Prospective Study of the Usefulness of Sputum Gram Stain in the Initial Approach to Community-Acquired Pneumonia Requiring Hospitalization

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From February 1995 through May 1997, we prospectively studied 533 patients with community-acquired pneumonia requiring hospitalization in order to assess the current usefulness of sputum Gram stain in guiding the etiologic diagnosis and initial antibiotic therapy when applied routinely. Sputum samples of good quality were obtained in 210 (39%) patients, 175 of whom showed a predominant morphotype. Sensitivity and specificity of Gram stain for the diagnosis of pneumococcal pneumonia were 57% and 97%, respectively; the corresponding values for *Haemophilus influenzae* pneumonia were 82% and 99%. Patients with a predominant morphotype were more frequently treated with monotherapy than were patients without a demonstrative sputum sample (89% vs. 75%; $P < .001$). Analysis of our data shows that a good-quality sputum sample can be obtained from a substantial number of patients with community-acquired pneumonia. Gram stain was highly specific for the diagnosis of pneumococcal and *H. influenzae* pneumonia and may be useful in guiding pathogen-oriented antimicrobial therapy.

The usefulness of sputum Gram stain in the initial approach to a patient with community-acquired pneumonia (CAP) is still controversial. Data from previous studies that vouch for its utility have also shown a limited sensitivity, but data also have shown a specificity of >80% for the diagnosis of pneumococcal pneumonia [1–5]. However, some authorities feel that there is no strong evidence in favor of its everyday use in diagnosing CAP. Indeed, although the Infectious Diseases Society of America guidelines recommend Gram staining of expectorated sputum for patients requiring hospitalization, the American Thoracic Society does not [6, 7].

We conducted a prospective study on hospitalized patients with CAP in order to assess the current usefulness of the sputum Gram stain in guiding the etiologic diagnosis and initial antibiotic therapy of CAP when applied on a routine basis.

Methods

Setting and study design. The study was conducted at Bellvitge Hospital, a 1000-bed university hospital for adult patients in Barcelona, Spain, which provides service to an area of 1,100,000 inhabitants. One hundred thousand patients are seen yearly in the hospital's emergency department; of this figure, 12,000 are admitted to the hospital every year, accounting for around 50% of the total hospital admissions. From February 1995 through May 1997, we prospectively studied all nonimmunosuppressed patients with CAP admitted to our institution. Patients with neutropenia ($< 1.0 \times 10^9$ granulocytes/L), acquired immune deficiency syndrome, and transplantation were not included in the study. A tutorial intervention was carried out before beginning the study to encourage emergency room physicians to collect sputum samples for Gram stain and culture. The study was prospective, longitudinal, and observational.

Sputum studies. Sputum specimens were usually collected under the supervision of a resident or nurse before antibiotic therapy was begun. Specimens were sent to the laboratory and processed immediately. No special procedures were performed to obtain sputum samples if they could not be obtained spontaneously. A Gram stain was performed on a purulent portion of each sputum specimen and examined by trained personnel. The slides were evaluated for quality under low power (×10). Salivary contamination was detected by noting the presence of squamous epithelial cells, and purulence was determined by noting the presence of polymorphonuclear cells. Sputum samples were considered of good quality if they had <10 squamous cells and >25 leukocytes per low-power field. Otherwise, the sputum sample was considered contaminated by saliva and rejected. Good-quality specimens were then screened for a predominant bacterial morphological type at oil immersion field (×100). A predominant morphotype was defined as the presence of a single morphotype that accounted for >75% of the organisms seen. Sputum cultures were processed immediately in blood agar, chocolate agar, and MacConkey agar media. Isolation of *Legionella pneumophila* was also attempted by use of buffered charcoal-yeast extract medium in selected cases.

Microbiological studies. At the initial evaluation of the patients, before therapy was begun, 2 sets of blood cultures were

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drawn. Paired serum samples from the acute and convalescent phases of illness (with intervals of 3–8 weeks) were obtained for serological studies. Standard serological methods were used to determine antibodies against the following pathogens: *Mycoplasma pneumoniae* (indirect agglutination), *Chlamydia psittaci* (immunofluorescence [IF]), *Chlamydia pneumoniae* (micro-IF), *Coxiella burnetii* (IF), *L. pneumophila* (serogroups 1–6) (enzyme immunoassay [EIA]), respiratory syncytial virus (EIA), parainfluenza 3 virus (EIA), and influenza A virus (EIA). The *L. pneumophila* serogroup I antigen in urine was detected by an immunoenzymatic commercial method (*Legionella* Urinary Antigen, Binax, Portland, ME). Latex agglutination and PCR detection of *S. pneumoniae* was performed in transthoracic needle aspiration samples as described elsewhere [8].

