

Risk Factors for Adverse Outcome in Persons With Pneumococcal Pneumonia*

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Objective: To identify risk factors for death and respiratory failure in persons with penicillin-sensitive pneumococcal bacteremia and pneumonia from data available at initial clinical evaluation.

Design: Retrospective chart review of persons with pneumococcal bacteremia and pneumonia.

Setting: Tertiary care medical center (University of California Davis Medical Center, Sacramento).

Patients: One hundred two consecutive adults admitted to the hospital for treatment of pneumococcal pneumonia with bacteremia.

Results: Of 102 persons, 25 (25%; 95% confidence interval [CI], 17 to 34%) died and 17 (16%; 95% CI, 10 to 25%) survived mechanical ventilation for respiratory failure. In univariate analyses, persons with preexisting lung disease (relative risk [RR], 2.0; 95% CI, 1.3 to 3.1), initial body temperature <38°C (RR, 2.1; 95% CI, 1.3 to 3.6), or nosocomial infections (RR, 2.5; 95% CI, 1.8 to 3.6) or who were ≥48 years old (RR, 2.7; 95% CI, 1.5 to 4.8) were at greater risk for adverse outcomes than persons without these risk factors. Of 25 persons without these risk factors, only one (4%; 95% CI, 0 to 20%) died, and

the remaining 24 persons did not require intensive care. Using these risk factors in a multivariate logistic model, death or respiratory failure would have been predicted in 67% of persons and better outcome predicted in 83% of the persons. In multivariate analysis, nosocomial infection was the greatest risk factor (adjusted odds ratio, 17.3; 95% CI, 3.1 to 98).

Conclusions: Risk factors identified at hospital admission can predict the outcome in persons with pneumococcal pneumonia and bacteremia. Identifying these factors may allow earlier use of intensive care or more aggressive treatment. Independent of age, nosocomially acquired infections were the greatest risk factor for death or respiratory failure. (*Chest* 1995; 107:457-62)

ARDS=adult respiratory distress syndrome; CI=confidence interval; IL=interleukin; RR=relative risk; RRM-H=Mantel-Haenszel weighted relative risk; UCDMC=University of California at Davis Medical Center

Key words: epidemiology; logistic regression; mortality; pneumonia; *Streptococcus pneumoniae*

Despite the use of antibiotics over the past 35 years, mortality rates for persons with pneumococcal pneumonia and bacteremia remain between 20% and 45%.¹⁻⁶ Numerous studies have attempted to identify persons who do not benefit from antibiotic treatment and disproportionately contribute to this high mortality. Advanced age, alcoholism, abnormal leukocyte response, immunosuppressive conditions, and multilobar pneumonia are risk factors that have been previously associated with mortality rates of 50% or greater despite appropriate antibiotic therapy.¹⁻⁸

A predictive model to determine risk for mortality

or respiratory failure in persons with pneumonia would allow improved triage and early identification of persons at high risk for these adverse outcomes who may benefit from admission to the intensive care unit (ICU). Similar models to predict mortality have been developed for elderly persons with pneumonia to identify those who may require transfer from rural hospitals to ICUs in referral hospitals.⁸ A predictive model of outcome may increase our understanding of the pathogenesis of pneumonia and provide an objective basis to allocate critical care resources, and to evaluate the efficacy of future therapies for sepsis, eg, colony-stimulating factors, monoclonal antibodies, immunomodulating therapy. In a retrospective chart review of a specific subset of persons with pneumonia, those with lobar pneumonia and positive blood cultures for *Streptococcus pneumoniae*, we identified risk factors for death or respiratory failure and defined a discriminating statistical model to identify persons at high risk for death or respiratory failure.

