Cost-effectiveness of Epinephrine and Dexamethasone in Children With Bronchiolitis

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KEY WORDS

children, bronchiolitis, cost-effectiveness, epinephrine, steroids, dexamethasone

ABBREVIATIONS

CanBEST—Canadian Bronchiolitis Epinephrine Steroid Trial
ED—emergency department
CHEO—Children's Hospital of Eastern Ontario
CI—credible interval

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WHAT'S KNOWN ON THIS SUBJECT: Despite the large economic burden of bronchiolitis, there have been no economic evaluations of the effectiveness of intervention with bronchodilators or steroids.

WHAT THIS STUDY ADDS: Economic analysis reveals that treatment infants with bronchiolitis with combined epinephrine and dexamethasone results in the lowest health care system and societal costs.

abstract

FREE

OBJECTIVE: Using data from the Canadian Bronchiolitis Epinephrine Steroid Trial we assessed the cost-effectiveness of treatments with epinephrine and dexamethasone for infants between 6 weeks and 12 months of age with bronchiolitis.

METHODS: An economic evaluation was conducted from both the societal and health care system perspectives including all costs during 22 days after enrollment. The effectiveness of therapy was measured by the duration of symptoms of feeding problems, sleeping problems, coughing, and noisy breathing. Comparators were nebulized epinephrine plus oral dexamethasone, nebulized epinephrine alone, oral dexamethasone alone, and no active treatment. Uncertainty around estimates was assessed through nonparametric bootstrapping.

RESULTS: The combination of nebulized epinephrine plus oral dexamethasone was dominant over the other 3 comparators in that it was both the most effective and least costly. Average societal costs were $1115 (95% credible interval [CI]: 919–1325) for the combination therapy, $1210 (95% CI: 1004–1441) for no active treatment, $1322 (95% CI: 1093–1571) for epinephrine alone, and $1360 (95% CI: 1124–1624) for dexamethasone alone. The average time to curtailment of all symptoms was 12.1 days (95% CI: 11–13) for the combination therapy, 12.7 days (95% CI: 12–13) for no active treatment, 13.0 days (95% CI: 12–14) for epinephrine alone, and 12.6 days (95% CI: 12–13) for dexamethasone alone.

CONCLUSION: Treating infants with bronchiolitis with a combination of nebulized epinephrine plus oral dexamethasone is the most cost-effective treatment option, because it is the most effective in controlling symptoms and is associated with the least costs. *Pediatrics* 2010; 126:623–631

Bronchiolitis is the most common lower respiratory tract infection in the first year of life. Although the mortality rate is low in high-income countries, bronchiolitis is an important illness worldwide because of the frequency that affected infants require medical care and hospitalization[1–3] and because of the burden on patients and families resulting from the length and severity of symptoms.[4] The number of hospital admissions for bronchiolitis has doubled over the last 10 to 15 years in both Canada and the United States.[1,2] In 1996, ~16% of all US hospital admissions in the first year of life were for bronchiolitis,[1] and in 1998, annual hospital charges for respiratory syncytial virus–associated bronchiolitis were estimated at $365 to $691 million.[5] Canadian statistics show that 35 in 1000 infants younger than 1 year are admitted annually with bronchiolitis, and annual costs were conservatively estimated 15 years ago at US $18 million.[3]

Despite the large economic burden of bronchiolitis, only 2 economic analyses of bronchiolitis management have been published. Respiratory syncytial virus immunoprophylaxis in infants at high risk was examined in 1 of them,[6] and in the other, the utility of chest radiographs was examined.[7] To our knowledge, there have been no economic evaluations of the effectiveness of bronchodilator or steroid intervention. As highlighted by Tugwell et al[8] and Hartling et al,[9] economic evaluations are an essential step in the overall process of establishing whether a therapy is beneficial. More specifically, this type of analysis establishes the relative efficiencies of therapies in terms of their costs and effects and provides decision-makers with cost/benefit information.[10]

