REFERENCES

1. Glezen WP, Denny FW. Epidemiology of acute lower respiratory disease in children. N Engl J Med 1973;288:498–505.
2. Garofalo R, Sabry M, Jamaluddin M, et al. Transcriptional activation of the interleukin-8 gene by respiratory syncytial virus infection in alveolar epithelial cells: nuclear translocation of the RelA transcription factor as a mechanism producing airway mucosal inflammation. J Virol 1996;70:8773–81.
3. Harrison AM, Bonville CA, Rosenberg HF, Domachowske JB. Respiratory syncytial virus-induced chemokine expression in the lower airways: eosinophil recruitment and degranulation. Am J Respir Crit Care Med 1999;159:1918–24.
4. Becker S, Reed W, Henderson FW, Noah TL. RSV infection of human airway epithelial cells causes production of the beta-chemokine RANTES. Am J Physiol 1997;272:L512–20.
5. Everard ML, Swarbrick A, Wrightham M, et al. Analysis of cells obtained by bronchial lavage of infants with respiratory syncytial virus infection. Arch Dis Child 1994;71:428–32.
6. Smith PK, Wang SZ, Dowling KD, Forsyth KD. Leucocyte populations in respiratory syncytial virus-induced bronchiolitis. J Paediatr Child Health 2001;37:146–51.
7. Domachowske JB, Rosenberg HF. Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. Clin Microbiol Rev 1999;12:298–309.
8. van Woensel JBM, Wolfs TFW, van Aalderen WMC, Brand PLP, Kimpen JLL. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. Thorax 1997; 52:634–7.
9. Falsey AR, Formica MA, Walsh EE. Diagnosis of respiratory syncytial virus infection: comparison of reverse transcription-PCR to viral culture and serology in adults with respiratory illness. J Clin Microbiol 2002;40:817–20.
10. van Elden L, Nijhuis M, Schipper P, Schuurman R, van Loon A. Simultaneous detection of Influenza virus A and B using real-time quantitative PCR. J Clin Microbiol 2001;39:196–200.
11. Pollack M, Ruttiman U, Gettson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16:1110–16.
12. Tasker RC, Gordon I, Kiff K. Time course of severe respiratory syncytial virus infection in mechanically ventilated patients. Acta Paediatr 2000;89:938–41.
13. Buckingham SC, Jafri HS, Bush AJ, et al. A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSV) infection: effects on RSV quantity and clinical outcome. J Infect Dis 2002;185: 1222–8.
14. Sheeran P, Jafri H, Carubelli C, et al. Elevated cytokine concentrations in the nasopharyngeal and tracheal secretions of children with respiratory syncytial virus disease. Pediatr Infect Dis J 1999;18:115–22.
15. Newth CJ. Time course of severe respiratory syncytial virus infection in mechanically ventilated infants. Acta Paediatr 2000;89:893–5.
16. Gardner PS, McQuillin J, Court SD. Speculation on pathogenesis in death from respiratory syncytial virus infection. Br Med J 1970;1:327–30.
17. Neilson KA, Yunis EJ. Demonstration of respiratory syncytial virus in an autopsy series. Pediatr Pathol 1990;10:491–502.
18. Hall CB, Douglas RGJ, Geiman JM. Respiratory syncytial virus infections in infants: quantitation and duration of shedding. J Pediatr 1976;89:11–15.
19. Hall CB, Douglas RGJ, Geiman JM. Quantitative shedding patterns of respiratory syncytial virus in infants. J Infect Dis 1975;132:151–6.

