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Rapid Bacterial Antigen Detection Is Not Clinically Useful

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Latex agglutination (LA) of capsular polysaccharide bacterial antigen is a frequently performed laboratory procedure, but its use is controversial. To assess the clinical utility of this test, we reviewed all LA tests performed over a 10-month period at two sites, a major university-based referral center and a private specialty pediatric hospital. Samples were assayed either individually or as a panel for the group B streptococcus, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and three sets of *Neisseria meningitidis* serogroups (A and Y, C and W135, and B and *Escherichia coli* K1). Of 5,169 assays performed on 1,268 clinical samples (786 urine and 478 cerebrospinal fluid, 3 pleural fluid, and 1 synovial fluid sample), 57 (1.1%) were positive, including 1.7% of urine and 0.3% of cerebrospinal fluid samples. All LA true-positive cerebrospinal fluid samples showed the causative microorganisms by Gram stain. Detailed chart review of these 57 positive samples showed that the LA result was false-positive in 31 (54%), true-positive in 22 (38%), and indeterminate in 4 (7%) samples. Therapy was not altered on the basis of any of the true-positive LA results. The 31 false-positive results led to additional cost, prolonged hospitalization, and some clinical complications. Total patient charges were $175,000 ($7,954 per true-positive), with no detectable clinical benefit. Our retrospective study does not support the current use of LA for rapid antigen detection. What, if any, specific indications exist for this test remain to be elucidated.

The clinical utility of a diagnostic test is determined not only by laboratory factors such as sensitivity, specificity, and ease of use but also by such factors as the epidemiology of the target pathogen and patterns of test usage. It is to be expected, therefore, that diagnostic tests may have excellent operating characteristics and still not provide useful clinical information in actual practice.

Latex particle agglutination (LA) tests to detect the capsular polysaccharide antigen of specific invasive pathogens are frequently performed in North American laboratories. Indeed, their use has become routine for the evaluation of patients thought to have sepsis or meningitis. Despite their frequent use and documented sensitivity and specificity, questions remain about the clinical usefulness of LA tests.

Vaccine-related changes in the epidemiology of invasive infection caused by *Haemophilus influenzae* type b (Hib) are certain to have changed the predictive value of assays, including LA tests, designed to detect this organism. These changes prompted us to reevaluate the utility of assays for Hib polysaccharide as well as other bacterial antigens. We report results of a retrospective examination of the utility of LA for bacterial antigen detection as performed in two hospitals in the United States. Data were gathered with the intention of determining patterns of test use, incidence of false-positive or misleading results, and clinical utility of test results.

MATERIALS AND METHODS

Study sites. Data for analysis came from two hospitals, a university-based referral center in North Carolina (Duke University Medical Center [DUMC]) serving both pediatric and adult patients and a subspecialty pediatric hospital in Texas (Cook/Fort Worth Children's Medical Center [C/FWCMC]). DUMC has 1,124 beds (157 pediatric), and about 35,000 inpatients and 600,000 outpatients are seen yearly. C/FWCMC has 184 beds, and about 6,000 inpatients and 80,000 outpatients are cared for yearly.

Data collection. Microbiology records of all LA tests performed during a 10-month period in 1992 at each of the two study sites were examined. The medical records of all patients with a positive LA test were reviewed carefully. In the case of neonates, maternal records were reviewed as well. Case selection was sequential and inclusive. Patients were excluded from the study only in the event that their medical record was not available for review. To obtain an estimate of the frequency of LA testing of cerebrospinal fluid (CSF), the number of CSF cultures was determined during the study period and compared with the number of LA tests performed on CSF. The assumption was made that almost all CSF samples tested by LA also were subjected to routine culture.