METHODS

Case Finding and Definitions

Persons with pneumococcal bacteremia were identified from

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Table 1—Possible Risk Factors Sought in a Chart Review of 102 Persons With Pneumococcal Pneumonia

Demographic: Age; sex; race

History of present illness: Nosocomial acquisition; presence of fever, cough, or rigors prior to presentation; days of symptoms; quality of sputum; history of lung cancer and treatment; smoking history (active, packs per day, pack-years); clinical history of a preexisting lung disease (emphysema, chronic bronchitis, other mixed obstructive pulmonary disease, sarcoid, other restrictive lung disease, recurrent aspiration pneumonia, pulmonary hypertension, pulmonary fibrosis, or history of pulmonary tuberculosis)

Medical history: Current medications; recent use of antipyretics; intravenous drug abuse (IVDA); any immunosuppressive condition or medication; alcoholism; history of AIDS-defining opportunistic infection; or other preexisting medical* or neurologic diseases

Examination and laboratory results: Oral temperature; respiratory rate; additional site of infection besides the lungs; white blood cell (WBC) count; WBC <5,000; WBC >10,000; absolute band cell count; initial sputum Gram's stain or sputum culture results; chest radiograph with evidence of multilobe involvement; oxacillin sensitivity of the isolate

*Includes clinical history of diabetes mellitus, acute or chronic renal failure, cirrhosis or chronic hepatitis, coronary artery disease, hypertension with end-organ damage, congestive heart failure, sickle cell disease, or rheumatologic disease.

logbooks in the University of California at Davis Medical Center (UCDMC) microbiology laboratory. Chest radiographs obtained within 24 h of drawing the index blood culture were reviewed by an attending physician from the UCDMC Section of Critical Care and Pulmonary Medicine to confirm a lobar or multilobar pneumonia. Persons with pneumococcal bacteremia with pneumonia, who were 12 years old or greater, and hospitalized during the period January 1987 through December 1989 were included in this analysis. All were admitted from the emergency department or adult outpatient facility, transferred from a referring hospital or skilled nursing facility, or previously admitted to a UCDMC medical-surgical ward. Persons in the intensive care unit at the time of the index blood culture were excluded from analysis. Emergency department treatment sheets, laboratory reports, and microbiologic culture results were retrospectively abstracted to identify risk factors that a physician could have specified during the initial clinical evaluation (Table 1).

Human immunodeficiency virus (HIV) antibody status and pneumococcal vaccine status were documented for less than 10% of the records and were not included in the analysis. Nosocomial infection was defined as a pneumococcal infection in a person hospitalized at UCDMC, a referring hospital, or skilled nursing facility during the 3- to 7-day period before the index blood culture. Immunosuppressed persons were persons with previously documented *Pneumocystis carinii* pneumonia, *Mycobacterium avium-intracellulare* infection, lymphoma, hematologic malignancy, or asplenia, or who received exogenous corticosteroids (≥ 10 mg of prednisone per day), chemotherapy, or other immunosuppressive drugs. Adverse outcomes included death or mechanical ventilation from respiratory failure, ARDS during the index hospitalization or both. ARDS was a clinical diagnosis made by an attending UCDMC intensivist and defined by mechanical ventilation, increasing FIO_2 requirement, decreased lung compliance, and chest radiographs showing progressive bilateral infiltrates without evidence of cardiogenic pulmonary edema. Persons were followed up until the time of death or discharge from this index hospitalization.

Univariate Analysis

Continuous variables were analyzed with Student's *t* test. Significant continuous variables were dichotomized at the median value to calculate relative risk and for use in the logistic model. Each pulmonary and medical condition was analyzed independently and then grouped into "preexisting lung and medical diseases," respectively (Table 1). Relative risk (RR) with exact 95% confidence intervals (95% CI), Mantel-Haenszel weighted relative risk (RRM-H), Fisher's exact test with two-tailed results, and Student's *t* test were calculated (with EPI-INFO).⁹ Rates with 95% CI were calculated (using EpiStat).¹⁰

Multivariate Analysis

Significant factors from univariate analysis were included in a backward stepwise multivariate regression using a logistic model.^{11,12} To select the best combination of risk factors predictive of adverse outcome, models were evaluated using a likelihood-ratio χ^2 statistic.¹³ For this statistical comparison, the number of persons within each nested model was appropriately adjusted.¹² Results are reported as an adjusted odds ratio with 95% CI. To evaluate the efficiency of the resulting model, there was a predicted probability of adverse outcome for each person.¹³ The probabilities were dichotomized (<0.50 and ≥ 0.50) and compared with the actual outcomes.