Pediatr Infect Dis J, 2003;22:726–31 Vol. 22, No. 8

Extrapharyngeal group A *Streptococcus* infection: diagnostic accuracy and utility of rapid antigen testing

HERBERT W. CLEGG, MD, STEVEN D. DALLAS, PHD, OLIVER F. RODDEY, MD, EDWARD S. MARTIN, MD, RAYMOND L. SWETENBURG, MD, ELIZABETH W. KOONCE, MD, MARY B. FELKNER, MD, AMY G. RYAN, MD AND THE PRESBYTERIAN PEDIATRIC RESEARCH GROUP

Background. **Antigen tests have been well-studied and are widely used in pediatric practice for rapid detection of group A *Streptococcus* (GAS) infections in the throat, but they have not been examined sufficiently for the detection of infection of skin sites, such as the perineal region or impetiginous lesions.**

Methods. **During the 3-year period 1999 to 2002, we evaluated 239 patients with suspected GAS skin infection, in 5 pediatric practices, using 3 Dacron swabs for each site. The first swab was tested in the pediatric office laboratory with an antigen detection kit. For the first 91 patients,**

Accepted for publication April 22, 2003.

From Eastover Pediatrics and Department of Pediatrics (HWC, OFR, ESM, RLS, EWK, MBF, AGR) and Presbyterian Laboratory Services, Microbiology Department (SDD), Presbyterian Hospital, Charlotte, NC.

Key words: Group A *Streptococcus*, *Streptococcus pyogenes*, rapid antigen test, diagnostic accuracy, sensitivity and specificity, extrapharyngeal infections.

Reprints not available.

the Abbott Test Pack Plus antigen detection test (ADT) was used. The Abbott Signify Strep A ADT was used to test subsequent patients. The second swab was tested with BD Directigen 1-2-3 ADT in the hospital laboratory. The third swab was placed in modified Stuart's transport medium for comparison of recovery of GAS from culture in broth or on agar. A positive culture served as the reference standard. Test performance and test accuracy were determined for each ADT.

Results. **Of the 247 ADTs and cultures performed on 239 patients, 91 with suspected skin infection were tested with the Test Pack Plus test, 149 with the Signify Strep A test and 247 with the Directigen test. Eighty-six (35%) cultures were positive, 73 from perineal sites (54 rectal, 13 vaginal, 6 penile) and 13 from impetiginous lesions. There was 100% concordance for the 86 cultures positive for GAS in a comparison between dry Dacron swabs and swabs that had been placed in modified Stuart's transport medium. Test Pack Plus and Signify Strep A ADTs had similar performance characteristics for skin infections: sensitivity, 92 and 88%; specificity, 99 and 97%; positive predictive value, 96 and 94%; and negative predictive value, 97 and 93%. Directigen ADT had sensitivity 78%, specificity 100%, positive predictive value 100% and negative predictive value 89%. Accuracy for the tests varied from 92 to 97%.**

Conclusion. **Tests designed to detect GAS carbohydrate antigen in patients with pharyngitis can be used rapidly and accurately to detect GAS antigen in patients with cutaneous lesions suspected of GAS infection.**

INTRODUCTION

Rapid antigen testing has been well-studied and applied in clinical practice for group A *Streptococcus* (GAS) infection in the throat,[1] but limited attention has been given to antigen detection testing for other sites.[2–8]

The skin and soft tissues are the primary nonthroat sites of GAS infection in children.[9, 10] Perineal GAS infection is a recognized, perhaps underdiagnosed, clinical entity in children and includes perianal infection characterized by perianal erythema and/or itching, anal fissure, painful defecation, blood-streaked stools and mucopurulent discharge;[2, 11, 12] vulvovaginitis in prepubertal girls;[13] and balanitis in prepubertal, especially uncircumcised, boys.[14] Group A streptococci are also a common cause of impetigo in children.[9, 10]

Culture results for skin samples may take 24 to 72 h, and most office laboratories do not have the capability of performing the service. An antigen detection test (ADT) may aid in rapid differentiation of cutaneous GAS infection from entities such as candidiasis, nonspecific diaper dermatitis, pinworm infestation, apparent fissures with local trauma or even suspected sexual abuse. We undertook this study to determine whether ADTs could be accurately and rapidly used to detect GAS at the common sites of GAS infection other than the pharynx, particularly perineal and other superficial skin sites. Secondary aims were to evaluate the concordance of ADTs in use in our office and hospital laboratories and to assess the need for transport media for recovery of GAS from skin sites.

