Noncompliance in the immediate initiation arm included starting antibiotics before culture (except for patients in shock) and failure to stop antibiotics after 72 hours if cultures were negative. Noncompliance in the specimen-initiated arm included initiation of antibiotics in the absence of objective evidence (except for patients in shock), failure to initiate antibiotics when objective evidence was present, and failure to stop antibiotics if final cultures were negative. Secondary outcomes included all-cause in-hospital mortality at 30 days and ventilator-free-alive days at 30 days following culture.

Statistical Analysis

Continuous variables were compared using Wilcoxon rank sum, while categorical variables were compared using χ^2 or Fisher's exact tests as appropriate. Outcomes were compared both as an intention-to-treat and per-protocol analysis. Subgroup analysis was further conducted for patients on vasopressors, patients with an increase in sequential organ failure assessment (SOFA) scores of at least 2 from the time of admission to culture, patients with pneumonia, and excluding patients already on antibiotics for another indication. Potential clustering effects by site were evaluated and did not reveal evidence of site-level differences in the associations between treatment arm and any trial outcome. Given minimal statistical evidence of cluster effects, no change to study conclusions, and convergence complications

with model estimation due to underpowered analyses, standard statistical techniques for individual-level comparisons were used. Significance was set at $p < 0.05$. The analysis was conducted with SAS software, version 9.4 (SAS Institute, Cary, NC) and R (version 4.1.1). Study data were stored in an online Research Electronic Data Capture database.[22,23]

RESULTS

A total of 186 patients were included with 50% in each protocol (Fig. 1). The population consisted of 94.6% trauma patients. A total of 244 respiratory cultures were obtained, and there was no difference in the median number of cultures between groups (1 vs. 1; $p = 0.88$). The overall pneumonia rate per the initial cultures was 65.6%. Demographics and comorbidities are listed in Table 1. The median age was 50.5 years, and 21% of the overall cohort was female. Fewer patients in the specimen-initiated arm required surgery during their admission. Other than the operative rate, there were no statistical differences between the two groups. Descriptive statistics per site are listed in Supplemental Digital Content (Appendix Tables A–D, http://links.lww.com/TA/C790).

Characteristics of each culture episode are listed in Table 2. There were no differences in the days from admission to culture, the number of patients requiring vasopressors, and the number of patients on antibiotics for another indication. Sequential organ

