Clinical Implications of Microbiologic Treatment Failure in the Setting of Clinical Cure of Bacterial Pneumonia

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(See the Editorial Commentary by Shorr et al on pages 3042–3.)

Background. Microbiologic cure is a common outcome in pneumonia clinical trials, but its clinical significance is incompletely understood.

Methods. We conducted a retrospective cohort study of adult patients hospitalized with bacterial pneumonia who achieved clinical cure. Rates of recurrent pneumonia and death were compared between patients with persistent growth of the index pathogen at the time of clinical cure (microbiologic failure) and those with pathogen eradication (microbiologic cure).

Results. Among 441 patients, 237 experienced microbiologic cure and 204 experienced microbiologic failure. Prevalences of comorbidities, ventilator dependence, and severity of acute illness were similar between groups. Patients with microbiologic failure experienced significantly higher rates of recurrent pneumonia or death following clinical cure than patients with microbiologic cure, controlling for comorbid conditions, severity of acute illness, appropriateness of empiric antibiotics, intensive care unit placement, tracheostomy dependence, and immunocompromised status (90-day multivariable adjusted odds ratio [OR], 1.56; 95% confidence interval [CI], 1.04–2.35). This association was observed among patients with pneumonias caused by *Staphylococcus aureus* (90-day multivariable adjusted OR, 3.69; 95% CI, 1.73–7.90). A trend was observed among pneumonias caused by nonfermenting gram-negative bacilli, but not *Enterobacteriaceae* or other pathogens.

Conclusions. Microbiologic treatment failure was independently associated with recurrent pneumonia or death among patients with bacterial pneumonia following clinical cure. Microbiologic cure merits further study as a metric to guide therapeutic interventions for patients with bacterial pneumonia.

Keywords. pneumonia; ventilator-associated pneumonia; hospital-acquired pneumonia; severe community-acquired pneumonia.

Bacterial pneumonia is a major source of morbidity and mortality in hospitalized patients, with recurrence rates totaling 10–40% depending on case definitions, populations surveyed, and duration of follow-up [1–5]. Efforts to identify predictors of recurrence following successful treatment of bacterial pneumonia are consequently of significant importance. One potential predictor of recurrence is microbiologic treatment failure, an outcome whose clinical significance remains poorly understood [6]. Unlike patients with infections involving sterile sites, such as the bloodstream, patients with bacterial pneumonia may fail to achieve sterility of their respiratory cultures, despite satisfactory responses to antibiotics and clinical cure [7].

The few studies that have examined the clinical implications of microbiologic treatment failure in pneumonia are hampered by significant methodologic limitations and have not examined downstream outcomes such as recurrent pneumonia or death [7–9]. Food and Drug Administration Registry trials of novel antimicrobials for pneumonia classify clinically cured patients without follow-up respiratory cultures as presumably microbiologically cured, a major limitation in making inferences about the relevance of microbiologic cure from existing data. Despite these limitations, many studies of pneumonia caused by multidrug-resistant (MDR) organisms have highlighted differences in rates of microbiologic cure associated with certain therapeutic interventions, despite comparable rates of clinical cure or mortality [10–14]. A clearer understanding of the clinical ramifications of microbiologic failure would help readers to more effectively appraise these studies and assist clinicians at the bedside in determining the relevance of microbiologic failure.

The objective of this study was to determine the association between microbiologic treatment failure and subsequent recurrent pneumonia and death among patients who were treated for bacterial pneumonia and achieved clinical cure.

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METHODS

Study Design and Setting

This was a retrospective cohort study conducted at University Hospital, Michigan Medicine, a 656-bed hospital, including 108 intensive care unit beds, in Ann Arbor, Michigan. The Institutional Review Board of the University of Michigan approved this study for waiver of informed consent.