MATERIALS AND METHODS

Patients. Patients eligible for inclusion were children 0 to 18 years of age with the clinical suspicion of GAS infection in the perineal region (anus/vagina/penis) and other superficial skin sites seen in our 5 pediatric office practices (22 providers). Clinical criteria for suspected perineal GAS infection included erythema and/or maceration in the perineal area or these findings with or without discharge from the vagina in girls or penis in boys and also included perianal itching, anal fissure, painful defecation, blood-streaked stools and discharge from or about the anus, vagina or penis. Skin lesions consistent with streptococcal impetigo were usually nonbullous, had erythematous bases and had honey-crusted exudates or crusts. We attempted to enroll consecutive patients meeting these criteria.

Children treated with an antibiotic within the previous week or who had another diagnosis explaining the findings were excluded. The protocol was approved by the Institutional Review Board of Presbyterian Hospital, Charlotte, NC. Informed, written consent was obtained at study entry.

Specimen collection and culture methods. Specimens were obtained by sequentially rubbing the affected site with three, sterile Dacron-tipped swabs (Fig. 1). The first two swabs were replaced in their original paper packets, and the third swab was placed in modified Stuart's transport medium (Starswab; Starplex Scientific, Etobicoke, Canada), as is the standard protocol for specimens for culture taken from the perineum or skin. These swabs were either hand-carried or transported by courier the same day (usually within a few hours) to the Eastover Pediatrics Clinic office on-site laboratory. This was staffed by a certified medical technologist and is Clinical Laboratory Improvement Amendments (CLIA)-approved for high complexity testing. Swabs 2 (dry) and 3 (in Stuart's transport medium) were then transported the same day by courier to the Presbyterian Hospital microbiology laboratory where all tests for these swabs were done by one of the authors (SD).

The first swab was inoculated onto a sheep blood agar (SBA) plate (Remel, Lenexa, KS) using standard

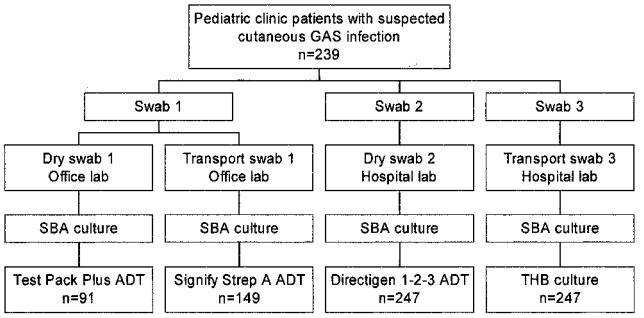

FIG. 1. Study design for evaluation of three ADTs for cutaneous GAS infection.

technique.[15] Six to eight stabs were made into the agar, and a bacitracin disk (Taxo A disk, 0.04 unit; BD Biosciences, Franklin Lakes, NJ) was applied at the junction of the primary and secondary streaks. Plates were incubated overnight aerobically at 35–37°C and interpreted by one of the authors (HWC or OFR). Plates negative for beta hemolysis the first day were reincubated and reinterpreted the next day. All plates were also evaluated in blinded manner by a microbiologist (SD). The second and third swabs were inoculated onto SBA. The third swab was then placed in a tube of Todd-Hewitt enrichment broth (THB) which was incubated for 18 to 24 h in 35°C and room air, then subcultured onto SBA, and incubated and interpreted as described above.

If isolated colonies suggestive of beta hemolysis were present on the original plates or after subculturing, a confirmatory GAS latex agglutination test was performed following the manufacturer's instructions (PathoDx Strep Grouping kit, Diagnostic Products Corp., Los Angeles, CA). If the organism was positive for GAS antigen, no further testing was performed. If the test was negative, the organism was Gram-stained and tested for group B, C, F and G antigens with the same grouping kit.