At chart review, data recorded included age, sex, medical record number, sample type, sample collection method, clinical history (including maternal history for neonates), antibiotic therapy, culture results from any source, LA test results from any source, results of Gram-stained examination of CSF, vaccination history, clinical impression prior to knowledge of the LA test result, and clinical use of the information obtained from LA testing. LA test results were considered true-positive, false-positive, or indeterminate on the basis of these findings. Conservative criteria were applied, and patients with a compatible clinical illness were considered to have a true-positive test result even if all cultures were negative. For a result to be considered false-positive, it was necessary that all cultures from sterile sites be negative for the pathogen detected by LA and that at least two of the following criteria also be present: negative repeat LA testing with a superior sample (e.g., urine from suprapubic aspiration or straight catheterization), absence of clinical history resembling that predicted by the LA test result (e.g., meningococcal antigen in urine of neonate in absence of any meningeal signs), and presence of an alternative explanation for the positive result (e.g., presence of a cross-reacting microorganism). Although the detection of the target antigen in the case of vaccination or contaminating growth of surface flora in urine is not caused by a failure of specificity on the part of the test, these results, which give misleading clinical information, also were classified as false-positive. Results were considered indeterminate when blood or CSF cultures or both were negative, characteristic clinical illness was absent, no other cause for a false-positive test was evident, and there were insufficient data to otherwise confirm the accuracy of the result. Test performance and usage varied markedly by sample type.

Laboratory methods. DUMC used the Wellcogen LA test (Murex Diagnostics Limited, Dartford, England), and C/FWCMC used the Directigen LA test (Becton Dickinson Microbiology Systems, Cockeysville, Md.) as recommended by the manufacturers. LA tests included reagents directed at antigens of *Streptococcus pneumoniae*, group B streptococcus (GBS), Hib, and *Neisseria meningitidis*. At DUMC, all urine samples were concentrated by filtration with a Minicon B-15 concentrator (Amicon Inc., Beverly, Mass.) before testing. At C/FWCMC, urine was concentrated if the volume was 10 ml or greater and otherwise was tested without concentration. As recommended, all clinical samples were subjected to 100°C heat before testing. At DUMC, the test for *N. meningitidis* type B and

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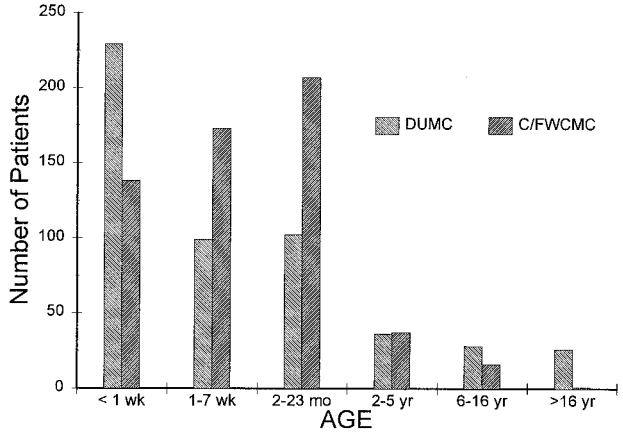

FIG. 1. Distribution of patients by age and hospital.

cross-reacting *Escherichia coli* K1 was not used and groups A, C, Y, and W135 were tested as a group with a single reagent. At C/FWCMC, *N. meningitidis* groups A and Y, groups C and W135, and group B/*E. coli* K1 antigens were sought separately.

RESULTS

Test ordering patterns. A total of 5,169 LA tests were performed on 1,268 clinical samples (786 urine, 478 CSF, 3 pleural fluid, and 1 synovial fluid sample) during the study period. The age of patients for whom LA testing was requested, which did not differ markedly at the two medical centers, is depicted in Fig. 1. The majority of samples tested (61%) came from infants in the first 8 weeks of life. Conversely, only 13% of samples came from patients over 2 years of age.

Of the 5,169 LA tests performed, a total of 57 (1.1%) were positive. Of the positive samples, CSF accounted for 7 (0.3%), urine for 49 (1.7%), and pleural fluid for 1. The frequency of positive results from DUMC (19 of 1,714, or 1.1%) was identical to that from C/FWCMC (38 of 3,455, or 1.1%). Patterns of test usage also varied remarkably little between the two disparate sites (Table 1). In both hospitals, LA testing could be requested to detect a specific antigen or antigens or could be requested as a panel. On average, the agglutination tests were ordered as a panel in 67% of urine samples and 88% of CSF specimens.

The frequency of LA testing after lumbar puncture also was identical at the two sites. During the study period, 1,943 CSF samples were sent for culture and 478 were sent for LA testing. Given that routine bacterial culture is almost always performed on CSF in which antigen detection is requested, this suggests that LA testing was applied to 24% of all CSF samples.