Cohort Description and Data Collection

A structured query through the institutional electronic medical record was used to retrospectively identify all patients 18 years of age or older hospitalized between 1 January 2008 and 1 January 2017 who met the following prespecified inclusion criteria: (1) a diagnosis of an index pneumonia, (2) achievement of clinical cure, and (3) a repeat respiratory culture obtained at the end of treatment (Figure 1). Potential cases of index pneumonia were identified using the following criteria: (1) growth of a pathogenic organism from respiratory tract culture (expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage), (2) chest imaging interpretation within 48 hours of culture order date containing prespecified keywords consistent with a diagnosis of bacterial pneumonia (Supplementary Table 1), and (3) initiation within 48 hours of culture order date and continuation for 5 or more days of pneumonia-specific antibiotics (antibiotics were considered pneumonia-specific if they were consistent with agents recommended in Infectious Diseases Society of America/American Thoracic Society [IDSA/ATS] guidelines) (Supplementary Table 2) [15, 16].

All potential cases of index pneumonia and associated imaging were reviewed by a blinded infectious diseases physician for diagnostic validity. Criteria used for pneumonia diagnosis included the IDSA/ATS definition of a “new lung infiltrate plus clinical evidence that the infiltrate is of infectious origin, which include new onset of fever, purulent sputum, leukocytosis and

decline in oxygenation” and the additional criterion that a more likely alternative diagnosis was not suspected [15]. Equivocal cases were adjudicated by a panel of 3 separate blinded infectious diseases physicians. For patients with multiple cases who met inclusion criteria for index pneumonia, only the first episode was included.

Clinical cure was defined as cessation of all antibiotics and survival (without discharge to hospice) for at least 48 hours after antibiotic completion without resumption of antibiotics. All included patients were required to have had at least 1 set of repeat respiratory cultures obtained between 3 days before through 7 days after clinical cure. Patients with persistent growth of any causative pathogen from their index pneumonia were classified as microbiologic failure and all others as microbiologic cure.

Relevant demographic characteristics, comorbidities, health-care exposures, and measures of acute severity of illness were collected at the time of index pneumonia culture order and at the time of clinical cure [17, 18]. Microbiologic data, including index pneumonia pathogen identification and susceptibility profile, were collected and independently reviewed by infectious diseases pharmacists to determine appropriateness of empiric coverage (treatment within 48 hours of culture order with an antibiotic to which the organism was susceptible) and definitive coverage (treatment after 48 hours of culture with an antibiotic to which the organism was susceptible). The presence of MDR pathogens (methicillin-resistant *Staphylococcus aureus* [MRSA]; MDR-*Pseudomonas aeruginosa* [defined as nonsusceptible to at least 1 agent in at least 3 different antimicrobial classes]; carbapenem-resistant *Acinetobacter baumannii*; extended-spectrum β -lactamase producing *Escherichia coli* or *Klebsiella* spp; and carbapenem-resistant *Enterobacteriaceae*) was similarly captured.

Outcomes of death and recurrent pneumonia were captured at prespecified time intervals of 7 days after clinical cure, 7–37 days after clinical cure, and 37–97 days after clinical cure

Figure 1. Inclusion criteria for the study cohort.

(to differentiate very early, early, and late outcomes, respectively). The primary study endpoints were a composite of recurrent pneumonia and/or death through the early and late follow-up intervals (henceforth referred to as 30- and 90-day primary outcomes). Composite outcomes were chosen as their individual components were deemed to be competing events. Recurrent pneumonia and death were individually examined as secondary outcomes in the very early, early, and late time periods. Further secondary outcomes included total hospital and intensive care unit lengths of stay following clinical cure.

Cases of recurrent pneumonia were identified through a structured query using the same methods as for index pneumonia but without the requirement for respiratory cultures, in an effort to capture all clinically relevant cases of recurrence in a nonbiased fashion. All potential cases of recurrent pneumonia were similarly adjudicated by blinded chart review by an infectious diseases physician for validity.

Data Analysis

For bivariate analysis, categorical variables were compared using Fisher's exact test and continuous variables were compared using *t* test or Wilcoxon rank sum test as indicated by normality of variable distribution.

For the primary analysis, 30- and 90-day primary outcomes were compared among patients with microbiologic cure with those with microbiologic failure. For secondary outcomes of mortality alone, proportions were calculated as the number of patients deceased within the specified time interval divided by total number of patients within the corresponding case or control group. For the secondary outcome of recurrent pneumonia alone, proportions were calculated as the number of patients with recurrent pneumonia divided by the total number of patients in the corresponding case or control group, excluding those already deceased from a cause other than antecedent recurrent pneumonia.

