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# MINIREVIEW

# Role of the Microbiology Laboratory in Diagnosis and Management of Pharyngitis

Paul P. Bourbeau*

*Division of Laboratory Medicine, Geisinger Medical Center, Danville, Pennsylvania 17822-0131*

Pharyngitis accounts for an estimated 40 million adult visits to medical facilities annually in the United States (41). Pediatric visits are clearly substantial as well. An estimation of the causes of pharyngitis is summarized in Table 1. While there are also differences between the epidemiology of various infectious agents related to the age of the patient, the season of the year, accompanying signs and symptoms, and the presence or absence of systemic disease, there is such an overlap in symptoms that diagnosis of a specific etiological agent based on clinical criteria alone is inadequate for effective management. For example, although a presentation of upper respiratory tract infection with cough and rhinorrhea is suggestive of a nonstreptococcal etiology, in one study of pediatric patients, 36% of those presenting with cough and 45% of pediatric patients presenting with coryza symptoms had throat cultures that were positive for group A streptococci (GAS) (41).

This article reviews the causes of pharyngitis, the tests that can be used to accurately establish the diagnosis, and the indications for performing this testing.

## GAS

GAS are the most common bacterial cause of pharyngitis (3), as well as the only cause of pharyngitis for which antimicrobial therapy is clearly indicated (5). The laboratory diagnosis of streptococcal pharyngitis can be accomplished by the use of three different methods.

**Culture.** Kellogg wrote an excellent article summarizing the multiple variables, which are inherent in the performance of a culture for GAS (29). The three main culture variables identified by Kellogg were medium, atmosphere of incubation, and duration of incubation. Medium and atmosphere of incubation cannot be independently discussed in a meaningful way because of the interrelationship of these two factors. Kellogg recommended four combinations for throat specimens: (i) sheep blood agar incubated anaerobically, (ii) sheep blood agar incubated aerobically with a coverslip over the primary area of inoculation, (iii) sheep blood agar with trimethoprim-sulfamethoxazole incubated either in 5 to 10% $CO_2$, or (iv) the same medium incubated anaerobically (29). Kellogg further recommended that the use of sheep blood agar incubated in 5 to 10% $CO_2$ be strictly avoided. Our own experience with GAS selective agar compares favorably with the four combinations recommended by Kellogg (1). The third variable described by Kellogg is the duration of incubation (29). In nine studies that he cited, incubation for a second night increased recovery in 22 of 23 (96%) of the medium-atmosphere combinations tested. For 87% of these combinations, the increase in recovery of GAS was 5 to 20%.

**Rapid antigen detection tests.** In 1978, El Kholy et al. (13) published the results of a study describing the identification of GAS directly from tonsillar scrapings within 30 min, by using a modified nitrous extraction procedure coupled with an immune precipitin reaction. This study proved to have a profound impact on the diagnosis of streptococcal pharyngitis, paving the way for the introduction of commercially available rapid antigen kits for GAS.

The first rapid antigen kit for GAS, which was introduced in the early 1980s, utilized a latex agglutination method. Over time the methodologies employed in the kits expanded to include coagglutination, enzyme immunoassay, liposomal, and optical immunoassay techniques. Two trends are apparent in the evolution of these products. First, endpoints have become easier to read, in large part because membrane enzyme immunoassay products replaced the earlier latex method. Second, assays have become generally easier to perform due to more tolerance in the timing of certain steps and fewer steps overall.

In addition to methodological differences in rapid antigen tests for GAS, commercial kits can be also divided into two groups based upon the complexity classification of the Clinical Laboratory Improvement Act of 1988: those with a waived status and those without a waived status. A current list of rapid antigen tests for GAS, waived and not waived, can be found at the U.S. Food and Drug Administration website.

Improvements in ease of performance and the proliferation of test products have not, in my experience, been accompanied by any significant improvement in test sensitivity. There are numerous published studies to demonstrate that the 90 to 95% sensitivity often claimed in package inserts is often not attained. For example, in three separate evaluations performed in the same laboratory, sensitivities of 73, 76, and 79% were achieved for the Abbott TestPack Strep A kit in comparison to culture (1, 25, 26). The package insert for the Abbott TestPack Strep A kit claimed a sensitivity of 95.7%. In contrast, however, the specificity of all of the rapid antigen tests for GAS is generally >97% (14).