RESULTS

Mortality

During these 3 years, 102 persons with pneumococcal bacteremia and pneumonia were identified and included in the analysis. Of these, 78 (76%) were

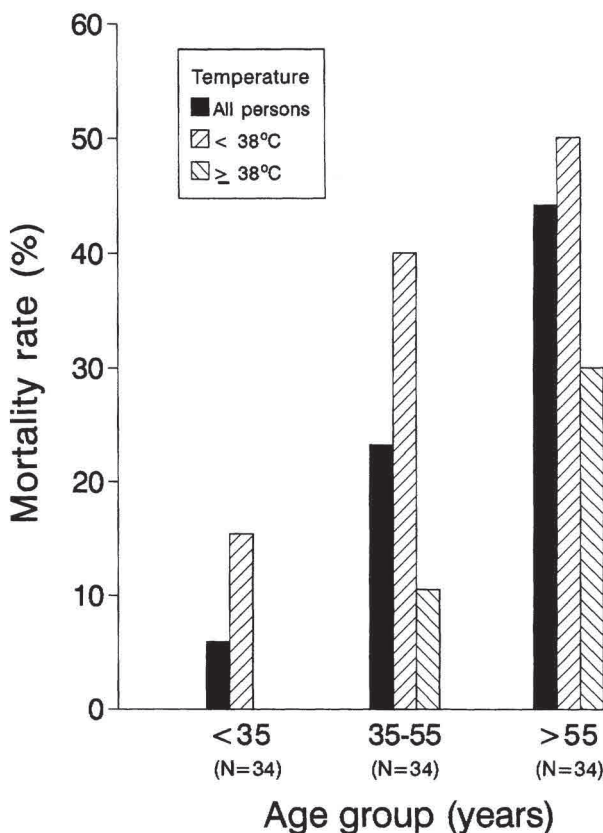


FIGURE 1. Age-specific mortality rates for persons with pneumococcal bacteremia and pneumonia, stratified by initial body temperature.

Table 2—Significant Risk Factors for Adverse Outcome in 102 Persons With Pneumococcal Bacteremia and Pneumonia From Univariate and Multivariate Logistic Regression Analyses

Risk Factor (No. of Persons)	Univariate Analysis		Multivariate Logistic Regression	
	Relative Risk	(95% CI)	Coefficient	Adjusted Odds Ratio (95% CI)
Age ≥ 48 yr (52)	2.7	(1.5-4.8)	1.194	3.3 (1.2-9.2)
Preexisting lung disease (24)	2.0	(1.3-3.0)	1.400	4.1 (1.3-13.0)
Temperature $<38^{\circ}\text{C}$ (52)	2.1	(1.3-3.6)	1.376	4.0 (1.4-11.4)
Nosocomial infection (14)	2.5	(1.8-3.6)	2.848	17.3 (3.1-97.5)
Chronic obstructive pulmonary disease (18)	1.7	(1.0-2.6)	Did not contribute to the logistic model	
History of pulmonary tuberculosis (8)	2.3	(1.5-3.4)	Did not contribute to the logistic model	
Preexisting medical disease (61)	4.2	(1.6-10.6)	Did not contribute to the logistic model	

men and 58 (57%) were non-Hispanic whites. The median age was 48 years (range, 20 to 88 years). Forty-two (41%) had an adverse outcome; 25 persons (25%; 95% CI, 17 to 34%) died and 17 others (16%; 95% CI, 10 to 25%) required mechanical ventilation. Of 39 persons who required mechanical ventilation, 22 (56%) died. Of the 13 persons with ARDS, 11 (85%) died. All pneumococcal isolates were sensitive to oxacillin. All persons received an appropriate doses of an intravenous antibiotic (penicillin, vancomycin, cefazolin, or erythromycin) within 8 h of the index blood culture.