Definitions. CAP was defined as an acute respiratory illness associated with ⩾1 of the following plus the presence of a new infiltrate on a chest radiograph: fever or hypothermia, cough, sputum production, pleuritic chest pain, dyspnea, and altered breath sounds on auscultation. All patients fulfilled at least one of the following criteria for hospitalization: age (⩾70 years; $Pao_2 < 60$ mm Hg or $Pao_2/Fio_2 < 300$; multilobar radiological involvement; hypotension or shock; and underlying disease such as alcoholism, chronic obstructive pulmonary disease, congestive heart failure, renal failure, chronic liver disease, splenectomy, or diabetes mellitus.

Etiologic diagnosis of CAP was considered definitive when there was isolation of a respiratory pathogen from a normally sterile specimen; isolation of *L. pneumophila* or *Mycobacterium tuberculosis* from sputum; detection of pneumococcal antigens by latex agglutination or pneumococcal DNA by polymerase chain reaction in pleural fluid or transthoracic needle aspiration specimens; detection of *L. pneumophila* serogroup 1 antigen in urine; or 4-fold increase in the antibody titer or seroconversion for the above-mentioned pathogens. Etiologic diagnosis was considered presumptive when a predominant microorganism was isolated from sputum samples of good quality. Presumptive aspiration pneumonia was diagnosed on clinical and radiological bases in patients with specific risk factors. The remaining cases were considered as pneumonia of unknown etiology.

The Pneumonia Outcome Research Team (PORT) risk class was calculated as described elsewhere [9].

Antibiotic therapy and assessment of evolution. Antibiotic therapy was administered in the emergency room after Gram stain results, when available, were assessed and according to the hospital guidelines, which recommended the administration of a β-lactam (amoxicillin-clavulanate or ceftriaxone) with or without erythromycin. Emergency room physicians were advised to administer single β-lactam therapy if they suspected bacterial pneumonia and analysis of the Gram stain of expectorated sputum showed a single predominant morphotype.

All patients were seen daily by one of the investigators, who completed a previously defined computer-assisted protocol and provided medical advice when indicated. A long-term follow-up visit was performed ~1 month after discharge.

Statistical methods. The final diagnosis of cases, as described above, was used as the standard for determining sputum Gram stain diagnostic usefulness in terms of sensitivity, specificity, and positive and negative predictive values. For the purposes of calculation, cases of mixed infections involving *Streptococcus pneumoniae* or *Haemophilus influenzae* were considered as pneumococcal or *H. influenzae* pneumonia, and cases with pneumonia of unknown origin were excluded. Cases without a sputum sample or with a sputum sample of poor quality were classified as false negative. Subanalyses of cases with definitive diagnoses were also performed.

Comparisons of proportions were performed by a χ^2 test with continuity correction, when appropriate. Significance was defined as $P < .05$ by a 2-sided test.

Results

Over the study period, a total of 533 nonimmunosuppressed adult patients with CAP were admitted to our institution: 371 men and 162 women (mean age, 64 years; range, 16–96 years). Three hundred fifty-eight patients (67%) had underlying diseases, mainly chronic obstructive pulmonary disease (122 patients), diabetes mellitus (84), ischemic heart disease (46), chronic liver disease (34), and congestive heart failure (29). PORT risk class stratification was as follows: class I, 51 patients; class II, 62; class III, 117; class IV, 198; and class V, 105. A total of 148 patients (27%) had received antibiotic therapy before hospitalization. Radiographic findings were as follows: lobar (53%), multilobar (33%), segmental (13%), and interstitial (1%). Cavitation was observed in 15 patients (3%) and pleural involvement in 107 (20%).

As shown in figure 1, sputum was processed for Gram stain in 343 (64%) of 533 cases. A total of 210 (39%) of 533 samples was considered of good quality, 175 (83%) of 210 showed a predominant morphotype, 9 (4%) presented polymorphonuclear leukocytes but no microorganisms; and mixed flora was observed in 26 (12%). A good-quality specimen showing a predominant morphotype was less frequently obtained from patients who had received antibiotics previously than from those who had not (38 [25%] of 148 versus 137 [36%] of 385; $P = .029$; 95% confidence interval [CI] of the difference, –18% to –4%).