Recently, results of the Canadian Bronchiolitis Epinephrine Steroid Trial (CanBEST) were published.[11] This multicenter, double-blind, placebo-controlled trial, which enrolled 800 patients, was designed to determine the effect of nebulized epinephrine and systemic corticosteroids in the treatment of outpatients with bronchiolitis. In this trial, combined therapy with epinephrine and dexamethasone, as compared with placebo, seemed to reduce the rate of hospital admission in the 7 days after study enrollment by 9% and showed a relative risk reduction of 35% ($P = .02$). Also, infants treated with this combination seemed to have a shorter length of stay, a more rapid return to quiet breathing, and greater improvement in respiratory rate and respiratory clinical score compared with those who received placebo. In contrast, neither epinephrine nor dexamethasone alone reduced the admission rate compared with placebo. The CanBEST results suggest that the combination of nebulized epinephrine and oral steroid treatment given to outpatients with bronchiolitis may reduce rates of hospital admission and improve some symptoms. Synergy between corticosteroids and β_2-agonists has been well documented in the treatment of asthma.[12–16] Although various models suggest mechanisms of action for this synergy,[16,17] results of in vitro studies of airway cells have indicated that β_2-adrenoceptor agonists can enhance the ability of corticosteroids to promote responses via the glucocorticoid receptor.[18] It is important to note that these findings reveal that β_2-adrenoceptor agonists are not only steroid-sparing but also enhance the maximal efficacy of the response to corticosteroids to a level that cannot be achieved by corticosteroids alone.[18] This effect can be said to mimic the clinic observations in the context of asthma.[15] In the context of wheezing infants and bronchiolitis, 3 small studies in similar populations have revealed similar synergy between both epinephrine and dexamethasone and albuterol and dexamethasone.[19–21]

Stemming from the CanBEST, the focus of this study was to assess the cost-effectiveness of combined treatment with epinephrine and dexamethasone in the treatment of outpatient infants with bronchiolitis.

METHODS

Randomized Controlled Trial

This analysis is based on a double-blind randomized controlled trial of 800 infants between 6 weeks and 12 months of age (median age: 5 months [interquartile range: 3–7]) with bronchiolitis who were seen at participating emergency departments (EDs). Patients were recruited during 3 bronchiolitis seasons (December through April) at 8 Canadian pediatric EDs from 2004 through 2007. All participating hospitals were members of the research group Pediatric Emergency Research Canada (PERC).

Written informed consent was obtained from all parents or guardians of included infants. The study was approved by Health Canada and by the ethics committee at each site. The results of the study were described elsewhere.[11]

Participants were eligible for inclusion in the study if they had a score of 4 to 15 on the respiratory distress assessment index[22] and had a diagnosis of bronchiolitis, defined as the first episode of wheezing associated with signs of upper respiratory tract infection. Excluded infants were those who had received previous bronchodilator treatments, had previous episodes of wheezing or a diagnosis of wheezing, any chronic cardiopulmonary disease, or immunodeficiency and infants who were in severe distress.

The computer-generated randomization sequence, stratified according

to center, used randomized permuted blocks of 8 and 12. To conceal the allocation sequence, the pharmacy at each site prepared patient packets in sequentially numbered, visually identical packages. The active drugs and placebo were identical in appearance, volume, weight, odor, and taste. The study nurse was responsible for allocating patients to their treatment groups.

Any child with a fever (rectal temperature > 38°C) at presentation in the ED received 15 mg/kg of acetaminophen. The only study to show a significant benefit to dexamethasone for outpatients with bronchiolitis[8] was criticized for not controlling for the antipyretic effect of dexamethasone.[27] It was postulated that the antipyretic effect of dexamethasone may have resulted in a lowering of respiratory rate in children in the dexamethasone group and influenced clinicians in their admission decision. As a result, the treatment of febrile infants was standardized in our trial.

Form of Analysis

A cost-effectiveness analysis was conducted with effectiveness measured as the time to resolution of individual symptoms (difficulties in infant feeding, sleeping, coughing, and noisy breathing) and all symptoms. The perspective taken for the economic evaluation was societal, and costs were classified as either payer (costs born by the province) or nonpayer (costs born by the families of children with bronchiolitis). Secondary analysis was conducted from the health care system perspective. Analysis included all health care costs and costs borne by the family during the 22 days after enrollment.

