Articles

Sputum Gram's Stain in Community-Acquired Pneumococcal Pneumonia
A Meta-analysis

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The usefulness of the sputum Gram's stain is controversial. This meta-analysis was designed to evaluate the sensitivity and specificity of the sputum Gram's stain in community-acquired pneumococcal pneumonia. Using a predetermined protocol, articles were discovered through a MEDLINE search (1966 to 1993) and the examination of bibliographies and were graded for quality by three blinded reviewers. Information on the reference standard, blinding, stain interpreter, control for antibiotic use, and definition of a positive test was collected. We found 12 articles containing 17 test characteristics to evaluate. The number of patients in each study ranged from 16 to 404. Sputum culture was the most common reference standard (10 of 17 estimations). Sensitivity ranged from 15% to 100% and specificity from 11% to 100%. Test characteristics varied markedly among studies and appeared related partly to the test interpreter. The sputum Gram's stain may yield misleading results in community-acquired pneumonia, as its sensitivity and specificity vary substantially in different settings. A practitioner electing to use the study should be well trained and use a specific definition for a positive test.

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Pneumonia is the sixth leading cause of death in the United States, accounting for more than 500,000 hospital admissions per year.[1] The case-fatality rate for pneumococcal pneumonia among patients admitted to a hospital was 9% in a recent prospective study[2] and ranges from 4% to 27% in published articles.[2–9]

The sputum Gram's stain is an inexpensive, rapidly performed test that is widely advocated as useful in identifying the etiologic agent in community-acquired pneumonia,[10–12] although the test has been criticized as unreliable.[13] We conducted a meta-analysis of published English-language articles to evaluate the sensitivity and specificity of the sputum Gram's stain in community-acquired pneumococcal pneumonia. We also wanted to determine whether a variation in test characteristics was related to factors such as the stain interpreter, the definition of a positive Gram's stain, or control for antibiotic use before testing.

Methods

Evaluation of Studies

Following a written protocol, we used the MEDLINE computer service to generate a list of relevant articles, using the key words "sputum," "Gram's stain," and "pneumonia." The bibliographies of these articles were searched to discover other pertinent articles. Of a total of 180 articles that were found, 27 compared the sputum Gram's stain with an independent reference standard and were assessed by reviewers (G.S.B., M.J.W., and R.H.G.) blinded to author and journal.[4,9,14–38] Reviewers judged whether articles met criteria for inclusion in the meta-analysis, specifically whether patients had community-acquired pneumonia, whether sputum Gram's stains were compared with an independent reference standard, and whether sufficient information was available to generate a 2×2 table of true-positives, true-negatives, false-positives, and false-negatives. Reviewers also assessed the quality of each study by determining whether inclusion and exclusion criteria were explicit; whether intraobserver and interobserver variability was assessed; the training of the test interpreter; whether the assessment of Gram's stain test characteristics was a specific objective of the study; and the general clarity of the study. In judging quality characteristics, reviewers used their own criteria for scoring.

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Seven articles initially reviewed met criteria for inclusion in the meta-analysis.[17,21,24–26,29,36] We wrote letters to the authors of all 27 articles, requesting raw data and clarification of other issues specified in our protocol, such as whether Gram's stain interpreters were blind to the reference standard results or vice versa and whether sputum was obtained before antibiotic use when such information was not explicitly given in the article. From this correspondence, we gained enough data to calculate sensitivity and specificity for five additional articles,[9,18,27,28,31] giving a total of 12 articles used in our analysis.

Statistics

A summary receiver-operator characteristic (ROC) curve was estimated using the methods proposed by Moses and colleagues.[39] This approach permits the combining of several independent studies of the same diagnostic test, where each study reports an estimated false-positive rate (equal to 1-specificity) and an estimated true-positive rate (sensitivity). The false-positive and true-positive rates are converted to logistic transformations, thereby defining a set of points. A regression line is fitted to the set of points so defined. Finally, the line is back-transformed to the relevant region of the ROC space.