Table 1 details the microbiological studies carried out in the 533 patients. Overall, there were 283 (55%) patients in whom an etiologic diagnosis was established. The diagnosis was classified as definitive in 170 (60%) of 283 cases and presumptive in 113 cases. Results of sputum Gram stain according to the etiologic diagnosis are provided in table 2. The majority of specimens showing a predominant morphotype (71%) were from patients with pneumonia due to classical bacterial pathogens, *S. pneumoniae, H. influenzae,* and gram-negative bacilli. Patients with atypical or *Legionella* pneumonia often did not produce sputum (50% and 37%, respectively), or, when present, it was frequently considered of poor quality (33% and 54%, respectively).

Table 3 shows the diagnostic usefulness of sputum Gram stain for pneumococcal and *H. influenzae* pneumonia in terms of sensitivity and specificity. A Gram stain showing gram-pos-

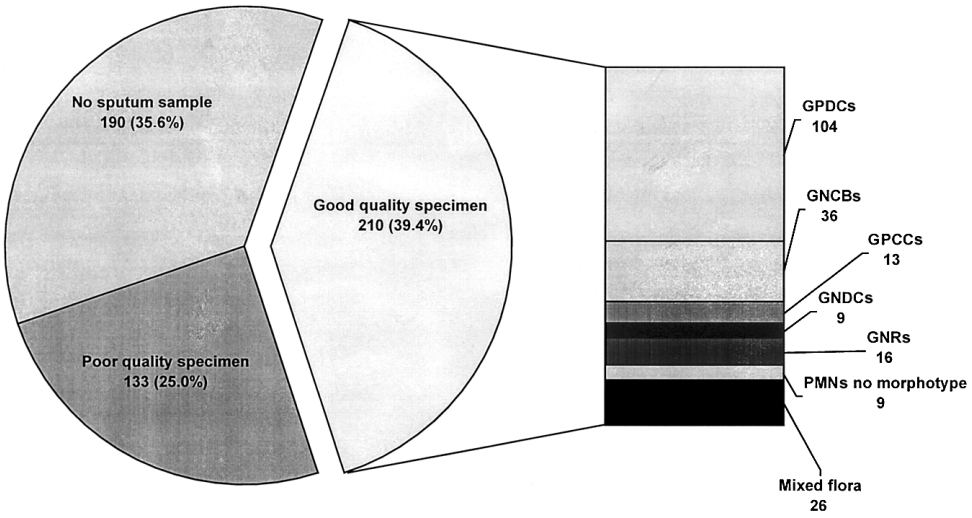

Figure 1. Results of sputum Gram stain in 533 patients hospitalized for community-acquired pneumonia. GPDCs, gram-positive diplococci; GNCBs, gram-negative coccobacilli; GPCCs, gram-positive cocci in chains; GNDCs, gram-negative diplococci; GNRs, gram-negative rods; PMNs, polymorphonuclear leukocytes.

itive diplococci was highly specific for pneumococcal pneumonia, when considering both all patients (97%) and only patients in whom a definitive diagnosis was established (97%). The sensitivity of the Gram stain for the diagnosis of bacteremic pneumococcal pneumonia was 34%, and the specificity was 100%. As regards *H. influenzae* pneumonia, sputum Gram stain showing gram-negative coccobacilli was also highly specific (99%).

Initial antibiotic therapy according to findings in sputum Gram stain and further modifications are detailed in figure 2. Patients in whom the sputum Gram stain showed a predominant morphotype were more often treated initially with a single antimicrobial agent than were patients without a demonstrative sputum (155 [89%] of 175 versus 269 [75%] of 358; $P < .001$; 95% CI of the difference, +7% to +19%). No significant differences were found in rates of modification of therapy when comparing patients with a predominant morphotype who were initially treated with a single agent and patients without a demonstrative sputum who received empirical monotherapy (13 [8%] of 155 versus 32 [12%] of 269; $P = .30$; 95% CI of the difference, –9.3% to +2.3%).