Medical records were available for review from all patients with a positive LA test result, and none was excluded. Of the 57 positive tests, 31 (54%) were false-positive, 22 (38%) were true-positive, and 4 (7%) were indeterminate. From 2,236 separate tests ordered on 478 CSF samples, there was a total of 7 positive LA test results, of which 5 (71%) were true-positive and 2 (29%) were false-positive. Of the 2,907 LA tests ordered on 786 urine samples, there were 49 positive results, of which 16 (33%) were true-positive, 29 (59%) were false-positive, and 4 (8%) were indeterminate. Of the true-positive results, almost all (15 of 16) identified GBS. One identified *S. pneumoniae*. A single pleural fluid specimen was tested; this was from a child with community-acquired pneumonia and empyema. The LA test was positive for *S. pneumoniae* (Table 2).

TABLE 1. LA test usage at two institutions

Institution	No. of tests positive/no. ordered (%)	No. of CSF/LA ordered/no. sent for culture (%)	No. of panels ordered/no. tested (%)	
			Urine samples	CSF samples
DUMC	19/1,714 (1.1)	235/984 (24)	215/332 (65)	188/235 (80)
C/FWCMC	38/3,455 (1.1)	243/959 (25)	308/454 (68)	241/243 (99)

TABLE 2. LA tests performed and number positive for bacterial antigens

Test ordered	No. tested	No. positive	No. true-positive
CSF			
S. pneumoniae	438	3	2
GBS	440	1	1
H. influenzae	439	1	0
N. meningitidis types A, Y	240	0	0
N. meningitidis types W135, C	240	0	0
N. meningitidis type B/*E. coli* K1	240	2	2
N. meningitidis types A, C, Y, W135	207	0	0
Urine			
S. pneumoniae	519	4	1
GBS	717	27	15
H. influenzae	521	3	0
N. meningitidis types A, Y	308	4	0
N. meningitidis types W135, C	308	0	0
N. meningitidis type B/*E. coli* K1	308	11	0
N. meningitidis types A, C, Y, W135	226	0	0
Pleural and synovial fluid			
Panel of tests	18	1	1
Totals	5,169	57 (1.1%)	22 (0.4%)

Test accuracy. The LA test was most accurate when applied to spinal fluid and least accurate when applied to urine. A review of positive CSF and blood cultures at one of the study sites (C/FWCMC) did not identify tested patients with false-negative LA results, thus suggesting high sensitivity of the tests. Overall test performance, however, was poor; 54% of positive results (29% of CSF and 59% of urine samples) were erroneous, and the significance of another 7% could not be determined.

Clinical impact of true-positive LA test results. Examination of medical records in all 22 true-positive cases revealed no instance in which antimicrobial therapy or other clinical management was changed on the basis of the LA test result. For all patients, antibiotic orders were written before the availability of LA results. In the seven true-positive patients with meningitis, LA testing added nothing to the Gram-stained examination of CSF, which was positive in all cases in this study. In all 15 infants with a true-positive urine LA test for GBS, GBS sepsis was the working diagnosis, and in all cases blood cultures (or culture of amniotic fluid, in one instance) were also positive. A report of the microscopic finding of lancet-shaped, gram-positive organisms in empyema fluid was available before the LA test result in the single patient whose pleural fluid was positive by LA. There were no positive LA tests from patients with negative cultures caused by previous or ongoing antimicrobial therapy. The patient charges for the LA tests performed during the study period were approximately $175,000, or $7,954 per true-positive result, with no detectable clinical benefit.

TABLE 3. Reasons for false-positive or misleading LA results

Reason	Positive antigen	No. of false-positive results
Contamination of urine	*N. meningitidis* type B/*E. coli* K1	9
	N. meningitidis types A and Y	4
	GBS	9
	S. pneumoniae	2
	Hib	1
Antigen excretion after vaccination	Hib (urine)	2
	Hib (CSF)	1
Infection with cross-reacting organism	*S. mitis* meningitis (*S. pneumoniae* by LA)	1
	E. coli urinary tract infection (*N. meningitidis* by LA)	2