Several studies provided results using different standards[21,26] or interpreters[28] for the same sample of subjects. To avoid overrepresenting one sample of patients when estimating the summary ROC, we used weighted linear regression, with each sample of patients represented equally. The "relevant range" summary ROC curve was calculated by excluding those studies with sensitivity or specificity below 50%. To explore the influence of study blinding, antibiotic use, Gram's stain definition, stain

TABLE 1.—*Characteristics of Studies of Sputum Gram's Stain Included in Analysis*

Reference*	Patients, No.	Purulent Sputum, %†	Reference Standard	Control for Antibiotics?‡	Blinded?§	Definition‖	Interpreter¶	Sensitivity, %	Specificity, %
British Thoracic Society, 1987[9]	404	NA	Combination	No	No	>50% organisms	Lab tech	15	98
Dans et al, 1984[17]	154	NA	Sputum	No	Yes	Unknown	House officer or student	52	88
	147	NA	Sputum	No	Yes	Unknown	House officer or student	63	80
Kalin et al, 1983[18]	71	76	Sputum	Yes	No	>10/oif	ID	84	85
Thorsteinsson et al, 1975[21]	16	NA	Sputum	Yes	No	Unknown	Unknown	100	67
	16	NA	Transtracheal	Yes	No	Unknown	Unknown	100	67
	15	NA	Bronchial	Yes	No	Unknown	Unknown	100	67
Boerner and Zwadyk, 1982[24]	76	92	Sputum	No	Yes	>50% organisms	House officer	94	64
Gleckman et al, 1988[25]	59	NA	Blood	Yes	Yes	>10/oif	Lab tech	69	83
Rein et al, 1978[26]	28	NA	Sputum	Yes	Yes	>50% organisms or >10/oif	Fellow	60	61
	42	NA	Combination	Yes	Yes	>50% organisms or >10/oif	Fellow	62	85
Lentino and Lucks, 1987[27]	40	NA	Sputum	No	Yes	>50% organisms	Fellow	55	94
Merrill et al, 1973[28]	53	NA	Sputum	Yes	Yes	Unknown	House officer or student	96	11
	30	NA	Sputum	Yes	Yes	Unknown	Lab tech	43	88
Xiaoping et al, 1988[29]	95	90	Sputum	No	Yes	>10/oif	Pulmonary	88	85
Lim et al, 1989[31]	40	NA	Combination	Yes	Yes	>50% organisms or >10/oif	Fellow	67	100
Fine et al, 1991[36]	36	47	Combination	No	Yes	>50% organisms	House officer	86	72

NA = not available

*Dans et al[17] included data for 2 distinct studies conducted in different years. Thorsteinsson et al,[21] Rein et al,[26] and Merrill et al[28] used the same patient population for different studies.
†Percentage of patients producing purulent sputum.
‡Yes indicates no antibiotic use before a sputum specimen was collected.
§Yes indicates that stain interpreter was blind to reference standard results.
‖Definition: >10/oif indicates an average of >10 organisms of proper pneumococcal structure per oil-immersion field; >50% organisms indicates that >50% of organisms on slide are of proper pneumococcal structure.
¶Lab tech refers to laboratory technician, student refers to medical student, Fellow indicates infectious disease fellow or attending physician, and Pulmonary refers to pulmonary staff.

TABLE 2.—*Quality Characteristics of Studies in Analysis as Judged by Blinded Reviewers*

Reference*	Inclusion/Exclusion Criteria*	Clarity of Definition†	Intra/Interobserver Variability‡	Interpreter Training§	Objective‖	Overall Clarity
British Thoracic Society, 1987[9]	Fair	Unclear	No	Unclear	Secondary	Fair
Dans et al, 1984[17]	Fair	Unclear	No	Fairly clear	Secondary	Fair
Kalin et al, 1983[18]	Good	Clear	No	Unclear	No	Fair
Thorsteinsson et al, 1975[21]	Fair	Unclear	No	Unclear	Secondary	Fair
Boerner and Zwadyk, 1982[24]	Fair	Fairly clear	No	Clear	Primary	Fair
Gleckman et al, 1988[25]	Fair	Clear	No	Fair	Secondary	Fair
Rein et al, 19782[6]	Fair	Clear	No	Clear	Primary	Good
Lentino and Lucks, 1987[27]	Fair	Clear	No	Unclear	Primary	Fair
Merrill et al, 1973[28]	Fair	Unclear	No	Fair	Secondary	Fair
Xiaoping et al, 1988[29]	Fair	Clear	No	Unclear	Secondary	Fair
Lim et al, 1989[31]	Good	Fairly clear	No	Unclear	No	Fair
Fine et al, 1991[36]	Good	Clear	No	Clear	Primary	Good

*Refers to the clarity of the inclusion and exclusion criteria.
†Refers to the clarity of the definition of a positive sputum Gram's stain result.
‡Refers to the assessment of interobserver and intraobserver variability.
§Refers to the clarity of the description of the training of interpreters of sputum Gram's stain.
‖Assesses whether test characteristics of sputum Gram's stain were primary or secondary objective of the study or not an objective.

interpreter (ranked according to level of training), and study size, we included these variables in the summary ROC model.[39,40] All *P* values are two-sided.