Mortality significantly increased with age. This increase was seen in febrile and afebrile persons (Fig 1); χ^2 for linear trend was 4.0 ($p=0.046$) for persons with initial temperature $<38^{\circ}\text{C}$ compared with χ^2 of 6.8 ($p=0.009$) for persons with higher temperature. After adjusting for each other, low temperature (RRM-H=2.7; 95% CI, 1.2 to 6.0) and age (χ^2 for linear trend=9.1; $p=0.003$) were independent risk factors for mortality. Sputum samples were obtained from 95 (93%) of these 102 persons and pneumococcus was isolated in the sputum of 34 of 95 (36%) of these persons. These persons had a 2.7 times greater risk (95% CI, 1.7 to 4.3) of death compared with persons who did not have *S pneumoniae* isolated from their sputum.

Univariate Analysis

Persons with adverse outcome were older and had a lower body temperature than persons with better outcome. The mean age of 42 persons with adverse outcomes was 55.9 years and significantly more than the mean age of 41.0 years for the 60 persons with better outcomes ($p\leq 0.001$). The mean oral temperature during the initial presentation was 37.3°C for persons who subsequently had adverse outcomes and significantly less than the mean of 38.2°C for the 60 persons with better outcomes ($p\leq 0.001$). There was no significant difference in days of prodromal symptoms, mean white blood cell count, number of involved lobes, or absolute band count.

Age and oral temperature were dichotomized at their median values, ≥ 48 years of age and $<38^{\circ}\text{C}$ temperature, respectively, to calculate the relative risk (Table 2). Of 52 persons 48 years or older, 31 (60%; 95% CI, 45 to 73%) had an adverse outcome, resulting in a relative risk 2.7 (95% CI, 1.5 to 4.8) times greater than persons younger than 48 years old. Of 52 persons whose temperature was less than 38°C , 29 (56%; 95% CI, 41 to 70%) had an adverse outcome, resulting in a relative risk that was 2.1 (95% CI, 1.3 to 3.6) times greater than that of persons who presented with fever.

In addition to older age and lack of fever, five other conditions (preexisting lung disease, chronic obstructive pulmonary disease, history of pulmonary tuberculosis, preexisting medical disease, and nosocomial infection) were significantly associated with increased risk of adverse outcome in the univariate analysis (Table 2).

Multivariate Analysis of Risk Factors

Four risk factors from the univariate analysis were independent and significantly contributed to a logistic model of adverse outcome (Table 2). Preexisting medical disease was not included in the model because much of the associated risk found in the univariate analysis was attributable to age ≥ 48 years. Nosocomial infection had the greatest associated risk of adverse outcome (adjusted odds ratio, 17.3) and had a significant effect on the resulting model. Despite this elevated risk, the attributable risk associated with nosocomial infection is small because of the infrequent occurrence of this factor in the study.

A probability of adverse outcome was generated for each person. These probabilities were grouped into eight risk levels based on similar probabilities of outcome and compared with the actual rate of an adverse outcome (Table 3). If none of the four risk factors were present or if only one risk factor other than nosocomial infection was present, the probability of an adverse outcome was <0.25 . Of 53 persons with probability <0.25 , nine (17%; 95% CI, 8 to 30%)

Table 3—Calculated Probability and Actual Rate of Adverse Outcome Rate for Eight Risk Levels in Persons With Pneumococcal Bacteremia and Pneumonia