Additional analyses were conducted for prespecified subgroups, including patients with index pneumonia caused by the following groups of pathogens: (1) *S. aureus*, (2) nonfermenting gram-negative bacilli (NFGNB: *P. aeruginosa*, *A. baumannii*, *Stenotrophomonas maltophilia*), (3) *Enterobacteriaceae*, and (4) community-acquired pneumonia pathogens (*Streptococcus pneumoniae*, *Beta-hemolytic streptococci*, *Haemophilus influenzae*, *Moraxella catarrhalis*). Post hoc exploratory analyses were conducted among patients stratified by ventilator requirements at the time of diagnosis and timing of follow-up culture and among a subgroup of patients who survived without very early death or recurrent pneumonia.

Multivariable logistic regression was performed to calculate adjusted odds ratios (ORs) for the study's primary outcome and other dichotomous outcomes for the overall cohort, as well as for pathogen-specific subgroup analyses. Linear regression was performed for continuous outcomes after log

transformation. Covariates were selected for regression models if they were deemed clinically relevant with regard to predicting the primary outcome (according to published literature/expert opinion) or if, in bivariate analysis, they were associated with either the primary outcome or microbiologic failure ($P < .20$) [5, 19–21]. Variables that were statistically significant in the model ($P < .05$) were retained. Additionally, if inclusion of a variable in the model induced confounding, determined by a change in the β -coefficient of the microbiologic cure covariate of greater than 10%, the confounding variable was retained. Crude rates of the 90-day primary composite outcome were compared between microbiologic cure and failure groups with the construction of a Kaplan-Meier curve and log-rank test.

Microbiologic causes of pneumonia were treated as potential effect modifiers and analyzed in the aforementioned prespecified pathogen subgroups, where the interaction between microbiologic failure and individual pathogen subgroups was explored using interaction terms in multivariable models. Missing data were supplanted by multiple imputation. All reported *P* values are 2-sided. Statistical analysis was performed in SAS version 9.4 (SAS Institute, Inc), with the exception of data imputation, which was performed using the missForest package in R version 3.4.2.

RESULTS

Patient Characteristics

A total of 655 cases of potential index pneumonia followed by clinical cure with follow-up cultures obtained in the prespecified time window were initially captured from the structured query. Following blinded chart and imaging review, 441 patients were determined to have pneumonia. The most common reasons for case exclusion were lack of convincing radiographic evidence of bacterial pneumonia (imaging more consistent with hydrostatic pulmonary edema or compressive atelectasis), a suspected or proven noninfectious cause of respiratory decompensation (aspiration pneumonitis, mucous plugging), or definite evidence of nonpulmonary infection treated with antibiotics. Within this cohort of 441 patients with a confirmed diagnosis of index pneumonia, 237 (53.7%) patients experienced microbiologic cure and 204 (46.3%) experienced microbiologic failure following treatment.

Microbiologic failure (as opposed to microbiologic cure) was more common in patients with non-Caucasian race, chronic renal disease, and tracheostomy dependence at the time of diagnosis (Table 1). Both groups had otherwise similar burdens of chronic illness and healthcare exposures prior to treatment. At the time of index pneumonia diagnosis, measures of acute severity of illness were similar between groups. At the time of clinical cure, both groups demonstrated similar improvements in maximum white blood cell counts, abnormal temperatures, A-a gradients, and APACHE II scores (Table 2).