Results

Characteristics of the accepted studies are given in Table 1. Only 4 of 12 articles contained information on the ability of patients to produce purulent sputum, which ranged from 47% to 92%, or 70% overall (399 of 569 patients). All but 4 studies (references 9, 17, 21, and 28) explicitly said that only purulent sputum was used for Gram's staining. Reference standards included sputum culture, culture of transtracheal aspirate, culture of bronchial aspirate, or a combination reference standard in which the result was deemed positive if one or more of several tests were positive. Blood culture was not evaluated as a reference standard because of poor sensitivity, except in one study in which all patients had bacteremia.

Study quality as defined by specific criteria is displayed in Table 2. Determining the performance characteristics was a primary objective in only 4 of the 12 studies. The definition used for a positive Gram's stain was judged to be clear in only 6 of the studies. In none of the studies was there any assessment of intraobserver or interobserver variability regarding the interpretation of Gram's stains.

Three basic definitions were used for a positive Gram's stain: an average of greater than 10 organisms of proper pneumococcal structure per oil-immersion field, greater than 50% of organisms on the slide of proper structure, or when either of these two criteria were met. For 12 of 17 estimations, the interpreters of the Gram's stain were judged blinded to the results of the reference standard. Smears were prepared mostly by technicians and house officers. Interpretation was done by attending physicians or fellows on the infectious disease or pulmonary service, laboratory technicians, house officers, or medical students.

Sensitivity ranged from 15% to 100% and specificity from 11% to 100%. In 7 of the 12 studies, the sputum Gram's stain had a sensitivity of less than 70%, meaning that nearly a third of patients with evidence of pneumococcal pneumonia had a false-negative Gram's stain. Of note, even those studies where an expert—the infectious disease or pulmonary specialist—interpreted the stain, only two of five studies had a sensitivity of 70% or greater. Finally, none of the three studies where the smear was reviewed by a laboratory technician (a likely interpreter in many hospital settings) had a sensitivity greater than 70%. Indeed, the sensitivity in these last three studies was poor: 15%, 43%, and 69%.

Of the four studies that used combination reference standards, three included blood, sputum, and pleural fluid cultures as part of the reference standard,[9,31,36] and two also included pneumococcal antigen in serum, urine, or sputum.[9,31] One used a combination of sputum culture, quellung reaction, and mouse inoculation for its reference standard.[26]

Figure 1 depicts the test characteristics of all studies; a summary ROC curve is shown. In Figure 2, studies are identified by the reference standard. In Figure 3, studies are identified according to the definition of a positive Gram's stain. Studies are classified according to test interpreter in Figure 4. Study size, study blinding, the definition of a positive test, and control for antibiotic use were not statistically related to test characteristics. This result must be interpreted with caution in light of the small number of studies evaluated. There was a trend ($P = .07$) for interpreter level of training to be positively associated with diagnostic accuracy. The only two studies with both sensitivity and specificity greater than 80% used infectious disease or pulmonary specialists as interpreters and a definition of greater than 10 organisms per oil-immersion field.

Discussion

Our results cast considerable doubt on the usefulness of the sputum Gram's stain in community-acquired