The performance characteristics of 12 studies involving a comparison of culture and a rapid antigen test are summarized

* Mailing address: Division of Laboratory Medicine, Geisinger Medical Center, Danville, PA 17822-0131. Phone: (570) 271-7467. Fax: (570) 271-6105. E-mail: pbourbeau@geisinger.edu.

TABLE 1. Microbial causes of acute pharyngitis[a]

| Pathogen | Syndrome or disease | Estimated % of cases[b] |
|---|---|---|
| Viral | | |
| Rhinovirus (100 types and 1 subtype) | Common cold | 20 |
| Coronavirus (≥3 types) | Common cold | ≥5 |
| Adenovirus (types 3, 4, 7, 14, and 21) | Pharyngoconjunctival fever, acute respiratory disease | 5 |
| Herpes simplex virus (types 1 and 2) | Gingivitis, stomatitis, pharyngitis | 4 |
| Parainfluenza virus (types 1 to 4) | Common cold, croup | 2 |
| Influenzavirus (types A and B) | Influenza | 2 |
| Coxsackievirus A (types 2, 4 to 6, 8, and 10) | Herpangina | <1 |
| EBV | Infectious mononucleosis | <1 |
| Cytomegalovirus | Infectious mononucleosis | <1 |
| HIV type 1 | Primary human immunodeficiency | <1 |
| Bacterial | | |
| *Streptococcus pyogenes* (group A beta-hemolytic streptococci) | Pharyngitis and tonsillitis, scarlet fever | 15–30 |
| Group C beta-hemolytic streptococci | Pharyngitis and tonsillitis | 5 |
| *Neisseria gonorrhoeae* | Pharyngitis | <1 |
| *Corynebacterium diphtheriae* | Diphtheria | <1 |
| *Arcanobacterium haemolyticum* | Pharyngitis, scarlatiniform rash | <1 |
| Chlamydial (*Chlamydia pneumoniae*) | Pneumonia, bronchitis, and pharyngitis | ND[c] |
| Mycoplasmal (*Mycoplasma pneumoniae*) | Pneumonia, bronchitis, and pharyngitis | <1 |

[a] Adapted from reference 20a with permission of the publisher.
[b] Estimated percentage of pharyngitis cases due to indicated organism in persons of all ages.
[c] ND, not determined.

in Table 2. These 12 studies are reasonably representative of the published literature. The sensitivities of these 12 rapid antigen tests ranged from 62 to 96% with specificities for all of >97%.

There are two major weaknesses for the rapid antigen tests for GAS. The testing is labor-intensive; to be truly useful, these tests need to be completed and acted upon before the patient leaves the clinic. Hence, any labor savings that might be obtained by batch testing cannot be achieved. The second major weakness of the rapid antigen tests is their lower sensitivity compared to a well-performed culture. The false-negative results obtained with rapid antigen tests cannot be assumed to be clinically not significant. In one study that measured the serological evidence of recent streptococcal infection, Gerber et al. showed that there was no significant difference between the percentage of individuals with an antibody response to GAS between those with true-positive and false-negative rapid antigen test results for GAS (18). Until recently, there has been a general consensus among the professional societies that negative rapid antigen tests for GAS should be confirmed by culture. The American Heart Association and others have recommended that all negative rapid antigen test results be confirmed by culture (8, 11). Indeed, the package inserts of some rapid antigen tests contain specific language recommending that negative test results be confirmed by culture. Recently, however, new guidelines have suggested that confirmation of negative rapid antigen test results for GAS in adults is either not necessary at all (5) or only if the sensitivity of the rapid antigen test is <80% (9). In lieu of the confirmation of negative rapid antigen test results by culture, some laboratories utilize the Group A Strep Direct Test (Gen-Probe, San Diego, Calif.) for confirmation (25). It is likely that additional studies with the LightCycler Strep-A assay (Roche Applied Science, Indianapolis, Ind.) will demonstrate it is also a suitable confirmatory test for a negative rapid antigen test.

**Nucleic acid testing.** There are two very distinct ways to perform nucleic acid testing for GAS by using commercially available kits. The Group A Strep Direct Test utilizes a direct nonamplified nucleic acid probe methodology, whereas the LightCycler Strep-A assay utilizes a real-time PCR method for detection of amplified GAS nucleic acid.