False-positive LA test results. The majority of positive LA tests were misleading. An analysis of these false-positive results is presented in Table 3. The most common cause of a false-positive result was contamination by skin flora of urine collected in a bag. In all cases in which the same urine sample was cultured, the LA test species, a known cross-reacting species, or mixed flora grew from the urine. In several cases, the urine sent for LA testing came from a bagged collection, whereas the sample sent for culture on the same patient was obtained by suprapubic aspiration or urethral catheterization. This was due in part to the volume of urine required for LA testing at one of the hospitals (DUMC). All patients with a positive LA test result from a bagged specimen in whom repeat LA testing was performed with a sterile collection method had negative LA results on retesting. Two of the samples reported as positive for *N. meningitidis* group B/*E. coli* K1 were from patients found to have *E. coli* urinary tract infections. These are arguably not false-positive results, since the test is designed to use this cross-reaction to detect invasive neonatal infection with *E. coli*. However, review of the medical records demonstrated that the results, neither of which came from infants, were either confusing or unhelpful to the physicians in these two cases. Of the 15 urine LA results indicating the presence of *N. meningitidis*, 100% were false-positive.

The second most frequent cause of a misleading LA test result was recent immunization with Hib conjugate vaccine. Two of these tests were performed on urine and one was done on CSF. The surprising false-positive CSF LA for Hib, which has been reported elsewhere (36), was received from an infant who had 48 h previously been immunized with a conjugate Hib vaccine: CSF had no cells; leukocyte count was normal; blood, urine, and CSF cultures were negative; and the child was treated for 48 h with antibiotics and released to recover without further intervention.

The clinical impact of false-positive results, in contrast to true-positives, was substantial. These results led to subspecialty consultation, to lengthened hospital stay, to prolonged courses of antibiotic therapy, and in some cases to important clinical complications. In one instance a chronically hospitalized infant with bronchopulmonary dysplasia and limited intravenous access had a urine sample tested by LA during a pulmonary exacerbation. The LA test was positive for *S. pneumoniae*, whereas urine and blood cultures were negative. Infectious diseases consultation was requested, and antibiotics were recommended. A central venous catheter was required to administer the course of intravenous antibiotic therapy, and line-related fungal sepsis supervened. Review of nursing notes disclosed that the sterile urine subsequently sent for culture had been obtained by catheter, whereas that sent for LA test was obtained from a perineal collection bag. The direct medical cost that could be ascribed to this and other false-positive results, although not calculated, was substantial.

DISCUSSION

At a time when rapid detection assays for a number of infectious pathogens are expected to augment or supplant routine microbiologic techniques, the LA test for bacterial polysaccharide capsular antigen has been a model assay of proven specificity and sensitivity and, therefore, has been widely applied. As found in this study, which presents data from two different hospitals, one private and one university based, the LA test has become so much a part of the routine evaluation of CSF that it is requested on 25% of all CSF samples collected and often is used to screen for neonatal sepsis as well.

Rapid antigen detection assays were developed during an era in which invasive infection with Hib was relatively common. The LA kits, which have replaced counterimmune electrophoresis, are in many ways ideal assays. They have the potential advantages of being rapid, technologically straightforward, specific, sensitive for detection of nanogram quantities of antigen, and positive despite prior antimicrobial therapy (1, 2, 8, 9, 10, 13, 16, 20, 30, 37, 39, 41, 42, 45). Additionally, urine can be used as the sample material, with the advantage that it is simple to collect and contains bacterial antigens concentrated 10- to 50-fold over those found in serum (1). During their development, the rationale for the clinical application of the various LA tests now available seemed clear.

Theoretically, the rapid availability of a diagnostic laboratory result allows the physician to focus the remainder of the diagnostic evaluation, to narrow or to abbreviate antimicrobial therapy, and to initiate chemoprophylaxis of contacts when necessary. Several factors, however, limit the clinical utility of bacterial antigen tests and make their routine use controversial. These factors include a decline in the incidence of Hib invasive disease following the advent of specific vaccination (35), imperfect antigen specificity (4, 6, 8, 11, 13, 21, 23, 25, 28, 30, 32), misleading positive results due to detection in urine or CSF of circulating Hib antigen after vaccination (7, 15, 36, 43, 44), contamination of urine with skin flora (3, 40), and, importantly, the common failure of physicians to respond to rapidly generated diagnostic test results (26). In this review of over 5,000 LA tests, we found no evidence of clinical utility to support their current common use and instead found a high incidence of confounding results. The poor performance of LA testing in this review resulted not from inherent technical problems with the assay but from the frequent occurrence of the above-mentioned factors and from nonselective use. For ex-