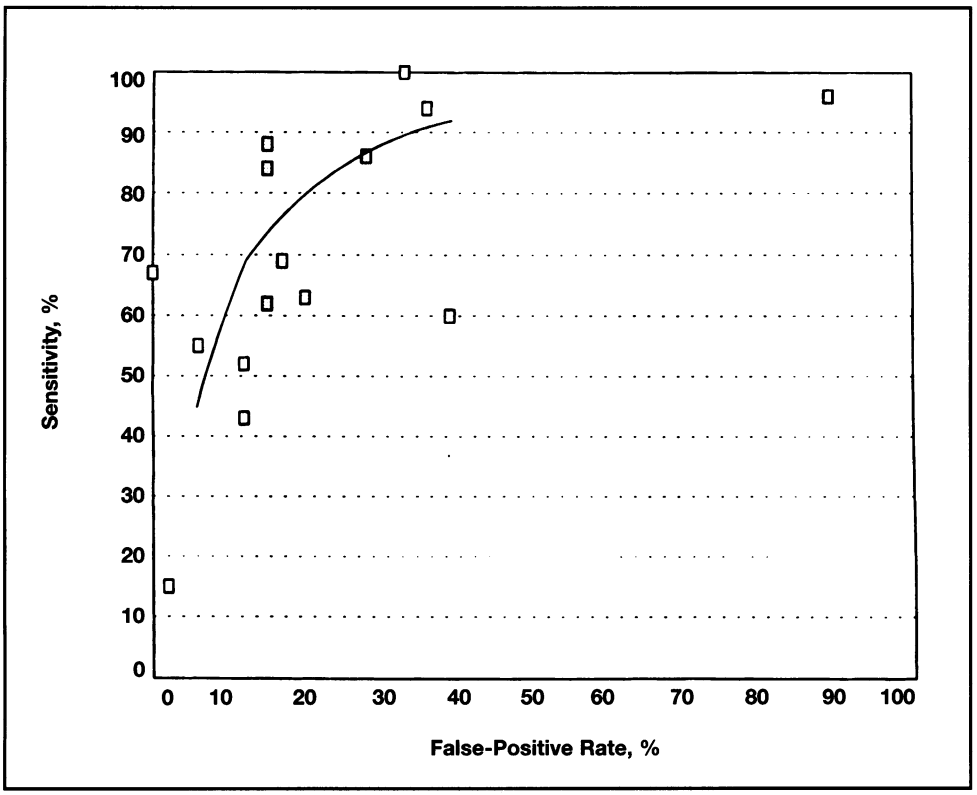

Figure 1.—Test characteristics of all studies with summary receiver-operator characteristic curve are shown.

pneumococcal pneumonia. Nearly a third of the patients were unable to produce adequate sputum—although only four studies reported this information—and there is pronounced variation among the studies in estimated sensitivity and specificity of the sputum Gram's stain. Some variation results from using different thresholds for a positive test. As the definition of a positive test becomes more lenient, sensitivity increases and specificity declines.[41] Not all of the variation in our analysis can be explained by this phenomenon, however, or all points would lie on the summary ROC curve.

Regardless of its source, the variation in sensitivity and specificity noted is likely to be confusing and even hazardous in a clinical setting. To understand the implications of a particular test result, each stain interpreter must determine the sensitivity and specificity for his or her technique of interpretation. Failure to do so could lead, for instance, to serious undertreatment. For example, if an interpreter assumed without confirmation that her Gram's stain interpretation was highly specific for pneumococcal pneumonia, she might treat with penicillin alone, despite the relatively high false-positive rate in many studies. Indeed, among house officers and students, the false-positive rate (equal to 1-specificity) was greater than 20% in four of five studies. It is important to note that our data come from research studies in which the participants generally knew they were being observed. In the setting of a rural emergency department or small urban community clinic, the Gram's stain might have even lower sensitivity and specificity.

The idea that the sputum Gram's stain is simple and inexpensive has probably been overstated. The initial step of obtaining a sputum specimen is often not successful and may lead to wasted efforts by nurses and respiratory therapists. Our data suggest that the level of training may be important for interpreting Gram's staining; thus, the time and expense of expert training is a part of the cost of the test as well. It is important to consider that the average community practitioner in the United States spends an average of 16 minutes per office visit, with 70% of visits lasting 15 minutes or less.[42] The time necessary to do a careful interpretation is not trivial under these conditions. One approach for a clinician under such circumstances might be to request interpretation by a laboratory technician. In the three studies in which the smear was reviewed by a laboratory technician, however, sensitivity was less than 70%.