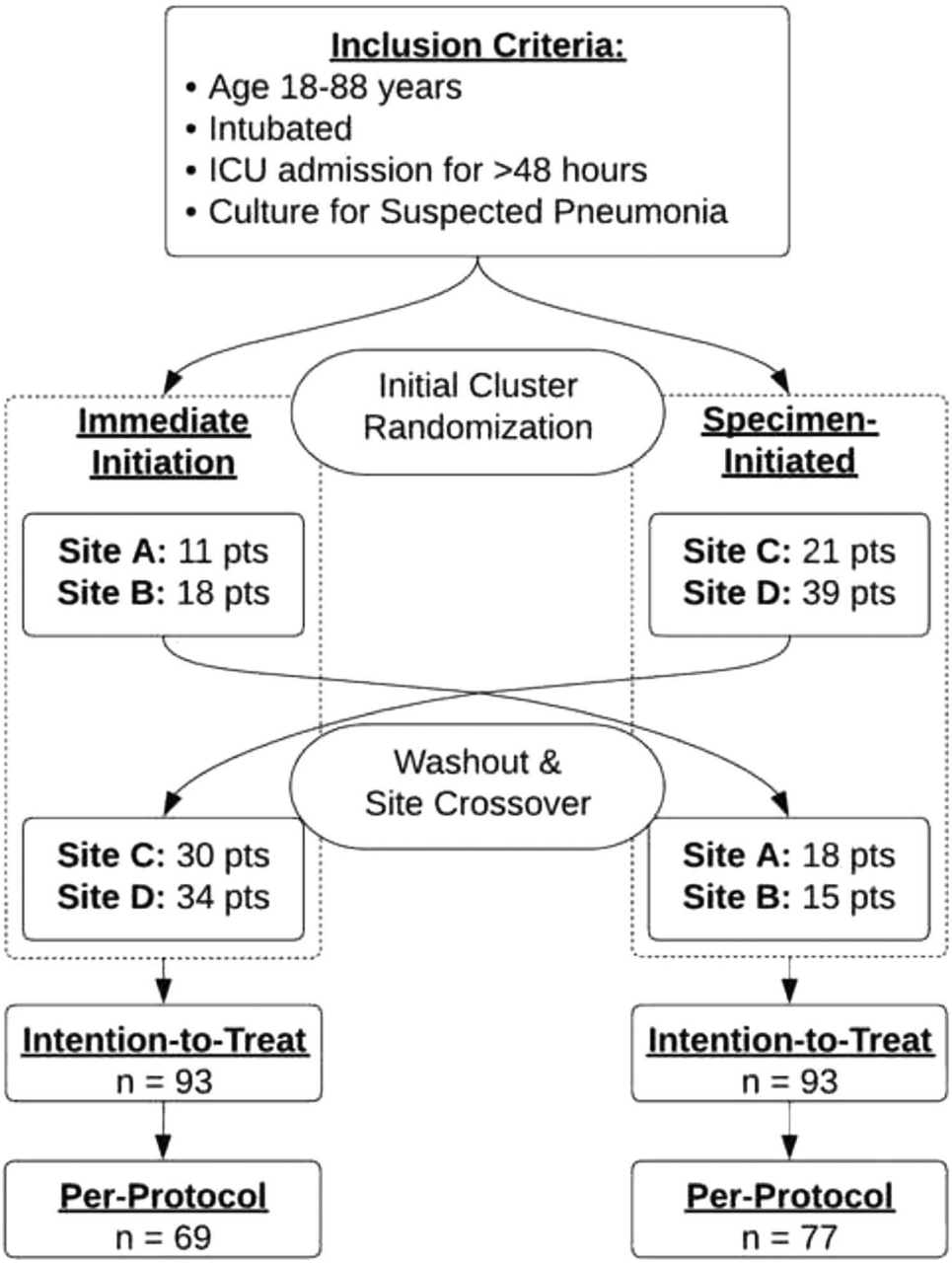

Figure 1. CONSORT diagram.

TABLE 1. Demographics and Comorbidities

Variable	Immediate 93		Specimen Initiated 93		*p*
Age, y	45	(30–61)	56	(36–66)	0.07
Female sex	20	21.5%	19	20.4%	0.86
Race*					0.57
White	69	74.2%	67	72.0%	
Black	14	15.1%	18	19.4%	
Other	9	9.7%	6	6.5%	
Unknown	1	1.1%	2	2.2%	
Ethnicity*					0.43
Hispanic or Latino	9	9.7%	5	5.4%	
Non-Hispanic/non-Latino	84	90.3%	86	92.5%	
Unknown	0	0.0%	2	2.2%	
Body mass index	29.3	(24.2–34.5)	28.3	(23.9–33.7)	0.48
Comorbidities					
Cardiac disease	14	15.1%	23	24.7%	0.1
Renal disease	1	1.1%	1	1.1%	1
Hemodialysis	2	2.2%	1	1.1%	1
Inflammatory bowel disease	0	0.0%	1	1.1%	1
Liver disease	0	0.0%	3	3.2%	0.25
Malignancy	3	3.2%	1	1.1%	0.62
Peripheral vascular disease	1	1.1%	4	4.3%	0.38
Pulmonary disease	4	4.3%	12	12.9%	0.06
Other	12	12.9%	22	23.7%	0.06
Transfusion during admission	63	67.7%	55	59.1%	0.22
ICU admission diagnosis					
Trauma: blunt	79	84.9%	78	83.9%	0.84
Trauma: penetrating	9	9.7%	10	10.8%	0.81
EGS: IAI	1	1.1%	1	1.1%	1
EGS: non-IAI	1	1.1%	3	3.2%	0.62
Vascular surgery	0	0.0%	1	1.1%	1
Scheduled postsurgical admit	1	1.1%	0	0.0%	1
Decompensation on ward	1	1.1%	0	0.0%	1
Other	1	1.1%	0	0.0%	1
Operation during admission	35	37.6%	20	21.5%	0.02
Active infection on admission	3	3.2%	5	5.4%	0.72
COVID-19 during admission	5	5.4%	3	3.2%	0.72
Admission scores					
APACHE II	15	(11–20)	16	(11–20)	0.95
SOFA	6	(4–7)	6	(3–7)	0.92
Injury Severity Score**	25	(16.5–34.5)	25	(16–34)	0.9
Glasgow Coma Scale	8	(5–13)	7	(3–14)	0.68
qSOFA					0.56
0	6	6.5%	9	9.7%	
1	39	41.9%	42	45.2%	
2	36	38.7%	35	37.6%	
3	12	12.9%	7	7.5%	
Site enrollment					0.27
A	11	11.8%	18	19.4%	
B	18	19.4%	15	16.1%	
C	30	32.3%	21	22.6%	
D	34	36.6%	39	41.9%	