The Group A Strep Direct Test is intended for the detection of GAS directly from pharyngeal specimens. The test uses a nonisotopic, chemiluminescent, single-stranded DNA probe

TABLE 2. Comparison of rapid antigen tests and blood agar cultures[a]

| Investigators (reference) | No. of samples tested | % Positive for GAS | Rapid method[b] | Rapid test | |
|---|---|---|---|---|---|
| | | | | % Sensitivity | % Specificity |
| Gerber et al. (19) | 339 | 32 | LA | 83 | 99 |
| Campos and Charilaou (6) | 415 | 36 | LA | 62 | 100 |
| Schwartz et al. (38) | 425 | 50 | LA | 93 | 90 |
| Roddey et al. (35) | 512 | 39 | LA | 72 | 98 |
| Schwabe et al. (37) | 365 | 27 | ELISA | 90 | 97 |
| Dobkin and Shulman (12) | 221 | 31 | ELISA | 96 | 97 |
| Yu et al. (42) | 648 | 20 | ELISA | 77 | 98 |
| Anhalt et al. (1) | 970 | 22 | ELISA | 74 | 99 |
| Chapin et al. (7) | 520 | 33 | OIA | 86 | 100 |
| Heiter and Bourbeau (26) | 801 | 31 | OIA | 92 | 95 |
| Campos and Mohla[c] | 411 | 26 | OIA | 84 | 99 |
| Harbeck et al. (22) | 475 | 24 | OIA | 97 | 96 |
| | 800 | 12 | OIA | 99 | 98 |

[a] Adapted from reference 17 with permission of the publisher.
[b] LA, latex agglutination; ELISA, enzyme-linked immunosorbent assay; OIA, optical immunoassay.
[c] J. M. Campos and C. Mohla, Abstr. 98th Annu. Meet. Am. Soc. Microbiol. 1994, abstr. C-41, p. 497, 1994.

TABLE 3. Comparison of Gen-Probe Group A Strep Direct Test results with culture

| Investigators (reference) | No. tested | Prevalence | % Culture sensitivity | GASDT[c] | | Swab type (sterilization method)[b] |
|---|---|---|---|---|---|---|
| | | | | % Sensitivity | % Specificity | |
| Heiter and Bourbeau (25) | 1,103 | 22.9 | 98.8 | 92.4 | 99.6 | Rayon w. Stuarts (EtO) |
| Pokorski et al. (34) | 767 | 11.9 | 96.7 | 88.6 | 97.8 | Rayon w. Stuarts (EtO) |
| Dunne et al.[a] | 1,140 | 24.0 | 100.0 | 92.0 | 98.0 | Rayon w. Stuarts (EtO) |
| Heelan et al. (24) | 318 | 25.0 | 100.0 | 91.4 | 97.0 | Rayon w. Stuarts (EtO) |
| Chapin et al. (7) | 520 | 33.0 | 99.4 | 94.8 | 100.0 | Dacron w. Amies (gamma) |

[a] W. M. Dunne, M. Jevon, C. Mohla, and J. M. Campos, Abstr. 93rd Annu. Meet. Am. Soc. Microbiol. 1993, abstr. C-340, p. 506, 1993.
[b] EtO, ethylene oxide; gamma, gamma irradiation. w., with.
[c] GASDT, Group A Strep Direct Test.

that is complementary to the rRNA target of the GAS. An important consideration for the performance of the Group A Strep Direct Test is the choice of the proper swab for testing. Early evaluations all utilized a Culturette or Culturette-like swab, i.e., an ethylene oxide sterilized rayon swab. When Becton Dickinson stopped production of the Culturette swab in 2001 and replaced it with the CulturePlus swabs, problems with the performance of the Group A Strep Direct Test with some of the CulturePlus swabs were reported by a manufacturer. Unlike the Culturette swabs, the CulturePlus swabs are sterilized with gamma irradiation. Exposure to gamma irradiation elevates the background chemiluminescence of the rayon fibers, resulting in false-positive Group A Strep Direct Test results (5a). This combination of rayon fiber and gamma irradiation sterilization is unacceptable for the Group A Strep Direct Test. However, gamma-irradiated Dacron swabs are acceptable for use in the Group A Strep Direct Test, as are rayon or Dacron swabs that are ethylene oxide sterilized.

