JOURNAL OF CLINICAL MICROBIOLOGY, May 1995, p. 1141–1144 Vol. 33, No. 5
0095-1137/95/$04.00+0

Quality Assurance Study of Bacterial Antigen Testing of Cerebrospinal Fluid

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Received 17 October 1994/Returned for modification 1 December 1994/Accepted 2 February 1995

Bacterial antigen testing (BAT) of cerebrospinal fluid (CSF) by latex agglutination is a low-yield procedure in patients whose CSF specimens have normal laboratory parameters. Between August 1992 and August 1994, we evaluated 287 bacterial antigen (BA) test requests to determine whether yields could be improved and whether patient costs could be reduced by canceling BAT for those patients with normal CSF parameters (cell count, protein, glucose) after consultation with physicians. A total of 171 (68%) BA tests were canceled by this approach. None of these CSF specimens was culture positive for an organism detectable by BAT. Of the remaining 116 CSF specimens tested, only 3 were positive by BAT, one each for *Neisseria meningitidis*, *Streptococcus pneumoniae*, and group B streptococcus. Only 43 of the CSF specimens tested had at least two abnormal parameters; the 3 positive CSF specimens were included in this group. In light of the low rate of positivity, the number of BA tests can be further reduced by establishing criteria that must be met before a CSF specimen is accepted for BAT. After review of our data and the literature concerning this topic, we concluded that only specimens with leukocyte counts of ≥50 cells per mm^3 should be tested. Of 287 specimens evaluated in our study, only 36 met this criterion, including the 3 BA-positive specimens. Enacting such a restriction would have reduced the total number of BA tests by 251 (87%) without compromising patient care. A laboratory cost savings of $6,500 per year would have been realized, with a substantial reduction in the cost per positive test. Patient charges would have been reduced by $12,500 per year.

In the early 1970s, immunodiagnostic methods for the detection of bacterial antigens (BAs) in cerebrospinal fluid (CSF) emerged to fill the need for prompt identification of common agents of bacterial meningitis (5, 11, 31). Numerous assays and commercial kits, including counterimmunoelectrophoresis, coagglutination, and latex particle agglutination, were rapidly developed to serve as adjuncts to routine culture and Gram staining (3, 8, 9, 17). During this era, chloramphenicol was used as empiric therapy for meningitis to ensure adequate coverage against β-lactamase-producing *Haemophilus influenzae* type b. Because of the toxicity associated with chloramphenicol use in children, bacterial antigen testing (BAT) was deemed particularly important in this setting to detect *H. influenzae* meningitis. A negative BA test for *H. influenzae* in CSF would, in many cases, lead to the early discontinuation of chloramphenicol.

In recent years, BAT has been dramatically affected by changes in infectious disease epidemiology and improvements in therapeutics. The value of BAT for detecting *H. influenzae* type b in CSF must now be called into question for these reasons. The extended-spectrum cephalosporins ceftriaxone and cefotaxime have been shown to be reliable therapeutic agents for empirically treating meningitis caused by *H. influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, thus making detection of these pathogens by BAT somewhat less important. More significantly, the widespread use of the conjugate *H. influenzae* type b vaccine has resulted in a substantial decline in the incidence of invasive *H. influenzae* disease. Over the past 22 months, no cases of invasive *H. influenzae* disease have been seen at our institution.

Although BAT has been used for more than a decade, much controversy has arisen over the proper use of this test. BAT was originally designed to be used in patients who demonstrated laboratory and clinical findings consistent with meningitis (3, 5, 8, 11). Despite these initial intentions, this test has been used much too often as a screening tool in cases of suspected meningitis in patients whose CSF specimens have normal chemistries and cell counts. The indiscriminate use of BAT without consideration of the chemical and cytological profiles of the CSF is a misuse of valuable resources.

In view of the present emphasis in the health care community on the cost-effective use of laboratory services and the changing epidemiology of bacterial meningitis, we felt that it was prudent to formulate a policy concerning the judicious use of BAT. We prospectively evaluated 287 BA test requests over a 2-year period in an effort to determine whether unnecessary testing could be reduced by recommending to physicians that the test be canceled if the CSF analysis was normal. We also determined whether certain CSF parameters would be reliable predictors of BA test positivity and, thus, would allow us to limit our testing to such specimens.