Ninety-nine (95%) of 104 patients with specimens showing gram-positive diplococci were initially treated with a single agent (93 patients received β-lactams, 4 macrolides, and 1 vancomycin). In 3 patients (3%), initial therapy was further modified (allergy, 1 patient; pneumococcal purulent pericarditis, 1; and nosocomial infection, 1). Thirty of 36 patients with samples showing gram-negative coccobacilli were given initial monotherapy, all of them with β-lactams. No further modifications were made in this group of patients.

Overall, 12 patients had mixed "typical + atypical" infection. Gram-stain–oriented therapy with β-lactams was administered in 8 (67%) of 12, and all of them were cured without further modifications of initial therapy.

Discussion

The usefulness of sputum Gram stain in the initial management of CAP is still a matter of controversy. Arguments against its use include the low yield cited in many reports, the belief that performing adequate sputum studies on a routine daily basis is a difficult task, and the low cost-effectiveness.

In our view, the low yield of sputum Gram stain may have been overestimated because of its indiscriminate use in patients without clinical or radiological evidence of pneumonia [10, 11]. However, in our series, in which all patients had a proven pneumonia, the sensitivity of sputum Gram stain for diagnosis of pneumococcal and *H. influenzae* pneumonia was also low. The major cause was the impossibility of obtaining a purulent sample, basically because of the absence of expectoration. An im-

Table 1. Microbiological studies performed in 533 patients with community-acquired pneumonia that required hospitalization.

Microbiological studies	No. performed	Percentage
Blood cultures	519	97.4
Sputum Gram stain	343	64.3
Sputum cultures[a]	242	45.4
Paired serologies[b]	378	77.9
Transthoracic needle aspiration	95	17.8
Legionella urinary antigen detection	87	16.3
Pleural fluid culture	34	6.4
Protected specimen brush	13	2.4

[a] The sputum cultures include the culture of *Legionella pneumophila* in selective media in samples that did not fulfill our quality criteria.

[b] The paired serologies were calculated for 485 patients who survived more than 3 weeks.

Table 2. Final diagnosis of results of the sputum Gram stain in 533 patients with community-acquired pneumonia.

Final diagnosis	No. of cases	No. of samples	Gram stain				
			PQS	GPDCs	GNCBs	GNRs	Other
Streptococcus pneumoniae[a]	135	25	21	77	—	—	12
Definitive diagnosis	82	25	21	29	—	—	7
Legionella pneumophila	35	13	19	—	—	1	2
Haemophilus influenzae[b]	34	2	—	—	28	2	2
Definitive diagnosis	7	2	—	—	3	1	1
Aspiration pneumonia	28	10	5	2	1	1	9
Atypical agents[c]	24	12	8	1	1	—	1
Virus[c]	10	8	1	1	—	—	—
Gram-negative bacilli[c]	9	2	1	—	—	6	—
Miscellaneous[c]	13	5	3	—	—	—	5
Unknown origin	250	114	75	23	5	6	26
Total[d]	533[d]	190	133	104	36	16	57

NOTE. For the purposes of calculation, patients with mixed infections involving *S. pneumoniae* or *H. influenzae* were considered to have pneumococcal or *H. influenzae* pneumonia, and patients with pneumonia of unknown origin were excluded. Cases of pneumonia without sputum sample or with sputum samples of poor quality were classified as false negative. GNCBs, gram-negative coccobacilli; GNRs, gram-negative rods; GPDCs, gram-positive diplococci; PQS, poor-quality specimen.

[a] Includes 15 patients with mixed infections with *S. pneumoniae* (atypical agents, 9; *H. influenzae,* 4; and *Moraxella catarrhalis,* 2).

[b] Includes 8 patients with mixed infections with *H. influenzae* (*S. pneumoniae,* 4; virus, 2; atypical agents, 1; and *Pseudomonas aeruginosa,* 1).

[c] Mixed infections not included.

[d] Sum is more than 533 because of mixed infections.

portant difference from previous studies is that cases without a purulent sputum sample were considered false negative for calculation purposes, significantly lowering the sensitivity of the technique. We think this is the proper way to evaluate sensitivity of the sputum Gram stain when used on a routine basis. On the other hand, when a purulent sample was available, the Gram stain gave a presumptive diagnosis in 175 (80%) of 210 of cases, mostly in patients who had not been treated with antibiotics before admission.