Test evaluation. After it was used to inoculate SBA at the Eastover Pediatrics Clinic office laboratory, the first swab was used by the office laboratory technologist to perform the rapid antigen test. The Abbott Test Pack Plus test (Abbott Laboratories, Abbott Park, IL), a CLIA-moderately complex enzyme immunoassay, was selected because it was the test kit in use for GAS antigen detection testing for throat specimens in our office laboratory when the study began. In 2000 this test kit and several others were removed from the market by an Food and Drug Administration consent decree[16] because of general quality control issues (and not specifically related to kit problems) at Abbott Laboratories. Ninety-one specimens had been evaluated with this test kit. Abbott substituted the kit with Signify Strep A, a CLIA-waived, color immunochromatographic test. This was used for the remainder of the study (as well as for ADT for throat specimens in the office). When this change was made, the first swab obtained from the patient (see Fig. 1) was placed in modified Stuart's transport medium (Starswab), because a prior verification exercise[17] in our office laboratory with the Signify Strep A kit for throat specimens had revealed improved sensitivity compared with a dry swab (unpublished data).

In the Presbyterian Hospital laboratory, the second dry swab (after replacement in its paper packet), was inoculated onto SBA and then tested for antigen using BD Directigen 1-2-3 (BD Biosciences), a CLIA-moderately complex liposome immunoassay. It was selected because it was the test kit in use for the hospital laboratory for throat specimens.

For each ADT the manufacturer's guidelines were followed in the performance and interpretation of the tests. Those reading the ADTs were blinded to the results of each other, and the readers of the culture plates were blinded to the ADT results.

Statistical analyses. The reference standard for the definitive presence of GAS was considered to be the isolation of a serologically confirmed group A *Streptococcus* by any one of the four cultures. Test performance characteristics (sensitivity, specificity, positive and negative predictive values) were calculated with standard definitions from 2×2 contingency tables along with 95% confidence intervals to estimate uncertainty.[18] Clinical accuracy, or test efficiency, was determined by dividing the total true positives and negatives by the total number of specimens tested.[17]

RESULTS

During the 3-year study period, 247 ADTs and cultures were performed on 239 patients with suspected extrapharyngeal GAS infection. There were 8 episodes of recurrent infection (in 6 patients), each >3 weeks apart, and these were included. Ninety-one were tested with the Test Pack Plus ADT, 156 with the Signify Strep A ADT and 247 with the Directigen ADT (Table 1). For the Signify Strep A ADT, 7 were excluded (for a total of 149) because the test was performed by someone other than the office medical technologist. The study group had a median age of 4.9 years (range, 0.9 to 18.8 years) for those with positive cultures and 3.9 years (range, 0.1 to 17.5 years) for those with negative cultures.

Of the 247 specimens cultured, 86 were positive (35%) with 73 from perineal sites (54 rectal, 13 vaginal and 6 penile) and 13 from nonperineal skin sites (all were impetiginous lesions). All 4 cultures (3 SBA plates and THB) were positive in 80 of 86 (93%). In no instance was the THB the only positive culture, and the THB culture was negative 3 times when at least one other culture was positive.

In the culture comparison for GAS between the dry

TABLE 1. Performance characteristics for three antigen detection tests for GAS from extrapharyngeal sites

Characteristic	Antigen Detection Test		
	Abbott Test Pack Plus (n = 91)	Abbott Signify Strep A (n = 149)	BD Directigen (n = 247)
Sensitivity (%)	92.3 (74.9–99.1)* [24/26]†	87.9 (79.5–96.3) [51/58]	77.9 (69.1–86.7) [67/86]
Specificity (%)	98.5 (91.7–100) [64/65]	96.7 (90.7–99.3) [88/91]	100 (98.1–100) [161/161]
Positive predictive value (%)	96.0 (79.7–99.9) [24/25]	94.4 (84.6–98.8) [51/54]	100 (95.7–100) [67/67]
Negative predictive value (%)	97.0 (89.5–99.6) [64/66]	92.6 (87.4–97.9) [88/95]	89.4 (85.0–93.9) [161/180]
Accuracy (%)‡	96.7 (90.7–99.3) [88/91]	93.3 (89.3–97.3) [139/149]	92.3 (89.0–95.6) [228/247]

* Numbers in parentheses, 95% confidence interval.