Table 3 summarizes several published evaluations of the Gen-Probe Group A Strep Direct Test. Sensitivities have ranged from 88.6 to 94.8% compared to culture. All had specificities of >97%. The table separates the evaluations by swab fiber type, whether or not the collection device contained any transport media, and the sterilization method. There are also two clinical studies (5a; S. Wood, H. Takahashi, and J. Fusco, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1567, p. 224, 1999) and one in vitro study (B. Heiter and P. Bourbeau, Abstr. 100th Gen. Meet. Am. Soc. Microbiol, abstr. C-157, p. 165, 2000) that suggest that the use of a dry swab with the Gen-Probe Group A Strep Direct Test increases test sensitivity.

The LightCycler Strep-A assay utilizes a real-time PCR method for the detection of GAS from throat swabs. Utilizing the LightCycler technology, a single light cycler can test 32 samples (specimens and controls) per run in ca. 1.5 h (40). In the only published evaluation to date, Uhl et al. (40) from the Mayo Clinic compared recovery of GAS from culture and the LightCycler Strep-A assay from pharyngeal specimens. Using culture as the "gold standard," Uhl et al. determined the LightCycler Strep-A assay to have a sensitivity of 93% and a specificity of 98%. In addition to a much shorter time to completion than traditional culture, these investigators reported that the LightCycler Strep-A assay required less than half the labor per specimen (3 min) than a combination of rapid antigen testing and culture (7 min). Uhl et al. included no reagent costs in their evaluations so, in addition to more studies to evaluate the performance characteristics of the LightCycler Strep-A assay in other laboratories, an analysis of the total costs for the assay is merited.

The true performance characteristics of the LightCycler Strep-A assay are difficult to assess because, as with some other nucleic acid amplification methods in which the sensitivity of the new test may exceed that of the culture gold standard, the determination of a true-positive result is problematic. For example, in this evaluation, there were seven specimens that were culture negative but LightCycler Strep-A assay positive (40). It is likely that at least some of these seven specimens were true-positive results but, without an alternative nucleic acid amplification method or possibly alternative primers, they should be categorized as false-positive test results. Much as has occurred with nucleic acid testing for chlamydia, a better definition of a positive patient should emerge over time.

## BACTERIA OTHER THAN GAS

**Non-group A beta-hemolytic streptococci.** While GAS are a known cause of pharyngitis and group B and group F streptococci are not associated with pharyngitis, the role of group C and group G streptococci as causes of pharyngitis is more controversial. Group G streptococci have been associated with discrete, food-borne outbreaks of pharyngitis. Although the older literature generally demonstrated that group C streptococci could be isolated as frequently from controls as from patients with pharyngitis (23), more recent studies have demonstrated an association with the large-group colony type of group C streptococci with pharyngitis (15). These large-colony types are now classified as *Streptococcus dysagalactiae* subsp. *equisimilis* (36).

***Arcanobacterium haemolyticum.*** *A. haemolyticum*, formerly known as *Corynebacterium haemolyticum*, has been implicated as a cause of pharyngitis, particularly in teens and young adults. *A. haemolyticum* infection has been associated with a scarlatina rash. There have been few extensive published studies on the prevalence of *A. haemolyticum* in patients with pharyngitis. Miller et al. reported that of 24,695 throat cultures performed over an 8-year period, 103 (0.4%) were positive for *A. haemolyticum* and 2,045 (8.3%) were positive for *S. pyogenes* (31). The true clinical significance of *A. haemolyticum* remains clouded. As noted by Funke et al. (16), the organism can be isolated in some individuals without disease, and it is often isolated in association with other potential pathogens.

*A. haemolyticum* can be difficult to culture and identify on the media used for a routine throat culture in most laboratories. Although the organism is considered to be beta-hemo-

lytic, that hemolysis is far more subtle than what is seen with GAS and can require 48 to 72 h for detection (10). Detection is clearly influenced by the choice of media and the atmosphere of incubation as well (10).