Table 1. Patient Characteristics

	Microbiologic Cure (n = 237)	Microbiologic Failure (n = 204)	P
Demographic characteristics			
Age, mean (SD), years	54.8 (17.5)	54.6 (17.6)	.94
Male, n (%)	162 (68.4)	149 (73.0)	.30
Caucasian race, n (%)	196 (82.7)	149 (73.0)	.02
Comorbidities			
Charlson comorbidity index score			
Mean (SD)	6.35 (4.39)	6.87 (4.20)	.21
Score >6, n (%)	102 (43.0)	97 (47.6)	.38
Chronic pulmonary disease, n (%)	107 (45.2)	100 (49.0)	.44
Chronic ventilator dependence, n (%)	12 (5.1)	19 (9.3)	.09
Tracheostomy, n (%)	28 (16.0)	62 (30.4)	<.01
Congestive heart failure, n (%)	90 (38.0)	93 (45.6)	.12
Diabetes, n (%)	73 (30.8)	68 (33.3)	.61
Cirrhosis, n (%)	17 (7.2)	16 (7.8)	.86
Chronic renal disease, n (%)	78 (32.9)	90 (44.1)	.02
Malignancy, n (%)	56 (23.6)	62 (30.4)	.13
Immunocompromised, ^a n (%)	41 (17.3)	45 (22.1)	.23
Acute severity of illness			
Ventilator-dependent respiratory failure, n (%)	164 (69.2)	150 (73.5)	.34
Vasopressor-dependent circulatory shock, n (%)	61 (25.7)	64 (31.4)	.21
ICU admission	129 (54.5)	123 (60.3)	.25
APACHE II score			
Mean (SD)	29.9 (6.8)	29.7 (7.7)	.75
Score >30, n (%)	115 (48.5)	92 (45.1)	.50
A-a gradient, mean (SD)	396.8 (169.9)	373 (168.7)	.14
Healthcare exposures			
Bronchoscopy in last 90 days, n (%)	83 (35.0)	68 (33.3)	.76
Diagnosis of pneumonia in last 3 months, ^b n (%)	35 (14.8)	32 (15.7)	.79
Inpatient length of stay prior to index pneumonia, median (IQR), days	2.50 (1.34–7.05)	3.50 (1.07–11.63)	.46
Hospital-acquired index pneumonia, ^c n (%)	143 (60.3)	117 (57.4)	.56

Abbreviations: A-a gradient, alveolar-arterial gradient; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II Score System; ICD-9, International Classification of Diseases, 9th revision; ICU, intensive care unit; IQR, interquartile range; mTOR, mammalian target of rapamycin; SD, standard deviation; TNF, tumor necrosis factor.

^aImmunocompromised defined as solid organ transplant, hematopoietic stem cell transplant, hematologic malignancy, or receipt of immunosuppressive medications including steroids, anti-TNF therapy, mTOR inhibitors, calcineurin inhibitors, and antiproliferative agents.

^bBased on ICD-9 codes in prior 3 months rather than study definition.

^cHospital-acquired index pneumonia defined as pneumonia occurring greater than or equal to 48 hours following hospital admission.

Microbiologic and Treatment Characteristics

The most common pathogens isolated at the time of index pneumonia diagnosis were *S. aureus* (147 cases, 33.3%) and *P. aeruginosa* (105 cases, 23.8%) (Table 3). *Enterobacteriaceae*

were pathogens in 133 cases (30.2%) cases and drug-resistant pathogens were found in 148 cases (33.6%). Patients with microbiologic treatment failure were more likely to have NFGNB isolated from their respiratory cultures than those with

Table 2. Severity of Illness at the Time of Index Pneumonia Diagnosis and Clinical Cure

	Microbiologic Cure (n = 237)	Microbiologic Failure (n = 204)	P
ICU at time of index pneumonia, n (%)	129 (54.4)	123 (60.3)	.25
ICU at time of clinical cure, n (%)	142 (59.9)	124 (60.8)	.92
A-a gradient at time of index pneumonia, mean (SD)	396.8 (169.9)	373.0 (168.7)	.14
A-a gradient at time of clinical cure, mean (SD)	230.6 (115.4)	226.8 (116.7)	.86
Vasopressors at time of index pneumonia, n (%)	61 (25.7)	64 (31.4)	.21
Vasopressors at time of clinical cure, n (%)	11 (4.6)	10 (4.9)	1.00
Abnormal temperature at time of index pneumonia, n (%)	119 (50.2)	102 (50.0)	1.00
Abnormal temperature at time of clinical cure, n (%)	42 (17.7)	28 (13.7)	.29
Max WBCs at time of index pneumonia, 10 ³ cells/μL (SD)	15.1 (7.7)	15.4 (9.0)	.65
Max WBCs at time of clinical cure, 10 ³ cells/μL (SD)	12.8 (6.5)	12.6 (7.2)	.77

Abbreviations: A-a gradient, alveolar-arterial gradient; ICU, intensive care unit; Max, maximum; SD, standard deviation; WBC, white blood cell.