Previous studies, mostly performed in the 1970s and 1980s, did not permit a precise definition of sensitivity and specificity values because of methodological limitations such as the small number of patients enrolled [4, 5, 12, 13], retrospective design [3, 14, 15], the fact that data were based on sputum samples reaching the laboratory [5, 16], and the lack of extensive microbiological studies [5, 12, 15, 17]. In this study, we analyzed a large series of patients with CAP, including those with definitive or presumptive diagnoses or with no etiologic diagnosis, and we also analyzed whether or not sputum samples could be collected. This approach allowed us to perform a more precise calculation of sensitivity and specificity values, providing a current assessment of the sputum Gram stain in everyday medical practice.

In our study, sputum stain showing gram-positive diplococci was highly specific for pneumococcal pneumonia and a useful tool for clinicians in their management of these patients. Interestingly, >95% of patients in whom a characteristic sputum was observed were treated initially with monotherapy. An additional benefit of the Gram stain findings is their assistance in the later interpretation of sputum culture [14, 18]. Today, because multiple-antibiotic–resistant pneumococci are on the increase worldwide, knowing whether *S. pneumoniae* is the cause of the pneumonia and susceptibility testing may have significant implications for antibiotic therapy [19, 20].

Table 3. Clinical usefulness of sputum Gram stain for pneumococcal and *Haemophilus influenzae* pneumonia in 533 patients with community-acquired pneumonia that required hospitalization.

Variable	Definitive and presumptive diagnosis (n = 283)		Definitive diagnosis (n = 170)	
	Pneumococcal pneumonia	*H. influenzae* pneumonia	Pneumococcal pneumonia	*H. influenzae* pneumonia
Sensitivity	57.0	82.3	35.4	42.8
Specificity	97.3	99.2	96.7	99.4
Positive predictive value	95.1	93.3	90.6	75.0
Negative predictive value	71.3	97.6	62.7	98.2

NOTE. Data are percentages. Overall, 135 patients had a final diagnosis of pneumonococcal pneumonia, of which 82 were classified as definitive, and 34 patients had a final diagnosis of *H. influenzae* pneumonia, of which 7 were classified as definitive.