Comparators

Treatment comparators were based on the study treatment groups from the clinical trial. Comparators were nebulized epinephrine plus oral dexamethasone, nebulized epinephrine alone, oral dexamethasone alone, and no active treatment (placebo). Patients received 2 nebulized treatments, administered 30 minutes apart, of 3 mL of generic 1:1000 epinephrine or an equivalent volume of saline. The oral treatments were 1.0 mg/kg of dexamethasone (maximum: 10 mg) or placebo given after the first nebulized treatment in the ED followed by 5 once-daily dexamethasone doses (0.6 mg/kg; maximum daily dose: 10 mg) or placebo. The dexamethasone suspension consisted of generic dexamethasone phosphate injection solution mixed with Ora-Plus/Ora-Sweet (Paddock Laboratories, Inc, Minneapolis, MN). The oral placebo consisted of Ora-Plus/Ora-Sweet.

Data Collection

Data on resource use and outcomes were derived from the clinical trial. Parents or guardians were contacted by telephone using a standardized telephone follow-up procedure,[25,26] and research nurses obtained data regarding compliance with administration to study medication after discharge, health care visits, and details about the infant's feeding, sleep, breathing, and coughing. Follow-up was done daily until day 7, every 2 days until day 14, and then every 3 days until day 22. A review of the patient's hospital chart was completed 22 days after enrollment.

Health Care Resource Use and Costs

Health care resource use was collected for all patients according to the study protocol. For simplicity we based all of our costs on 1 center in Ontario: the Children's Hospital of Eastern Ontario (CHEO). The principal resource items of interest were the cost of the treatment group medications, medications used in the hospital, ED visits (and repeat ED visits), hospital admissions (total cost of length of stay and repeat visits), investigations given in the hospital (blood work, cultures, viral studies, radiographs, and procedures), and costs of physician assessment and reassessments within the ED and hospital stay. The prices of all medications used in hospital were taken from CHEO's in-house pharmacy and included any associated discounts; ED visits and hospital admissions costs came from an updated cost model developed for the CHEO to estimate hospital costs,[27] and the cost of assessment and reassessments within the ED and hospital stay were based on the Ontario physician fee schedule.[28]

The principal resource items of interest for follow-up were visits to a health care provider outside of the hospital (family physician or walk-in clinic), visits to a specialist, and medications prescribed to the patients on discharge or by a health care provider. All health care and specialist visits costs were based on the Ontario physician fee schedule.[28] The cost of prescription medications was based on the Ontario Drug Benefit Formulary charges plus the markup and dispensing fee.[29] The costs for over-the-counter medications were obtained from local pharmacies. All medications administered in hospital or prescribed by physicians were recorded by drug name, volume, and units, which enabled an accurate calculation of costs for each patient.

A nasal pharyngeal aspirate for respiratory syncytial virus testing was obtained from each patient. Therefore, it was excluded from analysis because all patients received it. For any child with a fever (rectal temperature > 38°C) at presentation to the ED, we added the costs of acetaminophen (15 mg/kg of body weight). All costs are presented in 2009 Canadian dollars (see Appendix 1; summary in Table 1).

TABLE 1 Cost Data

Item	Unit cost, $	Source
ED visit	89.87	CHEO cost model[27]
Physician fees	15–86.90	Ontario Schedule of Benefits 2008[28]
Hospital admission (per day)	786.87	CHEO cost model[27]
Investigations	1.55–105.47	Ontario Schedule of Benefits 2008[27]
Radiography	22.25–650.00	Ontario Schedule of Benefits 2008[27]
Cost for private car, per km	0.45	Canadian Automobile Association, Driving costs 2008[30]
Ambulance trip	75.00	Ontario Schedule of Benefits 2008[27]
Study drug	0.46 (1 mg/mL)	CHEO Pharmacy
Oral dexamethasone (1 mg/kg) liquid preparation		
Nebulized epinephrine (3 mL; 1:1000)	8.74 (1-mL dose)	CHEO Pharmacy
In-hospital medication	Various	CHEO Pharmacy
Prescription medication	Various	Ontario Drug Formulary[29]
Over-the-counter medication	Various	Local pharmacies

Additional details are provided in the Appendix; added to all prescription costs was an 8% markup plus a $6.41 dispensing fee.

