JOURNAL OF CLINICAL MICROBIOLOGY, June 1997, p. 1579–1581 Vol. 35, No. 6
0095-1137/97/$04.00+0

NOTES

Cost-Effectiveness of Rapid Diagnosis of Viral Respiratory Tract Infections in Pediatric Patients

PATRICK C. Y. WOO,[1] SUSAN S. CHIU,[2] WING-HONG SETO,[1] AND MALIK PEIRIS[1]*

Departments of Microbiology[1] and Paediatrics,[2] Queen Mary Hospital, University of Hong Kong, Hong Kong

Received 12 December 1996/Returned for modification 7 February 1997/Accepted 5 March 1997

Rapid diagnosis of respiratory viral infections in children resulted in significantly reduced hospital stays, antibiotic use, and laboratory utilization compared with those of a matched group of patients from the previous year who were diagnosed by virus culture. We demonstrate that rapid diagnosis of respiratory infections in children is a cost-effective procedure.

Cost-effectiveness of medical care is a major concern around the world. It is therefore important to evaluate the clinical and economic impact of all procedures, interventions, and investigations used in clinical practice (14). In the past, viral diagnosis based on culture and serology was often slow and constituted retrospective diagnosis. Now diagnosis in a clinically relevant time frame for a range of viruses is a reality (3–5, 7, 10, 11, 13), though relatively expensive, so its impact on patient care and the conditions of its use need to be addressed. However, there is little published data documenting the clinical impact of viral diagnosis (2, 12). Potentially, the benefits include the following: (i) collection of epidemiological information for disease control and vaccination; (ii) infection control (9); (iii) guidance in the use of antiviral therapy (1); and (iv) the impact of a precise etiologic diagnosis on other aspects of patient management, e.g., antibiotic use.

The introduction of a rapid viral diagnostic service for respiratory (and other viral) infections at a tertiary-care university teaching hospital provided an opportunity to assess its impact on clinical care. The hypothesis was that the introduction of rapid diagnosis of respiratory viral infection would affect patient care outcomes, such as duration of hospital stay, antibiotic use, and laboratory utilization, and would be cost-effective even for patients not having an underlying disease.

The Queen Mary Hospital in Hong Kong is a 1,350-bed tertiary-care and university teaching hospital with 130 acute-care pediatric beds serving a population of 1.3 million. Pediatric patients aged 0 to 6 years who were admitted between September 1994 and September 1996 and for whom a virological diagnosis of respiratory tract infection was available were eligible for analysis. Only patients under the care of pediatricians who participated in patient care during both 1994–1995 (year 1) and 1995–1996 (year 2) were included. Index patients with a virologically documented infection were randomly selected from the year 1 admissions and matched with patients from year 2 for the following parameters: (i) a viral etiology of respiratory syncytial virus (RSV), influenza virus A, influenza virus B, parainfluenza virus type 1, 2, or 3, or adenovirus; (ii) age; and (iii) month of admission to the hospital. Patients with a major underlying disease (e.g., congenital heart disease or immunodeficiency) were excluded. Patient records were reviewed by a microbiologist and a pediatrician, neither of whom participated in the care of these patients during the period under study. Demographic information (age and sex of patients) and data on the outcome measures, including the duration of hospitalization, the number and duration of antibiotics used, and the number of other microbiological investigations performed, were obtained.

Rapid diagnosis was performed by detecting viral antigens in nasopharyngeal aspirates by immunofluorescence techniques (4, 10) with commercially available reagents from Dako Diagnostics Ltd., Bucks, United Kingdom, and Chemicon International Inc., Temecula, Calif. Virus culture was performed by conventional techniques (15) at the Government Virus Unit of the Department of Health, Hong Kong, a central public health virology facility serving the whole of the Territory of Hong Kong. Nasopharyngeal aspirates were inoculated onto MDCK, HEp-2, LLC-MK2, and Vero cells and observed for 7 to 10 days for cytopathic effects or hemadsorption activity, as appropriate.

In a questionnaire survey, pediatricians were asked to score the impact of viral diagnosis on clinical management on a scale from 0 (no impact) to 9 (high impact) during year 1 compared to during year 2 in relation to "discharging patients more confidently" and "stopping or reducing the use of antibiotics." The responses were analyzed anonymously.