Table 3. Microbiologic Characteristics Among Patients With Microbiologic Cure and Failure

Pathogen	Microbiologic Cure (n = 237)	Microbiologic Failure (n = 204)	P
<i>Staphylococcus aureus</i> , n (%)	74 (31.2)	73 (35.8)	.32
MRSA	30 (40.5)	46 (63.0)	.01
Nonfermenting gram-negative bacilli, ^a n (%)	40 (16.9)	99 (48.5)	<.01
<i>Pseudomonas aeruginosa</i>	28 (11.8)	77 (37.8)	<.01
Multidrug-resistant <i>P. aeruginosa</i>	7 (25.0)	27 (35.1)	.36
<i>Acinetobacter baumannii</i>	3 (1.3)	7 (3.4)	.20
Carbapenem-resistant <i>A. baumannii</i>	1 (33.3)	5 (71.4)	.50
<i>Stenotrophomonas maltophilia</i>	9 (3.8)	19 (9.3)	.02
<i>Enterobacteriaceae</i> , ^b n (%)	86 (36.3)	62 (30.4)	.23
ESBL producers	10 (11.6)	7 (11.3)	1.00
Carbapenem-resistant <i>Enterobacteriaceae</i>	2 (2.3)	0 (0.0)	.51
<i>Klebsiella</i> spp	28 (11.8)	17 (8.3)	.27
<i>Escherichia coli</i>	20 (8.4)	17 (8.3)	1.00
<i>Enterobacter</i> spp	22 (9.3)	18 (8.8)	1.00
<i>Serratia</i> spp	12 (5.1)	15 (7.4)	.32
<i>Proteus</i> spp	5 (2.1)	1 (0.5)	.22
Community-acquired pneumonia pathogens, ^c n (%)	51 (21.5)	11 (5.4)	<.01
<i>Streptococcus pneumoniae</i>	15 (6.3)	3 (1.5)	.01
Beta-hemolytic streptococci	9 (3.8)	4 (2.0)	.40
<i>Haemophilus influenzae</i>	27 (11.4)	6 (2.9)	<.01
<i>Moraxella catarrhalis</i>	6 (2.5)	1 (0.5)	.12
Other	11 (4.6)	5 (2.5)	.31

Abbreviations: ESBL, extended-spectrum beta-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*.

^aNonfermenting gram-negative bacilli defined as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*.

^b*Enterobacteriaceae* defined as *E. coli*, *Proteus* spp, *Klebsiella* spp, *Enterobacter* spp, *Citrobacter* spp, and *Serratia* spp. Note that the sum of individual organisms do not add up to the total as some cultures were polymicrobial in nature.

^cCommunity-acquired pneumonia pathogens defined as *S. pneumoniae*, *Beta-hemolytic streptococci*, *H. influenzae*, and *M. catarrhalis*.

microbiologic cure and were less likely to have community-acquired pneumonia pathogens isolated than those with microbiologic cure (Table 2). Among patients with index pneumonia caused by *S. aureus*, MRSA was more commonly isolated among patients with microbiologic treatment failure compared with those with microbiologic treatment cure. Among patients with index pneumonia secondary to NFGNB and *Enterobacteriaceae*, there were no significant differences in observed frequency of MDR pathogens between those with microbiologic failure versus cure.

Patients with microbiologic failure were significantly less likely to receive empiric antibiotics to which their index pathogen was susceptible compared with patients with microbiologic cure (83.8% vs 93.6%; OR, .35; 95% confidence interval [CI], .18–.67). Greater than 98% of patients received antibiotics for definitive treatment to which their index pathogen was susceptible. A trend towards longer antibiotic treatment duration was observed among patients with microbiologic cure (microbiologic cure median, 12 days; interquartile range [IQR], 8–17 days) versus microbiologic failure (11 days; IQR, 7–17 days) ($P = .06$).