Patient Costs

The principal resource items of interest for patient costs collected within the randomized controlled trial were parent or guardian's lost wages, parking expenses, public transportation, ambulance cost, kilometers traveled, out-of-pocket medication, and other out-of-pocket expenses. The cost of an ambulance was based on Ontario charges. The cost of private car travel was the product of the distance traveled and national estimates of travel costs per kilometer.[30]

Analyses

All analyses were conducted in SPSS 16.0 (SPSS Inc, Chicago, IL) and Microsoft Excel (Microsoft, Redmond, WA). If none of the therapies was shown to be dominant, cost-effectiveness was assessed by the incremental cost-effectiveness ratio (ICER) that corresponded to the difference in costs in Canadian dollars between treatment groups and their associated time with symptoms: ICER = $(C_A - C_B)/(E_B - E_A)$.

Uncertainty around estimates was assessed through probabilistic sensitivity analysis based on nonparametric bootstrapping whereby the original data were resampled to build an empirical estimate of the sampling distribution. Bootstrapping methods assumed that the empirical distribution of the data was an adequate representation of the true distribution of the data, and statistical analysis was based on repeatedly sampling from the observed data.[31,32] A random sample of each group from the original data were bootstrapped for each run of bootstrapping ($n = 5000$). We calculated health care costs, societal costs, and the duration of symptoms for each group, which allowed estimation of the 95% confidence intervals (CIs) around outcomes. In addition, data from the bootstrapping exercise were used to create a cost-effectiveness acceptability curve,[33] which provided the probability that each treatment was the most cost-effective given different values placed on the relief of symptoms. Given the stochastic nature of the data, probabilistic sensitivity analysis was the only sensitivity analysis conducted.

Because the purpose of an economic evaluation is to inform decisions related to funding of treatments, we have reported estimates of the expected values of treatments, not statistical inferences.

RESULTS

The average societal cost per patient was $1210 (95% CI: 1004–1441) for no active treatment, $1360 (95% CI: 1124–1624) for oral dexamethasone, $1323 (95% CI: 1093–1571) for nebulized epinephrine, and $1115 (95% CI: 919–1325) for the combination of nebulized epinephrine plus oral dexamethasone (Table 2).

The average cost per patient from the health care system perspective was $1019 (95% CI: 826–1232) for no active treatment, $1140 (95% CI: 934–1376) for oral dexamethasone, $1090 (95% CI: 880–1329) for nebulized epinephrine, and $865 (95% CI: 690–1062) for the

TABLE 2 Average Cost per Patient/Average Length of Symptoms per Patient

	Epinephrine and Dexamethasone	No Treatment	Epinephrine Only	Dexamethasone Only
Average health care costs per patient, $ (95% CI)	865 (690–1062)	1019 (826–1232)	1090 (880–1329)	1140 (934–1376)
Average societal costs per patient, $ (95% CI)	1115 (919–1325)	1210 (1004–1441)	1323 (1093–1571)	1360 (1124–1624)
Average length of symptom per patient, d				
Feeding problems	0.62	1.26	0.992	0.55
Sleeping problems	0.89	0.997	1.04	1.03
Coughing	12.08	12.54	12.72	12.37
Noisy breathing	3.83	4.74	4.41	4.38
Any symptom (95% CI)	12.17 (11–13)	12.69 (12–13)	13.02 (12–14)	12.62 (12–13)

Societal costs include health care costs and costs to the patient and their families; the 95% CIs are based on nonparametric bootstrapping.