MATERIALS AND METHODS

Study design. We prospectively studied the use of BAT of CSF in our institution from August 1992 to August 1994. All CSF specimens submitted to our laboratory for BAT were included in the study if the following CSF tests were done: protein, glucose, cell count, Gram staining, and bacterial culture. In order to reduce the number of unnecessary BA tests, we consulted the ordering physician and recommended that BAT be canceled if no abnormal CSF parameters (protein, glucose, cell count) were noted or if only one abnormal parameter was present. Normal values for these parameters at our institution are as follows: leukocyte (WBC) count, 0 to 5 cells per mm^3; protein concentration, 15 to 45

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TABLE 1. Comparison of findings for CSF specimens tested and not tested for BAs

No. of abnormal CSF parameters[a]	No. of CSF specimens evaluated	No. of specimens:		
		Not tested	Tested	BA positive
0–1	230	157	73	0
2–3	57	14	43	3
Total	287	171	116	3

[a] Cell count, glucose concentration, and/or protein concentration.

mg/dl; and glucose concentration, 50 to 75 mg/dl. During this initial phase of the study, age-related variations in protein concentrations and cell counts were not taken into account in determining when to call a physician concerning cancellation of the test. If the physician insisted that BAT be done, despite normal CSF parameters, he or she was asked to provide a brief explanation as to why such testing was deemed necessary. Upon completion of the study, the data were analyzed to determine if a further reduction in BAT could be achieved by establishing which CSF parameter(s) was indicative of bacterial meningitis and predictive of a positive antigen test. In this final analysis, age-related variations in protein concentrations and cell counts were taken into consideration in determining whether the parameter was abnormal. WBC counts also were adjusted on the basis of the number of erythrocytes in the CSF in instances of traumatic lumbar tap. One WBC per 700 erythrocytes was subtracted from the total WBC count in the CSF (4).

BAT. BAT was done with the Directigen meningitis combo panel (Becton Dickinson Microbiology Systems, Cockeysville, Md.) according to the manufacturer's recommendations. Capsular polysaccharide antigens detected by this kit include those from *H. influenzae* type b, *S. pneumoniae* (84 serotypes), *N. meningitidis* A, B, C, Y, and W135, group B streptococci, and *Escherichia coli* K1.

Bacterial culture. All CSF specimens were inoculated either directly or after centrifugation onto chocolate agar and 5% sheep blood agar and into thioglycolate broth. The agar plates were incubated for 4 days at 35°C in 5% CO_2 and were examined daily for growth. The thioglycolate broth was incubated under the same conditions for 7 days and was examined daily for growth.

RESULTS

Between August 1992 and August 1994, 303 CSF specimens were submitted to the Clinical Microbiology Laboratory for BAT. Sixteen of these specimens were excluded from the study because of a lack of a complete CSF analysis or bacterial culture. Two hundred thirty (80%) of the 287 CSF specimens included in the study exhibited either normal values for CSF protein, glucose, and cell count or one abnormal parameter (Table 1). Consultation with physicians concerning the 230 specimens resulted in cancellation of 157 of the requested BA tests. The remaining 73 specimens were processed at the insistence of physicians, and all were negative by BAT, Gram staining, and culture. The most frequent reason (59%) given to justify the testing of normal CSF specimens was the administration of antimicrobial therapy for some period of time prior to the lumbar puncture. Thirteen (18%) of the 73 specimens were tested because of insistence by physicians, although an explanation was never given as to why it was necessary to run the test. Other reasons given for performing the test included altered mental status or meningeal signs (8%) and immunosuppression (4%).

Fifty-seven (20%) of the 287 CSF specimens included in the study demonstrated at least two abnormal parameters (Table 1). Fourteen of these 57 requested BA tests were canceled by physicians. Of the 43 abnormal specimens tested by BAT, 3 were positive. Two patients with positive BA tests subsequently had positive CSF cultures for the organisms detected by BAT (Table 2). A third patient, with a positive BA test for *S. pneumoniae*, had a negative CSF culture. This patient had a positive blood culture for *S. pneumoniae* prior to transfer to our institution. No specimens were positive for *H. influenzae* type b by BAT or CSF culture. The 3 CSF specimens which were positive for BA represented 3% of the 116 CSF specimens tested by BAT. The total number of BA tests reduced by physician consultation was 171 (68%). At a charge to the patient of $100 for BAT, this represented a savings of $8,550 per year (Table 3). Laboratory costs for performing BAT were reduced by $4,400 per year.

DISCUSSION

In the current era of health care reform, many laboratories are critically evaluating the type of tests which are currently available and how to apply those tests to achieve clinically significant and cost-effective results. There is a movement toward limiting or discontinuing those tests which are unlikely to affect clinical decisions concerning patient care. BAT was initially designed to detect bacterial pathogens in the CSF of patients with clinical and laboratory findings consistent with meningeal infection and especially in those patients who had received antimicrobial therapy prior to lumbar puncture. Too frequently, physicians order BA tests as part of a battery of tests done on all patients from whom CSF is obtained. By failing to define the specific population in whom BAT may be of some value, i.e., those patients with evidence of meningitis, the rate of positivity of the test is exceedingly low. In our hospital population, only 3% of BA tests were positive. Others have found similarly low rates (2, 24, 26). Additionally, results from several studies have shown that positive BA test results rarely affect patient therapy (16, 24, 26). The low rate of positivity of this test as well as its minimal impact on patient care necessitate that the use of this test be reevaluated. Some would argue that in view of changes in the epidemiology of bacterial meningitis because of widespread *H. influenzae* type b vaccination, BAT is no longer of any clinical utility. Our position is that BAT continues to be of value but only if it is used appropriately.