Outcomes and Association With Microbiologic Failure

Within the entire cohort, 165 patients (37.4%) experienced the 30-day primary outcome and 194 patients (44.0%) experienced

the 90-day primary outcome (Table 4). Patients with microbiologic treatment failure had significantly higher rates of 30- and 90-day primary outcomes than did patients with microbiologic cure (30-day OR, 1.52; 95% CI, 1.03–2.24; 90-day OR, 1.64; 95% CI, 1.12–2.39) (Figure 2). In multivariable analysis, microbiologic treatment failure was significantly associated with the 90-day primary outcome (adjusted OR, 1.58; 95% CI, 1.06–2.35). Higher rates of all secondary outcomes were similarly observed among patients with microbiologic failure (Table 4). In sensitivity analyses performed excluding subjects with more than 5% missing values for a variable included in the final model, no significant change in the adjusted association between microbiologic treatment failure and the 90-day primary outcome was observed.

Subgroup Analyses

Microbiologic failure was strongly associated with primary outcomes in cohorts of patients with index pneumonia caused by *S. aureus* (Table 5). A similar, albeit nonsignificant, association was noted among patients with index pneumonia caused by NFGNB. In contrast, there were no significant associations between microbiologic failure and primary outcomes among patients with pneumonia secondary to *Enterobacteriaceae* or community-acquired pneumonia pathogens. A significant interaction was noted between *S. aureus* and microbiologic failure

Table 4. Outcomes Among Patients With Microbiologic Cure and Failure

Outcome	Microbiologic Cure (n = 237)	Microbiologic Failure (n = 204)	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
Primary outcomes, n (%)				
30-day recurrent pneumonia or death	78 (32.9)	87 (42.7)	1.52 (1.03–2.24)	1.40 (.93–2.12)
90-day recurrent pneumonia or death	91 (38.4)	103 (50.5)	1.64 (1.12–2.39)	1.56 (1.04–2.35)
Secondary outcomes, n (%)				
Recurrent pneumonia categorized by time after clinical cure ^b				
Very early endpoint	36 (15.6)	43 (21.8)	1.51 (.93–2.47)	1.49 (.88–2.47)
Early endpoint	53 (22.9)	59 (30.9)	1.44 (.93–2.21)	1.40 (.88–2.22)
Late endpoint	58 (28.4)	70 (40.9)	1.75 (1.13–2.68)	1.65 (1.04–2.61)
Mortality categorized by time after clinical cure				
Very early endpoint	6 (2.5)	7 (3.4)	1.37 (.45–4.14)	1.05 (.32–3.47)
Early endpoint	30 (12.7)	40 (19.6)	1.68 (1.00–2.82)	1.51 (.87–2.62)
Late endpoint	45 (19.0)	54 (26.5)	1.54 (.98–2.41)	1.41 (.86–2.32)
Median length of stay after clinical cure (IQR), days	10 (1–22)	14 (4–31)	<i>P</i> = .03	<i>P</i> = .03
Median ICU length of stay after cure (IQR), days	1 (0–10)	2 (0–13)	<i>P</i> = .28	<i>P</i> = .25

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio.

^aMultivariable logistic regression model controlling for appropriateness of empiric antibiotic coverage, tracheostomy dependence, APACHE II score >30, ICU admission, immunocompromised status, and Charlson Comorbidity Index Score >6.

^bPercentage calculated as number with recurrent pneumonia over number of nondeceased patients within time frame. Very early endpoint = up to 7 days after clinical cure, early endpoint = up to 37 days after clinical cure, late endpoint = up to 97 days after clinical cure.

and increased risk for the 90-day composite primary outcome (*P* = .04) but was not evident among other pathogen-specific subgroups (*P* > .05).

In stratified analyses (including by ventilator dependence at the time of index pneumonia diagnosis and by timing of

follow-up cultures) and in an exploratory analysis excluding patients with pneumonia caused by community-acquired pathogens, associations between microbiologic treatment failure and 30- and 90-day primary outcomes remained unchanged ([Supplementary Table 3](#)). Overall results were similar

Figure 2. Kaplan-Meier survival analysis for 90-day composite outcome of death and/or recurrent pneumonia as a function of microbiologic treatment outcome. The *P* value was calculated using the log-rank test.