The outcome measures of patients from year 1 and year 2 and the responses to the questionnaire were compared by the paired Student *t* test. The chi-square test was used as a test of association of categorical data. Statistical significance was defined as a P value of <0.05.

The average cost per day of a hospital stay in a general pediatric ward was provided by the Finance Department of the Queen Mary Hospital and included drug, nursing, medical, laboratory, and overhead costs. The costs for rapid virus diagnosis included reagent, labor, and overhead charges and was obtained from the clinical microbiology laboratory. In both cases, "cost" rather than "charge" was used.

The year 1 and year 2 groups were similar in relation to sex ratio and age distribution. The age of the 214 patients studied ranged from 3 days to 6 years with a male-to-female ratio of 2.1:1. Throughout the study period, the results of RSV diagnosis were available within 24 h, excluding Sundays and public

* Corresponding author. Mailing address: Department of Microbiology, University Pathology Building, Queen Mary Hospital, Pokfulam Rd., Hong Kong. Phone: (852) 28554888. Fax: (852) 28551241. E-mail: malik@hkucc.hku.hk.

TABLE 1. Clinical outcome parameters for years 1 and 2

Virus type and year group	Mean ± SEM (P^a)		
	No. of days in hospital	No. of antibiotic days[d]	No. of microbiological investigations
RSV[b]			
Year 1	5.09 ± 0.37	4.47 ± 0.58	4.04 ± 0.30
Year 2	4.65 ± 0.38 (0.35)	3.25 ± 0.69 (0.18)	4.51 ± 0.34 (0.34)
Influenza viruses A and B, parainfluenza virus, and adenovirus[c]			
Year 1	5.11 ± 0.28	7.34 ± 0.76	5.50 ± 0.34
Year 2	3.77 ± 0.26 (<0.001)	3.55 ± 0.56 (<0.001)	4.27 ± 0.26 (<0.05)

[a] A paired *t* test was applied to the data. Numbers in parentheses are *P* values for a comparison between data for years 1 and 2 in the same column.
[b] $n = 51$.
[c] $n = 56$ (influenza virus A or B, 25; parainfluenza virus types 1 to 3, 10; adenovirus, 21).
[d] Cumulative days of antibiotic therapy (i.e., if a patient received 4 days of concurrent therapy with two antibiotics, the number of antibiotic days would be 8).

holidays. During year 1, virological diagnosis for the other respiratory viruses was available only by conventional culture 4 to 12 days (median, 8 days) after collection of the specimen. During year 2, results of rapid virus diagnosis were available within 24 h for influenza virus, parainfluenza virus, and adenoviruses as well.

Analysis of patient outcomes for the 56 pairs of patients with a virological diagnosis of influenza virus, parainfluenza virus, or adenovirus infection revealed a mean reduction in hospital stay of 1.3 days during year 2 ($P < 0.001$) (Table 1). The duration of antibiotic use and the number of other microbiological investigations performed were significantly reduced (by 3.8 days and 1.2 investigations per patient) during year 2. When patients with different virus etiologies were analyzed separately, the reduction in the duration of hospital stay was still significant for influenza virus infections (5.3 versus 3.6 days; $P < 0.005$) and parainfluenza virus infections (5.8 versus 4.1 days; $P < 0.05$) but not for adenoviral infections (4.6 versus 3.8 days; $P = 0.19$). A reduction of antibiotic use in year 2 was observed for all three virus groups: influenza virus (5.2 versus 2.8 days; $P < 0.05$); adenoviruses (9.8 versus 4.4 days; $P < 0.01$); parainfluenza virus (7.4 versus 3.6 days; $P = 0.19$). None of the patients received specific antiviral therapy.

The patients with RSV infections constituted a control group for whom rapid diagnosis was available in both years of the study. When patients who had RSV infection in the two years were compared, there was no significant difference in any of the outcome measures. There was, however, a trend towards a reduction in hospital stay (of 0.44 days) and antibiotic use (of 1.22 days) and, conversely, towards an increased use of microbiological investigations (of 0.47 investigations per patient) during year 2. To compensate for changes in patient management other than the impact of rapid viral diagnosis, the analysis was repeated after the mean difference for clinical outcome between year 1 and year 2 for the RSV group (the expected difference attributable to confounding factors, e.g., 0.44 days for duration of hospitalization) was subtracted from the observed differences between years 1 and 2 for patients with other viral infections. After we adjusted for this trend over the two consecutive years, there still remained a significant reduction in year 2 of days in the hospital (of 0.9 days; $P < 0.05$), days of antibiotic use (of 2.6 days; $P < 0.001$), and the number of other microbiological investigations (of 1.7 investigations; $P < 0.001$) when patients with influenza virus, parainfluenza virus, or adenovirus infection were considered together.