Risk Factors (No. of Persons)	Risk Level	Probability of Adverse Outcome*	Actual Rate of Adverse Outcome†
No risk factors (25)	A	0.08	0.04
Age ≥ 48 yr, initial temperature $<38^{\circ}\text{C}$, OR preexisting lung disease (28)	B	0.24	0.28
Two of the above risk factors (24)	C	0.54	0.46
Nosocomial infection only (2)	D	0.59	1.00
Age ≥ 48 yr, initial temperature $<38^{\circ}\text{C}$, AND preexisting lung disease (11)	E	0.81	0.91
Nosocomial infection AND one of the following: age ≥ 48 yr, initial temperature $<38^{\circ}\text{C}$, OR preexisting lung disease (5)	F	0.84	0.80
Nosocomial infection AND two of the following: age ≥ 48 yr, initial temperature $<38^{\circ}\text{C}$, OR preexisting lung disease (7)	G	0.95	0.86
All four risk factors (0)	H	0.99	—

*Calculated from the resulting logistic regression model (Table 2).

†Proportion of persons who died or required mechanical ventilation. None of the 102 persons included in this analysis had all four risk factors.

had an adverse outcome (resulting in four deaths) during the index hospitalization. Persons with nosocomial infection or more than one of the four risk factors (risk levels C through H) had a calculated probability of an adverse outcome >0.5 (Table 3). Of 49 persons with a probability >0.5 , 33 (67%; 95% CI, 52 to 80%) had an adverse outcome (resulting in 21 deaths) during the hospitalization.

Model Efficiency

A probability of adverse outcome was generated for each person. Using a threshold probability of 0.50, these probabilities were compared with the actual outcome of each person (Table 4). Using clinical variables present during the evaluation of persons with lobar pneumonia, adverse outcome was correctly predicted, *ie*, positive predictive value, in 67% of the persons and a better outcome, *ie*, negative predictive value, was correctly predicted in 83% of the persons.

DISCUSSION

Overall, persons with pneumococcal bacteremia had 25% mortality, which is similar to the results of other studies performed in the antibiotic era.^{2,3,8} Mortality was not evenly distributed over this cohort. Only one death occurred among persons without any of four risk factors (age ≥ 48 years, initial temperature $<38^{\circ}\text{C}$, preexisting lung disease, or nosocomial infection) resulting in 4% mortality. But, among the remaining persons, mortality was 31% and an additional 22% required mechanical ventilation.

Advanced age continues to be an overwhelming risk factor for death or respiratory failure due to pneumococcal pneumonia. Using a logistic model, much of the risk attributed to preexisting medical

disease in univariate analyses was found to be actually due to age greater than 48 years. Austrian and Gold² reported a mortality rate of 37.7% in persons 50 years or older with pneumococcal bacteremia compared with a 10.3% rate for those younger than 50 years. In previous studies, increased mortality was attributed to the increased frequency of more virulent pneumococcal serotypes and the waning antibody titer to these more virulent serotypes in older persons.^{2,14} Although serotyping was not done in this study, it is unlikely that the power would allow partitioning the risk due to specific serotypes of pneumococcus pneumonia from the risk of being elderly with sepsis.^{15,16}

Persons without fever were more likely to die or experience respiratory failure. Inappropriately low body temperature in the setting of infection has previously been thought to be a marker of either chronic illness or advanced age, but this logistic model suggests the risk from lack of fever was independent of these other two factors. In fact, preexisting diseases other than lung diseases played little role in outcome in the derived logistic model. Using

Table 4—Comparison of the Probability of Adverse Outcome Generated From the Logistic Model to the Actual Outcome of 102 Persons With Pneumococcal Bacteremia and Pneumonia*

Probability of Adverse Outcome	Actual Outcome	
	Adverse	Better
≥ 0.5	33	16
<0.5	9	44
Total	42	60

*Sensitivity, 79%; specificity, 73%; positive predictive value, 67%; and negative predictive value, 83%.