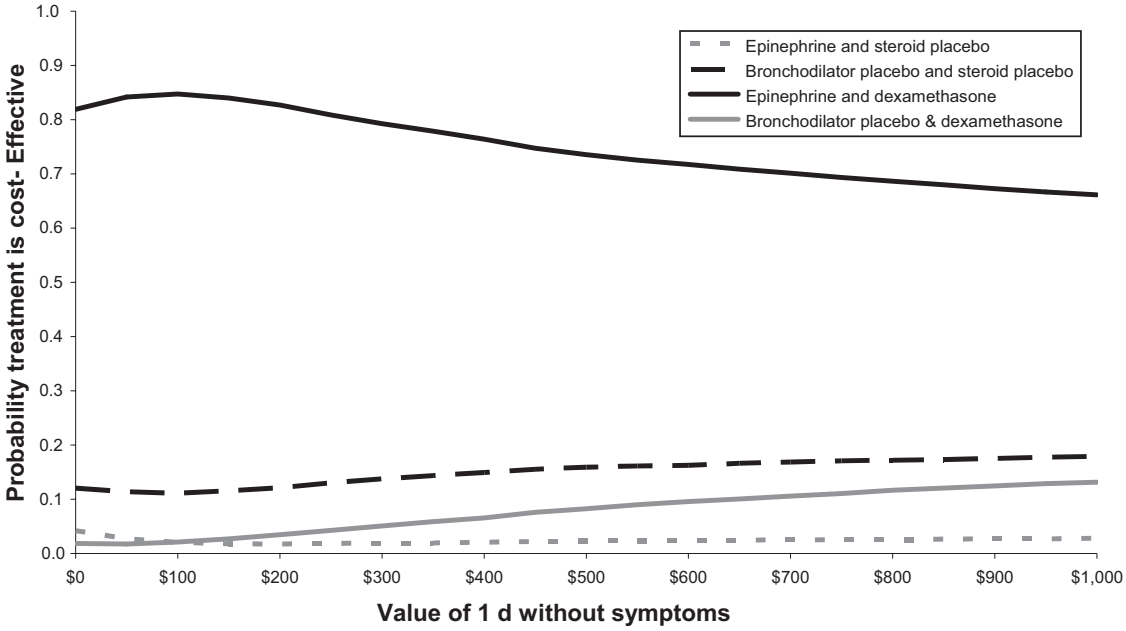

FIGURE 1
Cost-effectiveness acceptability curve.

combination of nebulized epinephrine plus oral dexamethasone (Table 2).

In terms of symptoms, the longest-lasting symptom seemed to be coughing followed by noisy breathing. The average time to relief of all symptoms was 12.69 days (95% CI: 12.00–13.00) for no active treatment, 12.62 days (95% CI: 12.00–13.00) for oral dexamethasone, 13.02 (95% CI: 12.00–14.00) for nebulized epinephrine, and 12.17 days (95% CI: 11.00–13.00) for the combination of nebulized epinephrine plus oral dexamethasone (Table 2).

Given the information discussed above, the combination of nebulized epinephrine plus oral dexamethasone was dominant over all other treatment options, because it is both least costly and most effective. In addition, no active treatment (ie, placebo) was dominant over nebulized epinephrine.

The cost-effectiveness acceptability curve depicts the probability that each of the treatment options is cost-effective for values of a day without symptoms, ranging from $0 to $1000 (Fig 1). For all values, the combination of nebulized epinephrine plus oral dexamethasone was the most likely to be optimal, and the probability of being most cost-effective was >75% for all scenarios.

DISCUSSION

In the CanBEST of the treatment of acute bronchiolitis in infants between 6 weeks and 12 months of age, combined therapy with epinephrine and dexamethasone seemed to reduce the hospital admission rate in the 7 days after study enrollment by 35% relatively and 9% absolutely. In this economic analysis, the combination of epinephrine and dexamethasone was also shown to be the most cost-effective treatment option in that it was both most effective and least costly. In addition, nebulized epinephrine alone was shown to be both more costly and no more effective than no active treatment, whereas oral dexamethasone alone may be cost-effective depending on a decision-maker's willingness to pay to avoid a symptom-day. However, in considering the use of dexamethasone alone, it is important to consider that within the clinical trial dexamethasone was not found to reduce the hospitalization rate and only shortened time to improved feeding when compared with placebo.[11]

Economic evaluations conducted alongside clinical trials are often criticized as not being generalizable on the basis that the trial does not represent the clinical setting in which treatments would be used in routine clinical practice. The design of the CanBEST, as an ED-based trial with broad inclusion criteria, minimizes this concern.