Table 5. 30- and 90-Day Primary Outcomes in Patients With Microbiologic Cure Versus Microbiologic Failure Stratified by Pathogen

Pathogen	Microbiologic Cure	Microbiologic Failure	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)
<i>Staphylococcus aureus</i> , n (%)	n = 74	n = 73		
30-day recurrent pneumonia or death	17 (23.0)	36 (49.3)	3.26 (1.60–6.63)	2.80 (1.31–5.99)
90-day recurrent pneumonia or death	19 (25.7%)	43 (58.9)	4.15 (2.06–8.35)	3.69 (1.73–7.90)
Nonfermenting gram-negative bacilli, ^b n (%)	n = 40	n = 99		
30-day recurrent pneumonia or death	11 (27.5)	42 (42.4)	1.94 (.87–4.33)	1.43 (.60–3.37)
90-day recurrent pneumonia or death	12 (30.0)	49 (49.5)	2.29 (1.05–5.00)	1.72 (.74–3.99)
<i>Enterobacteriaceae</i> , ^c n (%)	n = 86	n = 62		
30-day recurrent pneumonia or death	41 (47.7)	30 (48.4)	1.03 (.54–1.98)	1.13 (.57–2.26)
90-day recurrent pneumonia or death	49 (57.0)	34 (54.8)	.92 (.48–1.77)	.96 (.48–1.92)
Community-acquired pneumonia pathogens, ^d n (%)	n = 51	n = 11		
30-day recurrent pneumonia or death	12 (23.5)	1 (9.1)	.33 (.04–2.80)	.31 (.04–2.71)
90-day recurrent pneumonia or death	14 (27.5)	1 (9.1)	.26 (.03–2.26)	.23 (.03–2.03)

Abbreviations: APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II Score System; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

^aMultivariable logistic regression model for *S. aureus* and nonfermenting gram-negative bacilli controlling for appropriateness of empiric antibiotics, tracheostomy dependence, APACHE II score >30, ICU admission, immunocompromised status, and Charlson Comorbidity Index Score >6. Multivariable logistic regression model for *Enterobacteriaceae* computed without appropriateness of empiric antibiotics variable owing to model instability. Multivariable logistic regression model for community-acquired pneumonia pathogens without appropriateness of empiric antibiotics, tracheostomy-dependent, and immunocompromised status variables owing to model instability. Presence or absence of methicillin-resistance included as additional variable in model for *S. aureus* subgroup.

^bNonfermenting gram-negative bacilli defined as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*.

^c*Enterobacteriaceae* defined as *Escherichia coli*, *Proteus* spp, *Klebsiella* spp, *Enterobacter* spp, *Citrobacter* spp, and *Serratia* spp. Note that the sum of individual organisms do not add up to the total as some cultures were polymicrobial in nature.

^dCommunity-acquired pneumonia pathogens defined as *Streptococcus pneumoniae*, *Beta-hemolytic streptococci*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.

when polymicrobial index cultures were removed from analysis and when patients who received inadequate empiric antibiotic therapy were removed from analysis. When pathogen-specific subgroup analyses were performed only in patients with monomicrobial index cultures, pathogen-specific effect measures remained unchanged.

Recurrent Pneumonia Etiology

Among 128 patients who developed recurrent pneumonia, 13 did not have culture data available. Among the remaining 115 patients, those with microbiologic failure of their index pneumonia frequently had the same pathogen recovered at the time of recurrent pneumonia as was recovered at index pneumonia diagnosis (57/61, 93%). In contrast, only 22% (12/54) of patients with microbiologic cure and recurrent pneumonia had an identical pathogen recovered ($P < .0001$). Among patients with microbiologic failure who developed recurrent pneumonia, the causative pathogen was *S. aureus* or *P. aeruginosa* in over 50% of cases (*S. aureus*, 28.8%; *P. aeruginosa*, 23.8%; *S. maltophilia*, 11.3%; and *Enterobacter* spp, 11.3% of cases).

DISCUSSION

In this study of patients with bacterial pneumonia who achieved clinical cure, microbiologic failure was associated with higher rates of 30- and 90-day recurrent pneumonia and/or death, a finding that persisted in multivariable analysis for the 90-day outcome. This association was pathogen specific, driven largely by patients with pneumonia secondary to *S. aureus* and NFGNB.