Data are presented as n (%) or median (IQR).

*p Values are calculated exclusive of patients with "unknown" race or ethnicity.

**For trauma patients only.

IAI, intra-abdominal infection; APACHE II, Acute Physiology and Chronic Health Evaluation II; IQR, interquartile range; qSOFA, Quick Sequential Organ Failure Assessment.

failure assessment scores did not differ between groups at either the time of admission or the time of culture. Overall, 44.1% of patients had an increase in their SOFA score of at least 2 between admission and the time of culture. Antibiotics were started at a median of 0 hours after culture in the immediate initiation protocol and a median of 9.3 hours after culture in the specimen-initiated protocol. Antibiotics were avoided completely in 19.4% of patients in the specimen-initiated protocol. There were no differences in number of the antibiotic days prescribed for pneumonia or total antibiotic days between groups.

Outcomes are listed in Table 3. Overall protocol adherence was 78.5%. There was no statistical difference in the protocol adherence rate between groups. The listed causes of noncompliance were as follows: continuation of antibiotics despite negative cultures (72.5%), initiation of antibiotics before culture (17.5%), inappropriate continuation of antibiotics after transfer out of unit (5%), failure to start antibiotics immediately in the immediate initiation arm (2.5%), and 2.5% where the causes were unlisted. There were no statistical differences between the listed causes of noncompliance between groups. When analyzed on an intention-to-treat basis, there were no differences in the number of ventilator-free alive days, rate of mortality due to pneumonia, ICU mortality, or all-cause 30-day mortality between groups. Similarly, there were no statistical differences between groups when analyzed on a per-protocol basis. There were no differences in outcomes for any of the other subgroup analyses (Supplemental Digital Content, Appendix Tables E–I, http://links.lww.com/TA/C790). Notably, there was no difference in the timing of antibiotic initiation for patients who were on vasopressors (median, 0.38 vs. 1 hours; $p = 0.38$; Supplemental Digital Content, Appendix Table F, http://links.lww.com/TA/C790) and treated according to protocol, which was expected.

Isolated pathogens for patients with pneumonia are listed in Table 4. The most common organisms were methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *S. aureus* followed by *Escherichia coli* and *Klebsiella pneumoniae*. There were more isolates of *Klebsiella oxytoca* in the specimen-initiated group but otherwise no difference in pathogens between groups. The overall resistance rate was 25.4% with no difference between the immediate initiation and specimen-initiated protocols (24.2% vs. 26.8%; $p = 0.75$).

DISCUSSION

In this limited pilot trial, we have demonstrated that a protocol of specimen-initiated antibiotic administration for suspected hospital-acquired or ventilator-associated pneumonia not requiring vasopressors can be reliably and safely applied when compared with an immediate initiation protocol. The overall 78.5% protocol adherence rate was higher than we initially anticipated and did not differ significantly between groups. While overall antibiotic durations were similar between two groups, we were able to avoid antibiotics entirely in 19.4% of patients in the specimen-initiated arm.