We have chosen the term "reference standard" rather than "gold standard" because there is no universally accepted gold standard for the sputum Gram's stain. A sputum culture was the most commonly used reference standard in our analysis and has been criticized for lack of both sensitivity and specificity.[13,22,43,44] Blood culture is a reference standard that is highly specific but poorly sensitive compared with an ideal gold standard. In some published studies, sputum cultures were likely to be positive in patients with pneumonia and pneumococcal bacteremia,[3,20,25] whereas other studies have shown a poorer correlation.[18,35,45]

Although the lack of an ideal gold standard for identi-

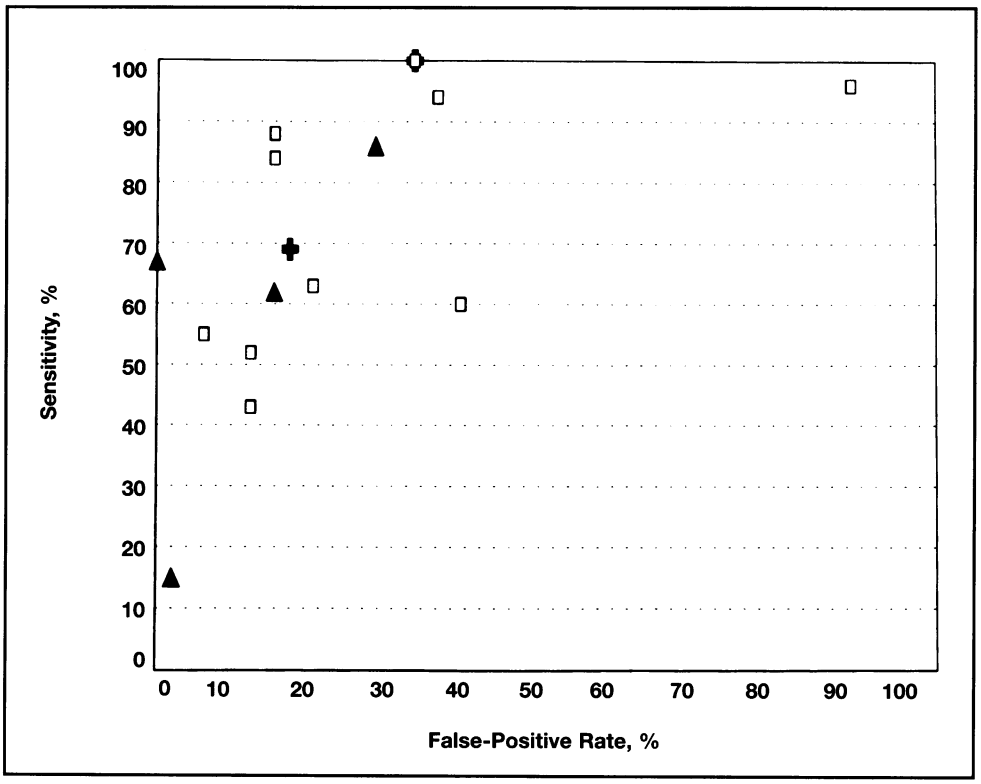

Figure 2.—Test characteristics are shown of studies identified by the reference standard. □ = sputum culture, ▲ = combination of tests (see Table 1), ✚ = other (blood culture, transtracheal aspirate culture, bronchial aspirate culture).