multivariate analysis, others have recently shown that persons with hypothermia or without shaking chills were more likely to die when sepsis was present.^{15,17} Low body temperature may be a result of increased vasodilatation and the loss of core temperature even when frank septic shock is not present. Or, it may be one measure of an inadequate granulocyte or interleukin (Il) response. Nonspecific production of Il-1, Il-6, and tumor necrosis factor, in response to the pneumococcal polysaccharide capsule, is known to be the main mechanism of the febrile response as well as a potent signal for granulocyte migration and killing.^{14,18-20} In this model, adverse outcome was associated with low body temperature but may be more correctly associated with poor granulocyte function (which was not measured in this study). Low body temperature may be acting as a surrogate measure for poor nonspecific host defenses.

Other simple scoring systems have been developed to predict mortality of persons with sepsis by specifying the number of organ systems involved at the initial presentation.^{18,21,22} Death was only one adverse outcome used in our model. Because timing of an ICU admission may be an important predictor of death in the ICU,²³ the goal of this study was to easily identify persons with pneumococcal pneumonia who may have benefitted from early admission to an ICU, based on their probability of death or impending respiratory failure. The positive predictive value, sensitivity, or specificity of this model is not significantly different from previous outcome analyses. However, this model provides an improved capacity to distinguish persons with lobar pneumonia who are unlikely to require intensive care, *ie*, negative predictive value of 83%. Persons without signs of respiratory failure or who have only one of three risk factors (excluding nosocomially acquired infection) during the initial clinical evaluation are unlikely to require intensive care.

Although there was a large proportion of adverse outcomes in this sample, this small cohort may limit the validity of the resulting statistical model. In general, logistic modeling maximizes the statistical power to distinguish significant risk factors²⁴ and appears to be biologically valid for many biologic processes. This model should be further tested prospectively in persons with lobar pneumonia with greater emphasis on determining HIV antibody, pneumococcal immunization status, and pneumococcal serotype.

Although nosocomially acquired pneumococcal infection occurred in only 14% of these patients, it was an overwhelming risk factor for adverse outcome and independent of the risk associated with age or preexisting lung disease. Mortality of 67% to 74% associated with nosocomially acquired pneumococcal pneumonia has been reported.^{4,5,25} Although it

can be associated with high mortality, *S pneumoniae* has been a rare cause of nosocomially acquired pneumonia. However, a recent report has suggested that up to 20% of nosocomial pneumonias may be due to pneumococcus.²⁶ The high mortality of nosocomially acquired pneumococcus in this study suggests that pneumococci were more virulent serotypes, *eg*, serotype 3, or more resistant to antibiotics, or that recently infected persons had less nonspecific immunity. The association between multiply resistant pneumococci, virulent serotypes, and hospital-acquired infection has been well described in South Africa and Europe since the mid-1970s.^{27,28} In this study, blood culture isolates were routinely tested for oxacillin resistance using a disk diffusion method; no resistance was noted. Serotyping was not routinely performed and the risk attributable to serotype could not be compared with other risk factors.

Microbiologic isolation of *S pneumoniae* from sputum was associated with a 2.7 times greater risk for adverse outcome while the presence of Gram-positive diplococci on Gram's stain of the sputum was not. Risk may be due to a greater burden of viable pneumococci that results from inadequate nonspecific response to pneumococcal infection such as secretory immunoglobulins to non-serotype-specific cell wall polysaccharide or surfactant protein A. Isolation of pneumococcus from the sputum was not included as a predictive variable because this information is not available during initial patient evaluation.

In this study, mortality for persons with pneumococcal bacteremia is similar to rates described by Austrian and Gold 30 years ago.² Most of these deaths can be attributed to nosocomially acquired infection, two specific host factors (age and preexisting lung disease), and, possibly, inadequate nonspecific host response to pneumococcal infection. These four factors can be modeled to distinguish persons who may benefit from early, intensive care from those who are unlikely to require such care.

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