Most data surrounding the timing of antibiotic initiation are focused on patients with potential sepsis who present in the emergency department. Levy et al.[24] found that rapid initiation of antibiotics was associated with decreased mortality. However, this study primarily evaluated overall sepsis bundle compliance

TABLE 2. Culture Episode Data

Variable	Immediate 93		Specimen Initiated 93		*p*
Days from ICU admission to culture	6	(5–9)	7	(4–9)	0.98
Vasopressors within 24 h of antibiotics	34	36.6%	30	32.3%	0.69
On antibiotics for other infection	10	10.8%	17	18.3%	0.15
Maximum temperature (°C) within 24 h of culture	38.6	(37.9–39.3)	38.8	(38.1–39.3)	0.9
Maximum WBCs (1,000 cells/mL) within 24 h of culture	15.1	(11.5–18.6)	15.8	(11.8–19.4)	0.18
Maximum SOFA within 24 h of culture	6	(5–9)	6	(5–8)	0.85
Maximum SOFA within 24 h of antibiotics	7	(5–9)	6	(4–8.5)	0.34
Change in SOFA from admission to culture	1	(−1 to 4)	1	(−1 to 3)	0.7
Change in SOFA from culture to antibiotics	0	(0–0)	0	(−1 to 1)	0.47
Increase in SOFA of ≥2 from admission to culture	40	43.0%	42	45.2%	0.77
Increase in SOFA of ≥2 from culture to antibiotics	11	11.8%	11	11.8%	1
Any growth on culture*	77	82.8%	80	86.0%	0.54
Clinical pneumonia based on culture results	66	71.0%	56	60.2%	0.12
Hours from culture to antibiotics	0	(0–2)	9.3	(0–26)	<0.0001
Never started antibiotics	0	0.0%	18	19.4%	<0.0001
Total days of antibiotics	14	(8–21)	13	(8–20)	0.45
Antibiotics for pneumonia, median (IQR)	7	(6–8)	7	(0–8)	0.05
Antibiotics for pneumonia, mean (SD)	7.3	3.49	5.9	4.31	

Data are presented as n/% or median (IQR).
*Includes any growth at all on reported on culture data including contaminants, normal oropharyngeal flora, or growth of pathogenic organism less than the 10,000 colony-forming unit threshold.
IQR, interquartile range; WBC, white blood cell.

and did not evaluate patients in shock or on vasopressors separately. A larger study by Seymour et al.[18] including 49,331 patients found that, while overall mortality was increased with delays in antibiotic initiation (odds ratio, 1.04; 95% confidence interval, 1.03–1.06), this was primarily driven by patients requiring vasopressors. Patients who did not need vasopressors did not have an association between the timing of antibiotics and mortality.[18] In our study, patients requiring vasopressors were started on antibiotics immediately regardless of intervention group. Accordingly, we found no statistical differences in the timing of antibiotics for patients on vasopressors with no difference in mortality compared with those patients not on vasopressors. Most recently, Bisarya et al.[19] demonstrated no association between the timing of antibiotics and mortality in a study of 74,114 patients presenting to the emergency department with suspected sepsis. In our study, while underpowered, patients with an increase in their SOFA scores of ≥2, consistent with the SEPSIS-3 definition, similarly had no differences in outcomes.[25] The PHANTASi (prehospital antibiotics in the ambulance for sepsis) trial by Alam et al.,[26] the only randomized trial in this population, also demonstrated no association between earlier initiation of antibiotics and mortality. A 2021 machine learning analysis of the PHANTASi trial data by Schinkel et al.[27] suggested that patients 76 years or older may benefit from rapid antibiotic administration. Unfortunately, we are underpowered to evaluate this subset of patients. The SSC has recently endorsed a brief period to reasonably assure that infection is the cause of organ dysfunction before initiating antimicrobial therapy.[9]