***Chlamydia pneumoniae.*** *C. pneumoniae* is a newly recognized cause of respiratory disease. Accurate laboratory diagnosis of this organism remains difficult, and therefore only limited information is available concerning the prevalence and types of disease caused by *C. pneumoniae*. Complicating our understanding is older literature associating *Chlamydia trachomatis* with disease of the respiratory tract. Although it is clear that *C. trachomatis* can cause disease of the respiratory tract, particularly in neonates, older information obtained by serological methods must be carefully interpreted because of the cross-reactivity of antibody with the chlamydial genus antigen found on both *C. trachomatis* and *C. pneumoniae*.

Our current understanding of the epidemiology of *C. pneumoniae* suggests that it is rarely a cause of simple pharyngitis compared to pharyngitis as an accompanying or secondary symptom of lower-respiratory-tract disease (28).

***Mycoplasma pneumoniae.*** *M. pneumoniae* has been implicated as a cause of pharyngitis, but the pharyngitis is generally considered to be a symptom of lower respiratory tract disease. With no widespread rapid diagnostic testing available for *M. pneumoniae*, no testing is generally warranted. Serology is often performed on patients with suspected pneumonia.

***Neisseria gonorrhoeae* and *Corynebacterium diphtheriae.*** Both *N. gonorrhoeae* and *C. diphtheriae* are known but rare causes of pharyngitis. Nonetheless, an assumption can be made that when a clinician orders a test for *N. gonorrhoeae* the request is based upon clinical evidence or patient history, and the test should be performed. With *C. diphtheriae*, it may be prudent to request a clinical consultation before the test is performed.

**Other bacteria.** If a request is received to identify the predominant organism from a throat specimen, this may be indicative of a lack of understanding of what is and is not normal pharyngeal flora. Hable et al. (21) published a simple but elegant study more than 30 years ago examining the flora (bacterial and viral) of two groups of children: one group with acute upper respiratory tract infections and another group composed of healthy controls. The results of that study are summarized in Table 4. Hable et al. drew two conclusions from their study. First, no children asymptomatically carried respiratory viruses, and second, only GAS was isolated more frequently from the ill than from the healthy children. Normal pharyngeal flora, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, should not be reported from routine throat cultures. To do so encourages inappropriate antimicrobial therapy.

**Viruses.** Viruses are the most common cause of pharyngitis in both adult and pediatric populations (3, 41). No specific testing is generally warranted to identify a specific viral etiology. Primary infection with herpes simplex virus may be indistinguishable from infections due to other viruses or GAS. However, vesicles and shallow ulcers on the palate, which are characteristic of herpetic infection can, when present, contribute to a differential diagnosis.

Not to be overlooked as a cause of pharyngitis is primary human immunodeficiency virus (HIV) infection. After a 3- to 5-week incubation period, patients can present with "flu-like" symptoms, including pharyngitis. Patient history, including an assessment of HIV risk factors, may suggest the need for HIV testing.

TABLE 4. Microorganisms isolated from two groups of 490 children each[a]

| Microorganism | Ill children | | Controls | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Bacteria | | | | |
| *Streptococcus pyogenes* (group A, beta-hemolytic) | 188 | 38.4 | 13 | 2.7 |
| *Streptococcus* species (beta-hemolytic, not group A) | 33 | 6.7 | 31 | 6.3 |
| *Streptococcus* species (group D) | 38 | 7.8 | 40 | 8.2 |
| Streptococci, viridans group | 472 | 96.3 | 466 | 95.1 |
| *Haemophilus influenzae* | 47 | 9.6 | 52 | 10.6 |
| *Haemophilus parainfluenzae* | 66 | 13.5 | 61 | 12.4 |
| *Haemophilus parahemolyticus* | 76 | 15.5 | 97 | 19.8 |
| *Haemophilus hemolyticus* | 3 | 0.6 | 3 | 0.6 |
| *Staphylococcus aureus* | 57 | 11.6 | 109 | 22.2 |
| *Staphylococcus epidermidis* | 375 | 76.5 | 340 | 69.4 |
| *Diplococcus pneumoniae* | 39 | 8.0 | 32 | 6.5 |
| *Neisseria* species | 478 | 97.5 | 460 | 93.9 |
| *Corynebacterium* species | 39 | 8.0 | 36 | 7.4 |
| *Klebsiella* species | 5 | 1.0 | 3 | 0.6 |
| *Enterobacter* species | 5 | 1.0 | 3 | 0.6 |
| *Escherichia coli* | 14 | 2.9 | 17 | 3.5 |
| *Pseudomonas aeruginosa* | 4 | 0.8 | 2 | 0.4 |
| *Herellea vaginicola* | 3 | 0.6 | 0 | 0 |
| Viruses | | | | |
| Influenza $A_2$/Hong Kong virus | 27 | 5.5 | 0 | 0 |
| Adenovirus | 24 | 4.9 | 1 | 0.2 |
| Parainfluenza virus | 23 | 4.7 | 0 | 0 |
| Rhinovirus | 6 | 1.2 | 0 | 0 |
| Herpes simplex virus | 9 | 1.8 | 0 | 0 |
| Respiratory syncytial virus | 3 | 0.6 | 0 | 0 |
| Coxsackie B virus | 2 | 0.4 | 0 | 0 |
| Cytomegalovirus | 2 | 0.4 | 0 | 0 |
| Poliovirus | 1 | 0.2 | 1 | 0.2 |