† Clinical accuracy, or test efficiency, is defined by dividing the total true positives and true negatives by the total number of specimens tested.

swab and the swab placed in modified Stuart's transport medium, there was 100% concordance for the 86 positive cultures for GAS. Of the 247 specimens transported in liquid transport medium, overgrowth of Gram-positive organisms occasionally occurred, the most common organism being *Staphylococcus aureus*. Only 2 cultures were overgrown with Gram-negative organisms, one with *Proteus* sp. and the other with *Pseudomonas* sp. Meticulous subculturing usually resolved any issues. However, cultures from dry swabs rarely grew organisms other than GAS to any degree.

Table 1 shows the performance characteristics for the three ADTs evaluated. In comparison with the reference standard (any positive culture), the Test Pack Plus ADT gave sensitivity 92%, specificity 99%, positive predictive value 96% and negative predictive value 97%. The Signify Strep A ADT had sensitivity 88%, specificity 97%, positive predictive value 94% and negative predictive value 93%. The sensitivity of the Directigen ADT tended to be lower in comparison with that of the Signify Strep A ADT, but this was not significant (78% *vs.* 88%, $P = 0.125$, chi square test). The Directigen ADT gave 100% specificity. The overall accuracy for the tests varied from 92 to 97%.

DISCUSSION

In previous studies of ADTs applied to extrapharyngeal sites, only two have included a substantial number of patients. Kokx et al.[2] identified perianal GAS infection in 31 children, 27 of whom had an ADT (Culturette Group A Rapid Strep ID, Marion Laboratories, Kansas City, MO) performed. Of these children 89% had a positive ADT, whereas none in a group of 119 well children was positive by ADT. Kaplan et al.[3] evaluated an ADT (Culturette Group A Rapid Strep ID) in 129 children with impetigo (84 culture-positive) and found a sensitivity of 94% and a specificity of 96%. Coffey[4] found positive ADTs in 6 children with impetigo, and Bourgeois and Bourgeois[5] used an ADT to diagnose GAS skin and soft tissue infection in 8 children. In case reports others have reported use of an ADT to make a rapid diagnosis of extrapharyngeal GAS infection.[6–8]

In our evaluation the Test Pack Plus ADT performed slightly better than its successor, Signify Strep A, for extrapharyngeal specimens, but the Test Pack Plus test is no longer commercially available. The waived ADT, Signify Strep A, had better sensitivity than the moderately complex Directigen test (88% *vs.* 78%), but the Directigen test was slightly more specific (100 *vs.* 97%). It is possible that the delay in performance of the Directigen test (because of transportation to the hospital laboratory) resulted in its poorer sensitivity, but we did not evaluate this possibility by direct parallel comparison in the office or hospital laboratory. We sought to compare the tests under the conditions in which they would usually be done (the waived test in an office and the moderately complex test in a referral or hospital laboratory).

Our findings are consistent with those in published studies of Test Pack Plus, Signify Strep A and Directigen ADTs for throat specimens. Sensitivities in these studies ranged from 82 to 91% for Test Pack Plus,[19–22] 80 to 89% for Signify Strep A[23–25] and 39 to 95% for Directigen.[26–30] In these same studies specificities are reported as between 85 and 100%.[19–30]

As with throat swabs for the recovery of GAS,[31] it appears that a moistened swab from perineal and other skin sites is not necessary for the culture recovery of GAS as the dry swab and swab placed in modified Stuart's transport medium showed 100% concordance for the 86 positive cultures. Use of a dry swab from these sites may also make interpretation easier as there was little overgrowth of other organisms with the dry swab compared with results from the swab placed in transport medium.

This study has several limitations. We enrolled only 42 patients with specimens from nonperineal cutaneous infections, and only 13 of these patients had positive cultures from impetiginous lesions. However, our findings are in accordance with those of the one other study that addressed ADT use for impetigo.[3] We also encountered no patients with invasive soft tissue or toxin-associated streptococcal infections. Nonetheless the spectrum of patients who were included represents the usual variety of suspected cutaneous GAS infections seen in pediatric outpatients.