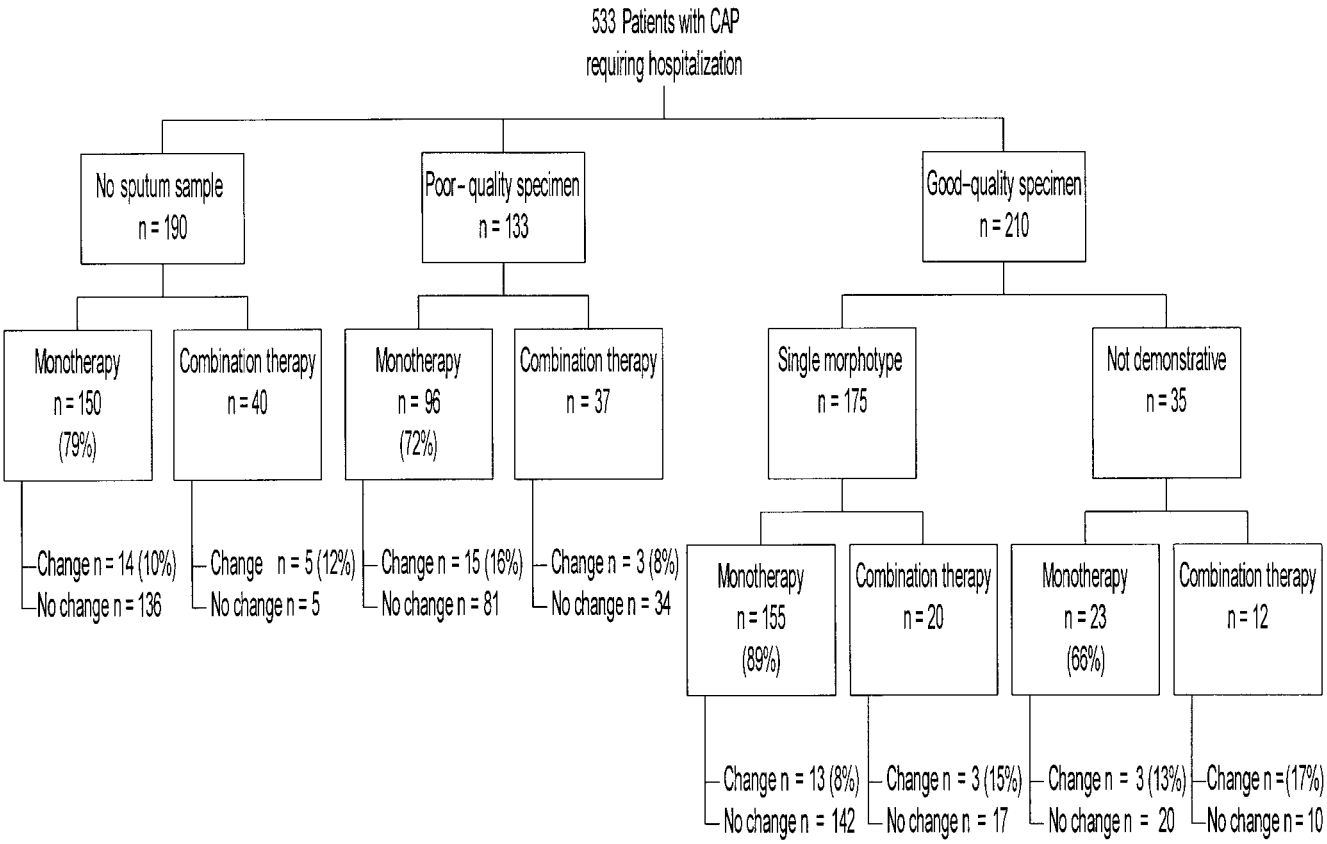

Figure 2. Empirical antibiotic therapy and further modifications in 533 patients with community-acquired pneumonia requiring hospitalization according to the results of Gram stain of sputum.

Sputum studies increased the number of *H. influenzae* pneumonia diagnoses in our series, particularly taking into account that *H. influenzae* bacteremia is infrequent. To date, the value of sputum Gram stain for the diagnosis of *H. influenzae* pneumonia has not been precisely defined; very few studies have evaluated its utility, and the design of these studies has not allowed calculation of specificity [1, 15, 21]. Our study shows that a sputum Gram stain showing gram-negative coccobacilli is highly specific for *H. influenzae* pneumonia. In fact, only 2 of 36 patients in whom gram-negative coccobacilli were observed in the Gram stain had pneumonia caused by other microorganisms. The early recognition of *H. influenzae* as the cause of the pneumonia also has implications for the choice of empirical antibiotic therapy because β-lactamase production is frequent and the activity of some macrolides is not adequate [22].

Significantly, sputum staining was highly sensitive for gram-negative pneumonia. Although infrequent, gram-negative pneumonia is associated with a high mortality rate, especially in patients not receiving adequate initial antibiotic therapy. Therefore, its early identification is particularly important [23].

A distinct case is that of mixed "typical + atypical" infections, especially when regarding the utility of the Gram stain to specifically tailor therapy. To date, the clinical significance of the second pathogen, especially considering that the diagnosis is nearly always confirmed later by serological data, is still unknown. It is not clear whether these agents act as co-pathogens or as predisposing factors in CAP. In our series, most patients who later were shown to have mixed infections had a definitive diagnosis of the bacterial agent, and many of them received Gram stain–oriented monotherapy with β-lactams. All of them were cured without modification of initial therapy. Therefore, we believe that there is no rationale to broaden the spectrum of antibiotic therapy in the presence of a presumptive pathogen in the sputum Gram stain.

The difficulty involved in the collection, transport, and processing of purulent samples in clinical practice has also been a major issue. It is clear that the impossibility of obtaining a sputum sample should not delay antibiotic therapy. In this regard, our study provides a practical example of the feasibility of the sputum Gram stain when used on a routine basis, because it was carried out over a long time in a busy emergency room, and good-quality samples were obtained from many patients.

Another argument against sputum Gram stain has been the

lack of documentation of its value in terms of cost or outcomes. Although our study was not specifically designed to evaluate cost-effectiveness, analysis of our data suggests that Gram stain may be useful in narrowing the spectrum of empirical antimicrobial therapy, which may result in a lower cost therapy [24].

In summary, a good-quality sputum sample can be obtained in a substantial number of patients with CAP. Gram staining is highly specific for the diagnosis of pneumococcal and *H. influenzae* pneumonia and may be useful in guiding pathogen-oriented antimicrobial therapy. From a clinical perspective, this information appears to be of great value for physicians caring for patients with CAP.