To our knowledge, this is the first study to comprehensively evaluate the clinical relevance of microbiologic failure

accompanying clinical cure of pneumonia. Our results carry implications for existing and future studies on the treatment of pneumonia. For example, in randomized controlled trials of pneumonia investigating antibiotic choice for MRSA nosocomial pneumonia, aerosolized antibiotics for gram-negative ventilator-associated pneumonia, and colistin-based combination therapy for MDR gram-negative pneumonia, response differences have been noted between comparator groups with respect to microbiologic cure, despite similar rates of clinical cure and mortality [10–14]. Our findings suggest that interventions associated with microbiologic cure might have benefit with regard to downstream clinical outcomes, even in the absence of differences in clinical cure or immediate mortality.

The results of this study similarly suggest that microbiologic outcomes might be relevant in the determination of pneumonia treatment durations. In a randomized controlled trial of 8 versus 15 days of antibiotic treatment for ventilator-associated pneumonia, higher rates of recurrent pneumonia were reported among a subgroup of patients with NFGNB treated with shorter course therapy [22]. Rates of microbiologic failure were not reported at the time of antibiotic completion in this study and might have contributed to this discrepancy in recurrent pneumonia rates.

Importantly, this study does not denote a causal link between failure of pathogen eradication and downstream recurrent pneumonia or death, nor does it suggest that patients with microbiologic treatment failure would benefit from extended courses of antibiotics to achieve pathogen eradication. Microbiologic failure may be a surrogate marker for nonmicrobiologic conditions associated with increased risk for death or recurrent

pneumonia, such as baseline abnormal lung architecture, impaired pulmonary toilet, aspiration frequency, impaired host immune response, and/or ongoing dependence on mechanical ventilation. However, it is also possible that in selected patients with certain pathogens microbiologic failure in the setting of clinical symptom resolution might represent incomplete eradication of infection. As such, we believe prospective analyses are warranted to assess the association between microbiologic eradication and recurrent pneumonia and/or death.

Additionally, this study suggests that, among patients with recurrent pneumonia occurring within 3 months following an index pneumonia in which they experienced microbiologic treatment failure, the causative pathogen has a high likelihood of being the same as it was for the index pneumonia. This association might assist clinicians in selecting appropriate empiric antibiotics when treating a suspected pneumonia recurrence.

This study has several limitations. First, the majority of patients in this study population were critically ill and thus its generalizability to patients who are less severely ill is uncertain. Additionally, the requirement for follow-up respiratory cultures in this population creates potential for selection bias and limits generalizability to patients who would not normally have had cultures performed at the end of therapy. Notably, a substantial number of “end of treatment” cultures in this study were obtained for clinical syndromes other than pneumonia (eg, surveillance bronchoscopies for inhalational burn patients or those on extracorporeal membrane oxygenation, tracheal aspirates for stable patients with failure to liberate from mechanical ventilation or episodes of mucous plugging) (data not shown). Nonetheless, the findings presented here should not be generalized to patients without posttreatment respiratory cultures, nor should they be taken as an indication for routinely culturing patients with pneumonia following successful treatment.

Moreover, as readmission data were only available for patients readmitted to the study hospital, patients readmitted to other hospitals for pneumonia were not captured. This study also did not require that subjects have quantitative respiratory cultures or distal sampling of the lungs. However, the use of rigorous and blinded clinician review for diagnostic case validity reduced the likelihood of including patients with respiratory colonization: a sum total of 936 cases of potential index or recurrent pneumonias that met study inclusion criteria were reviewed in the process of this study, of which, after blinded review, only 590 (63%) were deemed to be valid cases of pneumonia.

In conclusion, this study demonstrated that, in patients with bacterial pneumonia who achieved clinical cure, microbiologic failure was associated with recurrent pneumonia and death, a finding driven by pneumonia caused by *S. aureus* and NFGNB. In the setting of clinical cure of bacterial pneumonia, the relevance of microbiologic treatment failure to clinical practice as well as to the design of clinical trials warrants further study.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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