We conclude that the three ADTs evaluated have acceptable performance characteristics for the detection of GAS infections in extrapharyngeal sites. Their use can aid in the rapid differentiation of cutaneous

lesions, especially in the perianal area, and may limit inappropriate antibiotic therapy for non-GAS lesions. The Signify Strep A test is particularly attractive for office laboratory use given its excellent performance characteristics and its waived status. For hospitalized patients with suspected necrotizing fasciitis, a GAS ADT might be very useful in making a presumptive, rapid etiologic diagnosis.

Although the current generation of ADTs for GAS may eventually be supplanted by newer technology,[32] ADTs for GAS can be used for extrapharyngeal specimens as with throat specimens. The controlled conditions in this study may not reflect those in an office or other setting where an occasional rapid test for GAS may be done and, as with throat specimens, a negative result of a rapid test for an extrapharyngeal site should be confirmed with a conventional culture. ADTs for GAS should also be validated in the individual laboratory setting in which they will be used, especially when used for sites of infection for which there is no formal Food and Drug Administration approval.

APPENDIX

Members of the Presbyterian Pediatric Research Group: Timothy J. Eichenbrenner, M.D., Glenn C. Holladay, M.D., Elizabeth Pediatrics, Charlotte, NC; Charles M. Blanton, M.D., Michael W. Craig, M.D., Betty J. Crosby, M.D., Stephen J. Ezzo, M.D., Michele K. Parish, M.D., R. Scott Spies, M.D., Walter E. Thomas, M.D., Rachel L. Wiese, M.D., Pamela B. Young, M.D., Matthews Childrens Clinic, Matthews, NC; Wirt T. Neale, M.D., Neale Pediatrics, Charlotte, NC; Sharon M. Roncevich, M.D., Roncevich Pediatrics, Charlotte, NC; Judith H. Osborn, R.N., M.S.N., P.N.P., Jan E. Rapisardo. R.N., M.S.N., F.N.P., Jane L. Moss, R.N., Frances A. Lewis, C.L.S., N.C.A., Eastover Pediatrics, Charlotte, NC.