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References

1. Gleckman R, DeVita J, Hibert D, Pelleiter C, Martin R. Sputum Gram stain assessment in community-acquired bacteremic pneumonia. J Clin Microbiol **1988**; 26:846–9.
2. Bohte R, Hermans J, van den Broek PJ. Early recognition of *Streptococcus pneumoniae* in patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis **1996**; 15:201–5.
3. Dans PE, Charache P, Fahey M, Otter SE. Management of pneumonia in the prospective payment era: a need for more clinician and support service interaction. Arch Intern Med **1984**; 144:1392–7.
4. Rein MF, Gwaltney JM, O'Brien WM, Jennings RH, Mandell GL. Accuracy of Gram's stain in identifying pneumococci in sputum. JAMA **1978**; 239: 2671–3.
5. Schmid RE, Anhalt JP, Wold AD, Keys TF, Washington JA II. Sputum counterimmunoelectrophoresis in the diagnosis of pneumococcal pneumonia. Am Rev Respir Dis **1979**; 119:345–8.
6. Barlett JG, Breiman RF, Mandell LA, File TM. Community-acquired pneumonia in adults: guidelines for management. Clin Infect Dis **1998**; 26: 811–38.
7. The ATS Board of Directors. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Respir Dis **1993**; 148:1418–26.
8. García A, Rosón B, Pérez JL, et al. Usefulness of PCR and antigen latex agglutination test with samples obtained by transthoracic needle aspiration for diagnosis of pneumococcal pneumonia. J Clin Microbiol **1999**; 37:709–14.
9. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med **1997**; 336: 243–50.
10. Lentino JR, Lucks DA. Nonvalue of sputum culture in the management of lower respiratory tract infections. J Clin Microbiol **1987**; 25:758–62.
11. Reimer LG, Carrol KC. Role of the microbiology laboratory in the diagnosis of lower respiratory tract infections. Clin Infect Dis **1998**; 26:742–8.
12. Thorsteinsson SB, Musher DM, Fagan T. The diagnostic value of sputum culture in acute pneumonia. JAMA **1975**; 233:894–5.
13. Boerner DF, Zwadyk P. The value of sputum Gram's stain in community-acquired pneumonia. JAMA **1982**; 247:642–5.
14. Drew WL. Value of sputum culture in the diagnosis of pneumococcal pneumonia. J Clin Microbiol **1977**; 6:62–5.
15. Watanakunakorn C, Bailey TA. Adult bacteremic pneumococcal pneumonia in a community teaching hospital. A detailed analysis of 108 cases. Arch Intern Med **1997**; 157:1965–71.
16. Guckian JC, Christensen WD. Quantitative culture and Gram stain of sputum in pneumonia. Am Rev Respir Dis **1978**; 118:997–1005.
17. Geckler RW, Gremillion DH, McAllister CK, Ellenbogen C. Microscopic and bacteriological comparison of paired sputa and transtracheal aspirates. J Clin Microbiol **1977**; 6:396–9.
18. Skerret SJ. Diagnostic testing to establish a microbial cause is helpful in the management of community-acquired pneumonia. Semin Respir Infect **1997**; 12:308–21.
19. Liñares J, Pallares R, Alonso T, et al. Trends in antimicrobial resistance of clinical isolates of *Streptococcus pneumoniae* in Bellvitge Hospital, Barcelona, Spain (1979–1990). Clin Infect Dis **1992**; 15:99–105.
20. Thornsberry C, Ogilvie P, Kahn J, Mauriz Y. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* in the United States in 1996–1997 respiratory season. The Laboratory Investigator Group. Diagn Microbiol Infect Dis **1997**; 29:249–57.
21. Wallace RJ, Musher DM, Martin RR. *Haemophilus influenzae* pneumonia in adults. Am J Med **1978**; 64:87–93.
22. Berry V, Thornburn CE, Knott SJ, Woodnutt G. Bacteriological efficacies of three macrolides compared with those of amoxicillin-clavulanate against *Streptococcus pneumoniae* and *Haemophilus influenzae.* Antimicrob Agents Chemother **1998**; 42:3193–9.
23. Ruiz M, Ewig S, Torres A, et al. Severe community-acquired pneumonia: risk factors and follow up epidemiology. Am J Respir Crit Care Med **1999**; 160:923–9.
24. Gilbert K, Gleason PP, Singer DE, et al. Variations in antimicrobial use and cost in more than 2,000 patients with community-acquired pneumonia. Am J Med **1998**; 104:17–27.