All 17 questionnaires administered to pediatricians working in the hospital during both years of the study were returned and analyzed. Viral diagnosis was perceived to have a significantly higher impact on "discharge of patients from hospital" (a score of 4.5 for year 1 versus 7.2 for year 2; $P < 0.0001$) and on "stopping or reducing antibiotic usage" (a score of 4.4 versus 6.7; $P < 0.0001$) during year 2.

This analysis shows a reduction of hospital stay, antibiotic use, and laboratory utilization for patients with influenza virus, parainfluenza virus, and adenovirus infections after the introduction of a rapid viral diagnostic service for these viruses. No other specific initiatives were taken to reduce hospital stay or antibiotic use, and the same clinicians cared for the patients in both years. Only influenza virus infection, and to a lesser degree RSV infection, is likely to vary significantly in severity between years. The influenza virus A and B serotypes circulating during the two years of the study were similar, except that influenza virus A/Johannesburg/33/94 (H3N2) was partially replaced by influenza virus A/Wuhan/359/95 (H3N2) during the latter part of year 2 (7a). The influenza A outbreak in 1995–1996 was, if anything, more severe than that in the previous year owing to the introduction of a new influenza virus A serotype (A/Wuhan) in the latter part of 1995–1996. This would bias the data against the hypothesis being tested. In any case, the reduction in days in the hospital was still significant (1.7 days; $P < 0.05$) even when parainfluenza viruses were considered alone.

Laboratory diagnosis (for respiratory virus infections other than RSV) was carried out by cell culture in year 1, while antigen detection was used in year 2. Cell culture is more sensitive than antigen detection for viruses other than RSV and may identify patients with low virus titers in the nasopharynx who were not identified by antigen detection methods (8, 10). Such a difference would tend to include patients with milder illness in the year 1 cohort and to bias the data towards a shorter hospital stay and less antibiotic use in year 1, i.e., to bias it against the hypothesis being tested.

As predicted by our hypothesis, patients with RSV (the control group) had similar clinical outcomes in years 1 and 2, although there was a trend towards reduced hospital stay and antibiotic use in year 2. After correction for this general trend, there was still a significant clinical impact on patients with influenza virus, parainfluenza virus, and adenoviral infections. We believe this improved outcome reflects the impact of rapid virus diagnosis on patient care. This contention is supported by pediatricians' perceptions reported via a questionnaire.

At this hospital, an average of 2,830 nasopharyngeal specimens from children are submitted for rapid respiratory virus diagnosis annually, of which 700 yield a positive result by direct antigen detection. The average cost per hospital day in an

acute-care pediatric bed was estimated to be HK$1,385. The reduction of 0.9 days in hospital stay (corrected for trend) per patient would save 18% of pediatric hospital costs (700 × 0.9 × 1,385 = HK$872,550 annually). The cost of providing a rapid viral antigen detection service for 2,830 specimens annually (HK$170 per specimen) was HK$481,000. Rapid viral diagnosis for respiratory disease therefore decreases costs even in such a simple model.

The changed diagnostic service in year 2 may in fact have contributed to the trend towards reduced hospital stay that was observed in the RSV group as well, due to a shorter turnaround time for rapid RSV diagnosis in year 2 (specimens were processed twice daily in year 2 as compared to once daily in year 1) and to the spillover of increased diagnostic confidence from having a rapid virus diagnosis in 25% (all viruses) of patients in year 2 rather than 8% (RSV only) of patients, as in year 1. If the uncorrected reduction in hospital stay (i.e., of 1.34 days) is used for calculation, rapid virus diagnosis results in a 26% saving in the cost of hospital care (a reduction of 938 days of hospital care for a saving of HK$1,299,130 annually).

Our study also demonstrated a 52% reduction in antibiotic use, including that within the hospital as well as that during continuation therapy at home. This reduction was achieved without any specific instructions to clinicians to withhold antibiotics pending virological results. Benefits of reducing unnecessary antibiotic use include fewer side effects and a reduced emergence of antibiotic-resistant bacteria (6). The availability of rapid diagnostic results also affects aspects of health care, such as infection control and improvement in clinical competence of trainee clinical staff, which are less easily quantifiable in economic terms. In conclusion, we have shown that the provision of a rapid viral diagnosis for patients with respiratory disease, even those without underlying complications, affects patient care and is cost-effective.