TABLE 4. Cross-reacting microorganisms in common LA tests

LA target species	Cross-reacting species (reference)
S. pneumoniae	Alpha streptococci (21) GBS (24) *N. meningitidis* (24) *Klebsiella pneumoniae* (24)
GBS	*Staphylococcus aureus* (13) Group G streptococci (6) *S. pneumoniae* (11) *Proteus* sp. (23)
Hib	*Staphylococcus aureus* (30) *S. pneumoniae* (4) *N. meningitidis* (8) *E. coli* (28)
N. meningitidis	*Haemophilus parainfluenzae* (32) *Escherichia coli* (25)

ample, LA testing was unnecessary on CSF because all true-positive samples already showed the causative bacteria by Gram stain.

Infection or contamination with an agent bearing cross-reacting antigens was responsible for a majority of false-positive results in our study. Lack of specificity of LA tests has been noted in multiple previous publications. Although the problem is diminished by pretest heat treatment of clinical samples, nonspecific agglutination may still result from artifacts introduced during sample preparation, such as filtration with polysulfone (46), and from infection or sample contamination with an organism bearing cross-reacting antigens (4, 6, 8, 11, 13, 23, 25, 28, 30, 40, 47). As tabulated in Table 4, many bacteria that cross-react with antibodies directed against each of the four agents for which LA tests are commonly performed have been identified (4, 6, 8, 11, 13, 21, 23, 25, 28, 30, 32).

Urine is a convenient sample in which to detect concentrated capsular antigen; however, contaminating flora in samples obtained in a nonsterile manner is a frequent cause of false-positive LA test results. There was early hope that bacterial antigen detection assays would detect only excreted antigen and not live organisms (18, 27), but this is not the case and infection cannot be differentiated from colonization on the basis of LA testing (5, 13, 22, 33). Whole-cell bacteria, when contaminating urine specimens, yield positive LA results when present in quantities of 5.7×10^4, and even a single organism is capable of causing a positive result if held at body temperature for 8 to 10 h before testing (47). This growth of contaminating flora in urine is particularly problematic in neonates from whom urine is often collected into an adhesive bag placed on the perineum. This results in the common and difficult clinical problem of positive urinary LA tests for GBS and *N. meningitidis* or *E. coli* K1 in neonates without clear evidence of disease. Sanchez et al. (40) demonstrated in a cohort study that colonization was responsible for the majority of positive LA tests for GBS in nonseptic infants and concluded that the testing of bag urine specimens in neonates could best be considered a screening test for colonization (40).

Murphy et al. (33) have shown that nasopharyngeal colonization with *H. influenzae* may result in urinary antigen excretion, and the possibility of antigen absorption and excretion in infants heavily colonized with GBS has also been proposed (17). We did not evaluate this possibility in the present study; infants with a positive LA test from urine collected by catheter or suprapubic aspiration were considered infected (true-positive) even if they had negative blood and CSF cultures prior to the administration of antibiotics and remained clinically well. It remains possible that some of these infants, bathed in streptococci in utero, may have been excreting absorbed antigen.

None of the 15 patients in this study whose urine LA tests were positive for *N. meningitidis* had any evidence of infection with this organism. Although two of these patients had evidence of urinary tract infection with *E. coli*, neither was a neonate being screened for *E. coli* sepsis and the results were of no clinical utility. The remainder of false-positive *N. meningitidis* results were due to contamination of urine with skin flora. This impressively poor clinical yield of LA testing for *N. meningitidis* has been reported elsewhere. In a recent study of the clinical usefulness of 111 consecutive urine LA tests positive for *N. meningitidis* or *E. coli* K1, Boyer et al. found no identifiable cases of infection with *N. meningitidis* and no cases of *E. coli* sepsis or bacteremia (3).

There were few positive LA test results for *H. influenzae* or *S. pneumoniae* in this study, but the ability of the test to detect infection with these agents was poor. Of the eight tests positive for *S. pneumoniae*, only half were true-positive. One false-positive CSF result was found in a patient with meningitis due to *Streptococcus mitis*. A second CSF sample in this case reconfirmed both the identity of the organism and the false-positive LA reaction.