Proposals have been made to perform laboratory testing on

TABLE 2. Characteristics of patients with positive BA results

Patient characteristic	Patient 1	Patient 2	Patient 3
Age (yr)	80	36	15
Glucose concn (mg/dl)	6	47	7
Protein concn (mg/dl)	1,358	147	180
Cell count (% PMNs[a])	21,525 (96)	2,300 (87)	1,850 (86)
Gram stain result	No organisms seen, moderate PMNs	Few gram-positive cocci heavy PMNs	Rare gram-negative cocci, moderate PMNs
Culture result	Negative	Rare group B strep	Few *N. meningitidis*
Antigen result	*S. pneumoniae*	Group B streptococci	*N. meningitidis* C, W135
Previous antibiotic treatment	Yes	Yes	No

[a] PMNs, polymorphonuclear cells.

TABLE 3. Comparison of reduction of BAT by physician consultation and WBC count

Reduction parameter	No. of specimens				Cost savings ($)/yr to:	
	Total	Canceled	Tested	Positive	Patient	Laboratory
Physician consultation	287	171	116	3	8,550	4,400
WBC count[a]	287	251	36	3	12,550	6,500

[a] WBC count, ≥50 cells per mm^3.

CSF in a logical sequence, relying on standard tests such as cell count, differential, protein and glucose concentrations, and Gram staining to guide the decision to order additional testing (10, 19, 25, 27, 29). The cell count and differential in CSF have been shown to be sensitive indicators of bacterial meningitis, more so than glucose and protein concentration estimations, which are often nonspecific and of limited diagnostic value (13, 19, 29, 34–36). Using a WBC count of ≥50 cells per mm^3 as a criterion for performing BAT, Werner and Kruger (36) achieved 100% sensitivity in predicting BA-positive specimens (36). Others have used both higher and lower cell counts with similar results (7, 29). In applying any biochemical or cytologic criterion for screening CSF, there is always the argument that immunosuppression or prior antibiotic therapy will alter the CSF picture. Clearly, immunosuppression can affect the cell count in CSF. Fishbein et al. (14) found that 6% of patients with meningitis seen over a 13-year period demonstrated an absence of CSF pleocytosis (<6 cells per mm^3). All of these patients had underlying conditions which were considered to contribute to a decreased immune response. Therefore, one must be cautious in applying any CSF screening procedure to such patients.

The effect of prior antimicrobial therapy on the CSF tends not to be as clear-cut as that of immunosuppression. Many of the normal CSF specimens that we tested for BA were tested at the insistence of physicians who were concerned that prior therapy had altered the bacterial picture of the CSF. In reviewing the literature, we were not convinced that prior therapy so drastically altered the cell count in CSF that it could not be used as a criterion for testing. In many pediatric patients with meningitis, prior therapy typically consists of antibiotics administered orally for otitis media, usually within 1 week of hospital admission. These partially treated patients may have a decreased likelihood of a positive CSF culture or Gram stain result, but the therapy has minimal effect on CSF parameters such as cell count (4, 6, 12, 15, 18, 20–23, 25, 28, 30, 32, 33, 35, 36). Even after institution of appropriate therapy for meningitis, the CSF picture can remain abnormal for 48 to 72 h (1). Persistent pleocytosis (>60 cells per mm^3) has been observed after 7 days of therapy in 50% of children treated for bacterial meningitis (4). With this information in mind, we sought to establish a criterion based on the cell count in CSF as a means of eliminating unnecessary BAT.

In reviewing numerous studies addressing various durations and types of antibiotic pretreatment, the cell count in CSF remained ≥50 cells per mm^3 in almost every clinical setting and was typically much higher (6, 12, 20–23, 28, 30, 32, 36). Therefore, we chose to adopt a cell count of ≥50 cells per mm^3 to distinguish those specimens most likely to be positive by BAT. Of a total of 287 specimens in the study, only 36 met this criterion, including the 3 specimens positive by BAT (Table 3). Enacting this cell count restriction would have resulted in a patient cost savings of $25,100 ($12,550/year) on the basis of a charge of $100 per test. Laboratory costs would have been reduced by $13,000 ($6,500/year). The cost for finding a positive test would drop from $2,000 to $620. We plan to institute this criterion on all future CSF specimens received in our laboratory for BAT, including those from patients who have received antibiotic therapy. CSF specimens from immunosuppressed patients, identified by physician consultation, will not be subject to this restriction.

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