We thank J. Karlberg, Department of Pediatrics, University of Hong Kong, for advice on data analysis; W. L. Lim and the staff at the Government Virus Unit, Department of Health, Hong Kong, for providing virological culture results; and K. H. Chan and the technical staff of the Department of Microbiology, Queen Mary Hospital, for providing rapid viral diagnostic results.

This work was supported by a research grant (no. 337/042/0014) awarded to M.P. by the Committee on Research and Conference Grants of the University of Hong Kong.

REFERENCES

1. **American Academy of Pediatrics: Committee on Infectious Diseases.** 1996. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. Pediatrics **97:**137–139.
2. **Chonmaitree, T., M. A. Menegus, and K. R. Powell.** 1982. The clinical relevance of CSF viral culture: a two year experience with aseptic meningitis in Rochester, New York. JAMA **247:**1843–1847.
3. **Dahl, H., J. Marcoccia, and A. Linde.** 1997. Antigen detection: the method of choice in comparison with virus isolation and serology for laboratory diagnosis of herpes zoster in human immunodeficiency virus-infected patients. J. Clin. Microbiol. **35:**347–349.
4. **Gardner, P. S., and J. McQuillin.** 1980. Rapid virus diagnosis: application of immunofluorescence, 2nd ed. Butterworths, London, England.
5. **Gleaves, C. A., T. F. Smith, E. A. Shuster, and G. R. Pearson.** 1984. Rapid detection of cytomegalovirus in MRC-5 cells inoculated with urine specimens by using low-speed centrifugation and monoclonal antibody to an early antigen. J. Clin. Microbiol. **19:**917–919.
6. **Kaplan, S. L.** 1995. The emergence of resistant pneumococcus as a pathogen in childhood upper respiratory tract infections. Semin. Respir. Infect. **10:**31–36.
7. **Kok, T., L. D. Mickan, and C. J. Burrell.** 1994. Routine diagnosis of seven respiratory viruses and *Mycoplasma pneumoniae* by enzyme immunoassay. J. Virol. Methods **50:**87–100.

7a. **Lim, W. L.** Personal communication.

8. **Madeley, C. R., J. S. M. Peiris, and J. McQuillin.** 1996. Adenoviruses, p. 169–190. *In* S. Myint and D. Taylor-Robinson (ed.), Viral and other infections of the respiratory tract. Chapman Hall, London, England.
9. **Madge, P., J. Y. Paton, J. H. McColl, and P. L. K. Mackie.** 1992. Prospective controlled study of four infection-control procedures to prevent nosocomial infection with respiratory syncytial virus. Lancet **340:**1079–1083.
10. **Matthey, S., D. Nicholson, S. Ruhs, B. Alden, M. Knock, K. Schultz, and A. Schmuecker.** 1992. Rapid detection of respiratory viruses by shell vial culture and direct staining by using pooled and individual monoclonal antibodies. J. Clin. Microbiol. **30:**540–544.
11. **Rowley, A. H., R. J. Whitley, F. D. Lakeman, and S. M. Wolinsky.** 1990. Rapid detection of herpes-simplex-virus DNA in cerebrospinal fluid of patients with herpes encephalitis. Lancet **335:**440–441.
12. **Schlesinger, Y., M. H. Sawyer, and G. A. Storch.** 1994. Enteroviral meningitis in infancy: potential role for polymerase chain reaction in patient management. Pediatrics **94:**157–162.
13. **Todd, S. J., L. Minnich, and J. L. Waner.** 1995. Comparison of rapid immunofluorescence procedure with TestPak RSV and Directigen FLU-A for diagnosis of respiratory syncytial virus and influenza A virus. J. Clin. Microbiol. **33:**1650–1651.
14. **Weinstein, M. C., and W. B. Stason.** 1977. Foundations of cost-effectiveness analysis for health care and medical practices. N. Engl. J. Med. **296:**716–721.
15. **Wiedbrauk, D. L., and S. L. G. Johnston (ed.).** 1993. Manual of clinical virology. Raven Press, New York, N.Y.