Application of diagnostic tests in populations different than those studied during the approval process is a very common phenomenon, and such testing in a low-incidence population gives a low predictive value to the results (34). In a 1-year prospective study of LA test use in adult patients with meningitis, for instance, Forward found no utility (12). Of the eight cases of meningitis during the study period, only three were caused by organisms targeted by commercial LA tests, and of those three, one was not tested for antigen because the cell counts were not indicative of bacterial infection, one was uninterpretable, and one was positive in a patient who had a positive Gram-stained smear of the CSF as well.

The advent of routine immunization of infants with Hib conjugate vaccines has led to a dramatic decline in the incidence of invasive Hib disease (35) and has changed the operational characteristics of antigen detection assays (7, 15, 19, 36, 43, 44). In fact, the epidemiologic situation under which the LA tests were developed no longer exists, and their continued use in the changed population is in part responsible for their poor performance. It is notable that during the 10-month study period not a single case of *H. influenzae* meningitis or sepsis was detected by LA testing.

Another consequence of vaccination against Hib has been the confusing detection of vaccine antigen by LA. The presence of circulating vaccine antigen following Hib vaccination was first noted in 1986 (43) and has been well documented (44). The majority of children vaccinated with polysaccharide vaccine have a positive urine LA for the first 4 days after immunization, with a number having a positive result for longer than a week. Urinary excretion of antigen is even more pronounced when conjugate vaccine is used. Goepp et al. found that the majority of infants had a positive LA test 2 weeks following Hib-conjugate vaccination and that 41% were still positive at 30 days (15). Immunization with conjugate vaccine may even result in LA-detectable Hib antigen in the CSF (7, 36). The declining incidence of invasive Hib disease and the frequency of detection of vaccine antigen resulted in a 100% incidence of false-positive LA tests for Hib in this study.

The strict requirements that new diagnostic tests are required to meet before licensure do not ensure that they will be

clinically useful. In practice, the value of a test will depend on how its results affect the process of diagnostic and therapeutic decision making, on how the test population is selected, and on other factors unrelated to the laboratory characteristics of the assay (38). For example, in a study carried out before the use of Hib-conjugate vaccines, Granoff et al. found that LA tests were sensitive and specific for the diagnosis of Hib meningitis, but results were not used to direct medical care and had no beneficial clinical impact (17).

Although the true value of a diagnostic laboratory test can only be determined by study of its performance when in common use, this secondary phase of analysis is often ignored. Additionally, once accepted into the diagnostic process, laboratory testing frequently becomes a matter of habit or protocol and critical analysis of the value of tests stops altogether. Since diagnostic testing is a substantial part of the total health care expenditure, evaluation of the actual clinical value of tests in common use is particularly important. Diagnostic assays may become standards of practice on the basis of their performance in clinical trials when in fact they have little or no utility in common use. Our assessment of the current use of LA testing for bacterial antigens exemplifies this reality; despite the excellent performance characteristics of these tests, they are of no clinical utility as currently employed. Previous recognition of these problems has prompted recommendations that these tests be performed only on selected specimens (14) or after a waiting period of 48 h (31). As pointed out by Maxson et al., oral therapy and parenteral therapy of <24-h duration before lumbar puncture do not necessarily negate Gram stain and culture results; in such situations, LA testing could be delayed for 48 h (31). On the basis of data from the current study as well as the work of others (14, 17, 19, 29, 31, 40), we offer the following specific laboratory and clinical recommendations: (i) bag collections of urine should not be accepted for testing; (ii) LA testing against a panel of antigens should not be offered; (iii) LA should not be performed on CSF unless the cell count is abnormal, the Gram stain is negative, and CSF and blood cultures remain negative at 48 h; and (iv) LA for Hib should not be requested or done for Hib-vaccinated children. Taken together, these restrictions point to a general recommendation that LA testing for rapid detection of bacterial antigens should no longer be available as a routine microbiological procedure since it rarely, if ever, contributes to improved patient care. Until educational efforts reduce requests in accord with these recommendations, clinical microbiology laboratories could require consultative approval before doing LA testing.

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