REFERENCES

1. Bisno AL, Gerber MA, Gwaltney JM, Kaplan EL, Schwartz RH. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 2002;35: 113–25.
2. Kokx NP, Comstock JA, Facklam RR. Streptococcal perianal disease in children. Pediatrics 1987;80:659–63.
3. Kaplan EL, Reid HF, Johnson DR, Kunde CA. Rapid antigen detection in the diagnosis of group A streptococcal pyoderma: influence of a "learning curve effect" on sensitivity and specificity. Pediatr Infect Dis J 1989;8:591–3.
4. Coffey JD Jr. Rapid antigen testing for streptococcal pyoderma in private practice. Pediatr Infect Dis J 1990;9:303.
5. Bourgeois SD, Bourgeois MH. Use of the rapid *Streptococcus* test in extrapharyngeal sites. Am Fam Physician 1996;54: 1634–6.
6. Ault MJ, Geiderman J, Sokolov R. Rapid identification of group A *Streptococcus* as the cause of necrotizing fasciitis. Ann Emerg Med 1996;28:227–30.
7. Bernard P, Toty L, Mounier M, Denis F, Bonnetblanc J. Early detection of streptococcal group antigens in skin samples by latex particle agglutination. Arch Dermatol 1987;123:468–70.
8. Hudson DA, Theron JE, Roditi DOJ, Bloch CE. Evaluation of a commercial kit for detection of *Streptococcus pyogenes* in a burns unit. S Afr Med J 1991;79:329–30.
9. Bisno AL, Stevens DL. Streptococcal infection of skin and soft tissues. N Engl J Med 1996;334:240–5.
10. Wannamaker LW. Differences between streptococcal infections of the throat and of the skin. N Engl J Med 1970;282: 23–30, 78–85.
11. Amren DP, Anderson AS, Wannamaker LW. Perianal cellulitis associated with group A streptococci. Am J Dis Child 1966;112:546–52.
12. Mogielnicki NP, Schwartzman JD, Elliott JA. Perineal group A streptococcal disease in a pediatric practice. Pediatrics 2000;106:276–81.
13. Straumanis JP, Bocchini JA. Group A beta-hemolytic streptococcal vulvovaginitis in prepubertal girls: a case report and review of the past twenty years. Pediatr Infect Dis J 1990;9: 845–8.
14. Orden B, Martin R, Franco A, Ibanez G, Mendez E. Balanitis caused by group A beta-hemolytic streptococci. Pediatr Infect Dis J 1996;15:920–1.
15. Wannamaker LW. A method for culturing beta hemolytic streptococci from the throat. Circulation 1965;32:1054–8.
16. Feigal D, Zoon KC. Dear colleague letter: Abbott Labs Consent Decree. November 3, 1999. Available at http://www.fda.gov/cdrh/ocd/abbottletter.html.
17. Elder BL, Hansen SA, Kellogg JA, Marsik FJ, Zabransky RJ. Verification and validation of procedures in the clinical microbiology laboratory. McCurdy BW, coordinating ed., Cumitech 31. Washington, DC: American Society for Microbiology, 1997.
18. Fletcher RH, Halstead SB. Evaluation of diagnostic tests. In: Thomas JC, Weber DJ, eds. Epidemiologic methods for the study of infectious diseases. New York: Oxford University Press, 2001:192–210.
19. Hoffman S, Witt K. Diagnosis in general practice of group A streptococcal pharyngotonsillitis with five antigen detection test kits and a rapid kit for C-reactive protein [Abstract C-22]. In: Proceedings and abstracts of the American Society for Microbiology, Chicago, May 30 to June 3, 1999. Washington, DC: American Society for Microbiology, 1999.
20. Laubscher B, Van Melle G, Dreyfuss N, deCrousaz H. Evaluation of a new immunologic test kit for rapid detection of group A streptococci, the Abbott TestPack Strep A Plus. J Clin Microbiol 1995;33:260–1.
21. Roe M, Kishiyama C, Davidson K, Schaefer L, Todd J. Comparison of Biostar Strep A OIA Optical Immune Assay, Abbott TestPack Plus Strep A, and culture with selective media for diagnosis of group A streptococcal pharyngitis. J Clin Microbiol 1995;33:1551–3.
22. Schroeder SM, Hadziyannis E, Cornish NE, Washington JA. Comparison of Abbott TestPack Plus Strep A with Biostar Acceava Strep A tests for laboratory diagnosis of streptococcal pharyngitis [Abstract C-241]. In: Proceedings and abstracts of the American Society for Microbiology, Los Angeles, May 21 to 25, 2000. Washington, DC: American Society for Microbiology, 2000.
23. Mossop L, Blecker Shelly D, McGowan KL. Evaluation of the Signify Strep A Test for the direct detection of group A streptococcal antigen (GAS) in throat swabs from a pediatric population [Abstract C-106]. In: Proceedings and abstracts of the American Society for Microbiology, Orlando, May 20 to 24, 2001. Washington, DC: American Society for Microbiology, 2001.
24. Roosevelt GE, Kulkarni MS, Shulman ST. Critical evaluation of a CLIA-waived streptococcal antigen detection test in the emergency department. Ann Emerg Med 2001;37:377–81.
25. Haller B, Nassos P, Wong M. Comparison of the Abbott Signify Strep A test with culture for detection of group A *Streptococcus* in throat specimens [Abstract C-31]. In: Proceedings and abstracts of the American Society for Microbiology, Salt Lake City, May 19 to 23, 2002. Washington, DC: American Society for Microbiology, 2002.
26. Huck W, Reed BD, French T, Mitchell RS. Comparison of the Directigen 1-2-3 group A Strep Test with culture for detection of group A beta-hemolytic streptococci. J Clin Microbiol 1989;27:1715–8.
27. Moyer NP, Quinn PJ, Showalter CA. Evaluation of the Directigen 1, 2, 3 Group A Strep Test for diagnosis of streptococcal pharyngitis. J Clin Microbiol 1990;28:1661–3.
28. Joslyn SA, Hoekstra GL, Sutherland JE. Rapid antigen