Our study is most directly comparable with the 2012 before-and-after, quasi-experimental study by Hranjec et al.[28] In that study, the authors demonstrated increased odds of mortality for ICU patients treated under what they deemed an aggressive initiation protocol, comparable with our immediate initiation protocol (odds ratio, 2.5; 95% confidence interval, 1.5–4.0). That study also demonstrated no difference in pneumonia-specific mortality.[28] A similar study published in 2021 by Le Terrier et al.[29] demonstrated lower overall and ICU-related mortality for patients treated under a restrictive antibiotic initiation protocol. In contrast to these studies, we failed to identify a difference in outcomes between our immediate and specimen-initiated protocols. However, we are not powered to detect small differences in our outcomes. The studies of Hranjec et al.[28]and Le Terrier et al.[29] are single-center nonrandomized and suffer from inherent bias because of their quasi-experimental design.[30] Both these studies are also significantly smaller than their emergency department–based counterparts and may be underpowered. Other observational studies of ICU-acquired infections have also demonstrated no association between antibiotics administration and outcomes.[31–33]

TABLE 3. Outcomes

Variable	Immediate 93		Specimen Initiated 93		*p*
Protocol adherence	69	74.2%	77	82.8%	0.15
Ventilator-free alive days at 30 d	7	(0–15)	8	(0–17)	0.6
Mortality due to pneumonia	2	2.2%	1	1.1%	1
ICU mortality	15	16.1%	14	15.1%	0.84
All-cause 30-d mortality	17	18.3%	17	18.3%	1

Data are presented as n (%) or median (IQR).
IQR, interquartile range.

TABLE 4. Pathogenic Organisms

Pathogens	Total		Immediate		Specimen Initiated		p
	122		66		56		
Methicillin-sensitive *Staphylococcus aureus*	45	36.9%	23	34.8%	22	39.3%	0.62
Methicillin-resistant *S. aureus*	20	16.4%	13	19.7%	7	12.5%	0.28
Escherichia coli	10	8.2%	7	10.6%	3	5.4%	0.34
Klebsiella pneumoniae	9	7.4%	7	10.6%	2	3.6%	0.18
Pseudomonas aeruginosa	9	7.4%	4	6.1%	5	8.9%	0.73
Enterobacter cloacae	8	6.6%	6	9.1%	2	3.6%	0.29
Haemophilus influenzae	8	6.6%	5	7.6%	3	5.4%	0.73
Serratia marcescens	7	5.7%	3	4.5%	4	7.1%	0.7
Enterobacter aerogenes	6	4.9%	4	6.1%	2	3.6%	0.69
Stenotrophomonas maltophilia	6	4.9%	1	1.5%	5	8.9%	0.09
Streptococcus spp.	6	4.9%	1	1.5%	5	8.9%	0.09
Acinetobacter baumannii	4	3.3%	2	3.0%	2	3.6%	1
K. oxytoca	4	3.3%	0	0.0%	4	7.1%	0.04
Proteus mirabilis	4	3.3%	3	4.5%	1	1.8%	0.62
S. pneumoniae	4	3.3%	3	4.5%	1	1.8%	0.62
Citrobacter spp.	3	2.5%	2	3.0%	1	1.8%	1
Corynebacterium spp.	3	2.5%	1	1.5%	2	3.6%	0.59
Hafnia alvei	1	0.8%	0	0.0%	1	1.8%	0.46

Data are presented as n/%.
Organisms add up to >100% since multiple organisms could be present in a single sample.