[a] Adapted from reference 21 with permission of the publisher. Percentage values refer to the number of swabs cultured (of 490 total in each group).

Patients with Epstein-Barr virus (EBV) infection may present with an exudative tonsillitis or pharyngitis. However, patients with EBV infection usually present with more systemic symptoms. The monospot test is the accepted standard diagnostic test. False-negative tests do occur, but repeat testing, 10 days after the first test, can usually confirm the diagnosis for patients with persistent symptoms. For young children, the monospot test is less sensitive (41). EBV serology may be indicated for children.

## ANTIMICROBIAL SUSCEPTIBILITY TESTING

Laboratories occasionally receive requests to perform testing for antimicrobial susceptibility to penicillin on a GAS isolate. The request is usually related to a patient with recurrent episodes of pharyngitis. As noted by Pichichero (32, 33), there are several common reasons for apparent penicillin treatment failure. These include (i) beta-lactamase-producing organisms in the oropharynx that inactivate penicillin; (ii) cases of repeat

infection, which may be of viral etiology; (iii) poor patient compliance in taking oral medication; (iv) possible patient reexposure to a GAS-positive family member or associate; or (v) patient is a GAS carrier (test of cure for GAS pharyngitis should not be routinely carried out) (33). The role of beta-lactamase-producing organisms in the oropharynx is supported by outcome data demonstrating a clinical failure rate that was 5% less for cephalosporins than with penicillin.

When treatment with erythromycin is likely, antimicrobial susceptibility testing for erythromycin is justified. Although, historically, the levels of resistance to erythromycin in the United States have generally been low, recent reports by Huovinen and Martin et al. (27, 30) on the sudden emergence of a clone of erythromycin-resistant GAS in Pittsburgh has increased interest in testing isolates of GAS for erythromycin resistance. In these studies, resistance rates went from 0 to 48% within a few months in isolates from children attending one school, and clonal isolates were isolated from other patients in the Pittsburgh area.

## SUMMARY

The microbiology laboratory plays a very important role in the diagnosis and management of patients with pharyngitis. Arguably, it is at least as important in identifying the 70 to 80% of patients with pharyngitis who do no require antimicrobial therapy as it is in identifying patients for whom antimicrobial therapy is appropriate. One of our educational responsibilities is to inform clinicians of the importance of performing diagnostic testing to establish an accurate diagnosis. Although some guidelines now suggest that clinical criteria alone may suffice for the diagnosis of GAS infection in adults (20), this topic remains controversial. Bisno et al. (4) have stated that these new recommendations should have been tested in a clinical trial before being published.

Laboratorians need to be strong advocates for both appropriate testing and judicial use of antimicrobial agents for diagnosis and management of pharyngitis. Antibiotic therapy is generally only indicated for pharyngitis caused by GAS (2, 9, 39) and the rare case caused by *C. diphtheriae* and *N. gonorrhoeae*. Additional study is needed to clarify the benefit, if any, for the diagnosis and treatment of for beta-hemolytic streptococci other than GAS. As noted by Bisno (3), the benefits of antimicrobial therapy against these organisms are currently unknown.

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