detection testing in diagnosing group A beta-hemolytic streptococcal pharyngitis. J Am Board Fam Pract 1995;8:177–82.
29. Reed BD, Huck W, French T. Diagnosis of group A beta-hemolytic *Streptococcus* using clinical scoring criteria, Directigen 1-2-3 group A streptococcal test, and culture. Arch Intern Med 1990;150:1727–32.
30. Donatelli J, Macone A, Goldmann DA, et al. Rapid detection of group A streptococci: comparative performance by nurses and laboratory technologists in pediatric satellite laboratories using three test kits. J Clin Microbiol 1992;30:138–42.
31. Roddey OF, Mauney CU, Clegg HW, Martin ES, Swetenburg RL. Comparison of immediate and delayed culture methods for isolation of group A streptococci. Pediatr Infect Dis J 1989;8:710–12.
32. Uhl JR, Vetter EA, Cockerill FR. Detection of group A *Streptococcus* from throat swabs using rapid homogeneous PCR [Abstract C-21]. In: Proceedings and abstracts of the American Society for Microbiology, Orlando, May 20 to 24, 2001. Washington, DC: American Society for Microbiology, 2001.

Pediatr Infect Dis J, 2003;22:731–5
Vol. 22, No. 8

Culture-negative osteomyelitis

REBECCA L. FLOYED, MD AND RUSSELL W. STEELE, MD

Objective. **To examine the natural history, clinical manifestations, laboratory changes and outcomes of children with culture-negative osteomyelitis and to compare findings with cases of culture-positive infection treated during the same time period.**

Design. **Retrospective review of consecutive admissions for osteomyelitis during the 4-year period 1998 through 2001, with a minimum follow-up of 1 year.**

Setting. **A single urban children's hospital with a large orthopedic referral service.**

Clinical and laboratory measures. **Age, gender, predisposing factors, clinical manifestations, maximum temperature, duration of pain, bone involved, laboratory changes, results of cultures from infected bone and blood and outcome after treatment.**

Results. **A total of 85 patients fulfilled study criteria, of whom 40 were culture-negative. Compared with culture-positive cases, culture-negative osteomyelitis patients were less likely to have antecedent trauma ($P = 0.0357$) and overlying skin changes ($P = 0.0001$), duration of pain and other symptoms was longer ($P = 0.0396$) and skeletal residua were rare. They were also older, with this difference approaching statistical significance ($P = 0.0586$).**

Conclusions. **Children with culture-negative osteomyelitis present initially differently from culture-positive cases and can be managed as presumed staphylococcal disease with excellent long term results.**

INTRODUCTION

The incidence of osteomyelitis in children has changed very little from the 1970s,[1–8] primarily because *Staphylococcus aureus* accounts for the majority of cases and little progress has been made in management and prevention of this pathogen. Diagnosis and management have also changed very little. Although magnetic resonance imaging (MRI) is often the diagnostic procedure of choice rather than the technetium bone scan as used during the previous three decades,[9] initial empiric therapy has remained relatively constant.[5–8, 10]

A review of current text chapters indicates that most references for pathophysiology, natural history, clinical presentations and outcome were published before 1980.[11–13] The only new observations have been the emergence of methicillin resistant *S. aureus*,[14] *Kingella kingae* as a significant pathogen in childhood septic arthritis occasionally involving bone[5] and the occasional case report of unusual pathogens such as *Bartonella henselae*[15] and *Borrelia bergdorferi*[16] causing bone infection.

One aspect of osteomyelitis that has received little attention in the literature is the natural history and outcome of those cases in which no bacterial pathogen

Accepted for publication April 22, 2003.
From the Division of Infectious Diseases, Department of Pediatrics, LSU Health Sciences Center, and Children's Hospital, New Orleans, LA.
Key words: Osteomyelitis, bone infection, bacterial infection, antibiotics, culture-negative.
Address for reprints: Russell W. Steele, M.D., Children's Hospital, 200 Henry Clay Avenue, New Orleans, LA 70118. Fax 504-894-5137; E-mail RWSteele@aol.com.