Bloos et al.[34] performed a cluster-randomized educational sepsis intervention focused on the timing and management of empiric antibiotics but ultimately failed to demonstrate a difference in the timing of antibiotics. Our study demonstrated an overall >9-hour median difference in the time to antibiotics between the two protocols with no difference in outcomes. This difference in antibiotic timing is significantly larger than that observed in the PHANTASi trial and is much longer than that suggested by the current SSC guidelines.[9,26]

While our limited findings did not demonstrate a difference in outcomes, we do not advocate changing practice based on this unpowered pilot, nor do we advise purposely withholding antibiotics in cases where an infection is clear. Surgical ICU and TICU patients are subject to numerous stressors that predispose them to infections from numerous sources including wounds, invasive catheters, and pneumonia. However, many of these same stressors make it difficult to diagnose pneumonia specifically or infections in general. Indeed, one study found that many critically ill patients with suspected sepsis were unlikely to have ever had an infection at all.[16] Diagnostic uncertainty is an inherent, but frequently ignored, aspect of the treatment of pneumonia and sepsis.[13] Our limited findings suggest, as the current SSC guidelines advise, that a short period of additional diagnostic workup may be safe in selected low-risk patients who do not require vasopressors.[9] In cases where the diagnosis of infection is certain, antibiotics should be started immediately. A recent study found that, while the timing of antibiotics was not associated with mortality, even for those in shock, delays in antibiotics were associated with an increased risk of progression to septic shock in some patients.[19] Avoiding antibiotic delays for those patients in whom antibiotics may be lifesaving, while constraining their use in those who cannot benefit, may require the application of biomarkers with the capability of specifically detecting the host response to infection, such as monocyte distribution width measurements or gene expression diagnostic assays.[35–40]

Our study is strengthened by its inclusion of multiple centers and the cluster-randomized crossover design. We also demonstrate applicability in a real-world setting. Our study also has several limitations worth considering. As a pilot trial, we did not conduct a formal power analysis and are unable to demonstrate small differences in outcomes. In addition, we did not control the choice of empiric antibiotics, the duration of antibiotics in the setting of pneumonia, or which patients should have been cultured. It is possible that practice variability between centers regarding the aggressiveness of obtaining cultures as well as variation in antibiotic choice or duration may introduce bias, although this may be mitigated somewhat by the crossover design. We also did not record data on specific antibiotics used and are unable to analyze outcomes based on antibiotic choice. However, when the antibiotic choices themselves are not the subject of the study, there is precedent for not recording these data.[41] We also do not have outcomes based on specific diagnostic sampling method (BAL, bronchial wash, or mini-BAL). In addition, the participating centers are not similarly sized, resulting in significant variability in enrollment per center. One center has a large proportion of the overall enrollment. This enrollment variability may also be a source of bias, but the influence of this bias on our ability to assess our intervention should be mitigated to a degree with the crossover design. Also, we did not include median days from intubation to culture and so are unable to provide a breakdown of outcomes for hospital-acquired versus ventilator-associated pneumonia. Finally, our population consists overwhelmingly of trauma patients and may not be broadly generalizable to a nontrauma population (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/C791).

CONCLUSION

This multicenter cluster-randomized crossover pilot trial demonstrates that a protocol of specimen-initiated antibiotic administration can be successfully applied to a population of intubated TICU and SICU patients who are suspected of having pneumonia but do not require vasopressors. We have demonstrated a high degree of protocol adherence and no differences in outcomes compared with a protocol of immediate antibiotic administration despite significant differences in the timing of antibiotics. We further demonstrated successful avoidance of antibiotics in a small subset of patients in the specimen-initiated protocol. Although in terms of outcomes we are unable to assert equivalence between our two protocols based on sample size, our data do suggest adequate equipoise to allow additional larger studies to verify our results in a wider population of patients.

AUTHORSHIP

C.A.G. and R.G.S. contributed in the literature review, concept, and study design. C.A.G., R.T.B., C.M.W., R.G.S., L.A., M.D., L.C.C., G.P.P., S.V., B.N.H., and J.C.O. contributed in the data collection. C.A.G. and L.C.H. contributed in the data analysis. C.A.G., R.T.B., C.M.W., R.G.S., L.C.H., and S.Q.S. contributed in the interpretation of results. C.A.G. contributed in the manuscript writing. All authors contributed in the critical review of manuscript.

DISCLOSURE

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