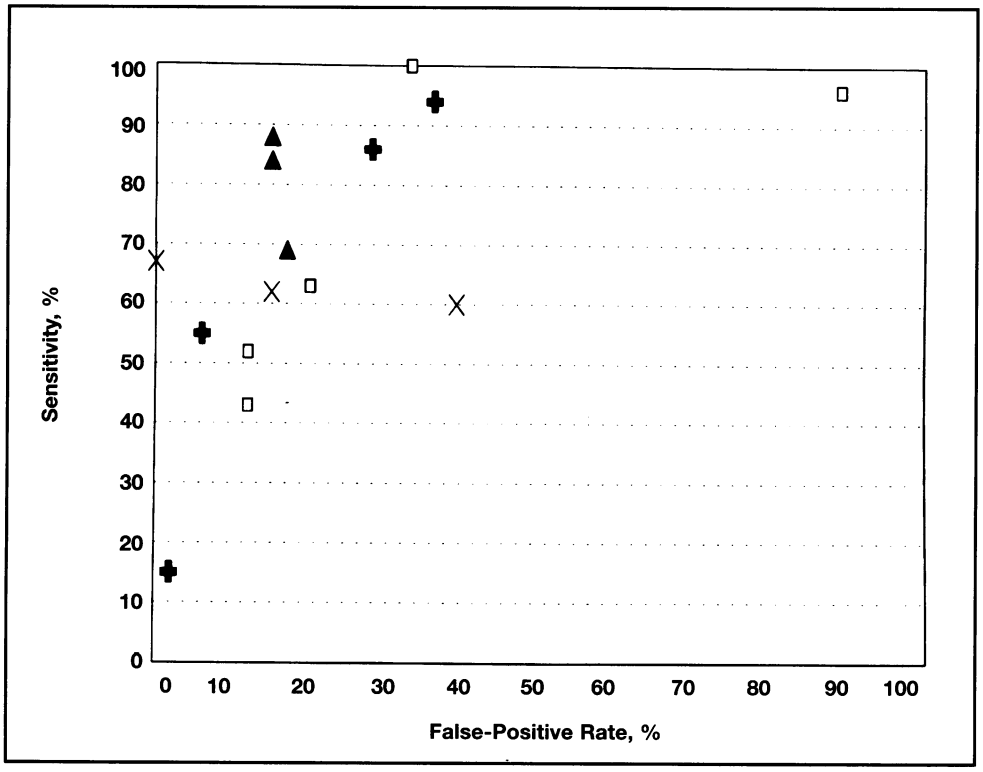

Figure 3.—Test characteristics are shown of studies identified by the definition of a positive Gram's stain. ▲ = >10 organisms/oil-immersion field, ✚ = >50% of organisms/oil-immersion field, × = >10/oil-immersion field or >50% (see Table 1), □ = unknown.

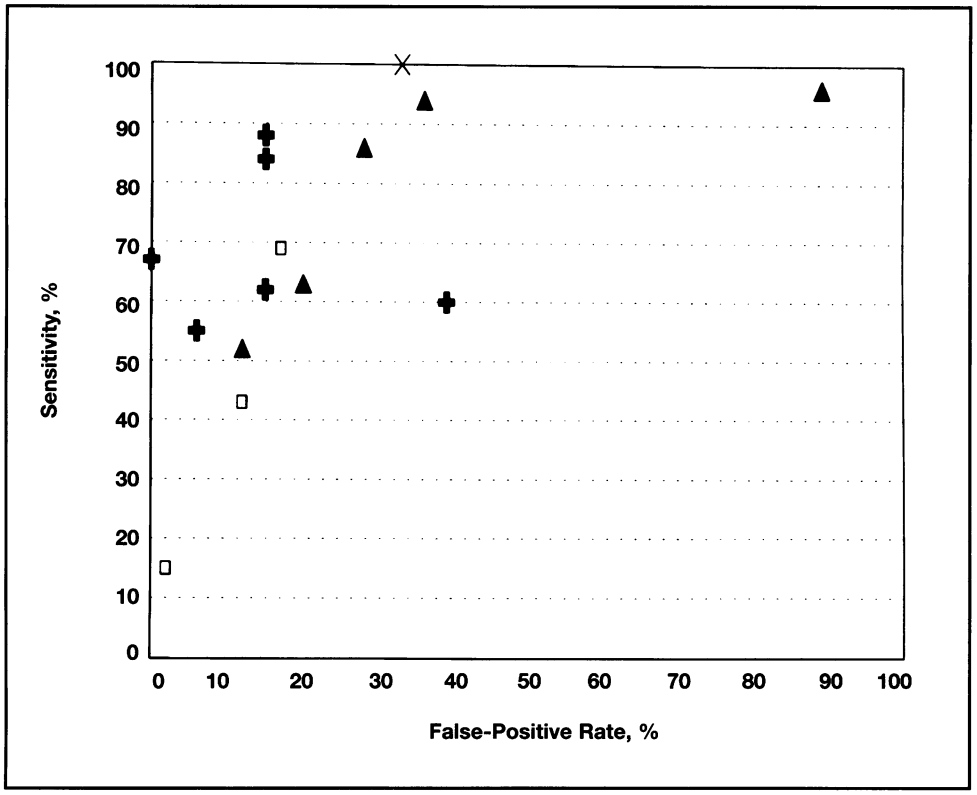

Figure 4.—Test characteristics are shown of studies identified by the interpreter of the Gram's stain. ✚ = infectious disease or pulmonary service staff or fellow, ▲ = house officer or medical student, □ = laboratory technician, × = unknown.

fying the etiologic agent in pneumonia complicates the interpretation of our results, it should be noted that the Gram's stain fared no better in the seven estimations that used reference standards other than a sputum culture. Some studies in our analysis used a combination reference standard.[9,26,30,31] For these studies, we have considered a positive result to exist when any of the components of the combination standard are positive. This approach should produce high sensitivity and low specificity, but this prediction is not borne out by our analysis. Two of these studies used the pneumococcal antigen test.[9,31] When an imperfect reference standard is used, the perceived sensitivity and specificity of the diagnostic test may be either better or worse than the actual test characteristics, depending on whether the test and the reference standard both misclassify the same patients.[46] There are not sufficient data on this issue to determine whether the test characteristics in the studies we analyzed would have been better or worse when compared with an ideal gold standard.

The studies analyzed in this review differed considerably in specific quality criteria, as shown in Tables 1 and 2. Whereas some studies had the estimation of the test characteristics of the sputum Gram's stain as a primary objective, other studies were primarily concerned with evaluating the cause of pneumonia or with the characteristics of a different test, such as the quellung reaction or pneumococcal antigen. All studies were prospective except for one that was a retrospective chart review.[17] By contacting the authors of these studies, we were able to evaluate raw data and to clarify specific questions related to our protocol. In some instances, this allowed us to include studies that would have been otherwise excluded. Because we had specific criteria for including studies and because our questions for the authors came from an a priori protocol, we think that our approach reduced publication bias and led to more accurate assessments of the characteristics of the studies analyzed. We did not search for unpublished studies, which is a possible source of bias in our analysis, but the results of such studies would be unlikely to alter our finding of pronounced variation of test characteristics for the sputum Gram's stain in different settings.

Guidelines for the conduct of a meta-analysis evaluating a diagnostic test have been published and were used in the design of our analysis.[40] This form of meta-analysis emphasizes the use of graphic displays to help explain the variability in study results. Unlike a meta-analysis of clinical therapeutic trials, a single summary statistic of results is often not appropriate in this type of meta-analysis. Instead, the summary ROC curve is used to describe how sensitivity and specificity would vary in relation to one another as a result of combining independent studies.

We recommend that practitioners who elect to use this test to guide therapy be taught a specific definition for a positive Gram's stain; an average of greater than 10

organisms of the proper pneumococcal structure per oil-immersion microscopic field in purulent sputum may be a reasonable choice. Competence not only at recognizing specific bacterial types but at adhering to a specific definition should be tested. For an individual patient, the pretest likelihood of pneumococcal pneumonia being present should be estimated whenever possible to aid interpretation of the Gram's stain result. Grading tests as weakly or strongly positive may also improve diagnostic accuracy—for example, defining greater than 20 organisms per oil-immersion field for a strongly positive test. Although its limitations in community-acquired pneumococcal pneumonia have been discussed, we have not assessed other special situations in which the sputum Gram's stain may prove to be helpful. The studies reviewed do not allow an assessment of the likelihood of "atypical" pneumonia or noninfectious lung disease in the presence of a properly done and reviewed Gram's stain that fails to reveal bacteria. Also not addressed is the use of the Gram's stain to detect organisms such as *Nocardia* species; *Haemophilus influenzae*, which may mimic *Pneumocystis carinii* in human immunodeficiency virus disease; and *Staphylococcus aureus* in nonresponding pneumonitis. The finding of these organisms may specifically alter therapy.

Conclusion

No single estimation of sensitivity and specificity can be made regarding the sputum Gram's stain in community-acquired pneumococcal pneumonia. Test characteristics vary dramatically depending on several factors. Thus, the sputum Gram's stain may be misleading, and its use may even be hazardous, especially if its interpreter is not well trained according to specific guidelines. Further studies may help clarify the role of the sputum Gram's stain in community-acquired pneumonia.

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Transubstantiation

Morning and a gray day wrapped
in rain and fog and Punxatawney Phil
saw six more weeks of winter.

Mr. Kelly has tapped out at eighty-three.

I started sad then hummed a bar
and shuffle-stepped across the floor
splashing puddles in my head.
My white socks spun just like Gene
who made it seem so easy
that even I could dance.

He played his ode to joy in Technicolor
radiant as stained glass. Gene Kelly's smile
beneath a downpour transmuted dance and song
and made a blessing out of rain.

CATHERINE CLARK-SAYLES
Mill Valley, California