In economic evaluations, the focus is on determining the optimal treatment regardless of statistical significance. Although the results of the clinical evaluation did not show statistical significance for all differences, it is still necessary to assess the cost-effectiveness of the options. The probability that the combined therapy is the most cost-effective treatment option is at least 75%, which would be considered sufficient to determine it to be cost-effective. When using economic evaluation to inform decision-making,

it is useful to consider the concept of type 3 error: the probability of doing the wrong thing. In the context of this study, not funding combined therapy, therefore, would have a type 3 error rate of at least 75%. Thus, to minimize a type 3 error, the correct funding choice would be to fund combined therapy.

Our analysis had a number of strengths. For example, we incorporated the most recent standards in the conduct of trial-based economic evaluations by adopting a probabilistic approach to analyzing the underlying uncertainty. Such uncertainty is illustrated through CIs and the depiction of a cost-effectiveness acceptability curve that highlights the probability that the various treatment options are optimal, which further strengthens our conclusion that the combination of nebulized epinephrine and oral dexamethasone is the most cost-effective.

CONCLUSIONS

The results of our economic analysis show that combined treatment of infants with bronchiolitis with epinephrine and dexamethasone results in the lowest health care system and societal costs. Examining only health care system costs, combination therapy results in a cost savings of approximately $200 per patient compared with the costs of no treatment, epinephrine alone, or dexamethasone alone. Although this is not a dramatic savings on an individual patient basis, given that bronchiolitis is the most common disease of the lower respiratory tract in the first year of life, such savings, on a wider scale, would be significant. As well, this analysis is based on health care costs within Canada, which may be lower than costs in the United States.[34] At this point, the choice for decision-makers is whether to adopt this cost-effective approach now or await stronger evidence for dexamethasone and epinephrine in the treatment of bronchiolitis.

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APPENDIX ED and Hospital Cost Data

Item	Cost per Visit/Test, $	Reference
ED visit	89.87	CHEO
Subsequent ED visits	89.87	
Comprehensive assessment and care, Monday through Friday, daytime (8:00 AM to 5:00 PM)	37.20	Ontario Schedule of Benefits 2008
Multiple systems assessment	32.25	
Reassessment and minor assessment	15.00	
Comprehensive assessment and care, Monday through Friday, evenings (5:00 PM to 12:00 AM)	46.30	
Multiple systems assessment	40.10	
Reassessment and minor assessment	18.70	
Comprehensive assessment and care, Saturdays, Sundays, and Holidays, daytime and evenings	63.30	
Multiple systems assessment	53.80	
Reassessment and minor assessment	25.50	
Comprehensive assessment and care, nights (12:00 AM to 8:00 AM)	73.90	
Multiple systems assessment	62.30	
Reassessment and minor assessment	29.80	
Hospital admission	786.87	CHEO RIW's
Reassessment	55.45	Ontario Schedule of Benefits 2008
Discharge day	55.45	
Subsequent visits	29.20	
Visit to a health care provider outside of hospital		Ontario Schedule of Benefits 2008
Doctor's visit, own doctor (limited consultation)	44.65	
Walk-in clinic	44.65	
Reassessment, family physician	42.35	
Specialists		
Neurology	82.90	Ontario Schedule of Benefits 2008
Dermatology	66.15	
Radiology	82.90	
Anesthesiology	103.85	
Nephrology	82.90	
Gastroenterology	82.90	
Urology	71.30	
Orthopedic surgery	71.30	
Respirology	82.90	
Ophthalmology	71.30	
General surgery	86.90	
Investigations		
Blood work		Ontario Schedule of Benefits 2008
Complete blood count	8.27	
Reticulocyte count	6.72	
Blood culture	15.51	
Sickle cell screen	2.59	
Hemoglobulin electrophoresis	17.58	
Prothrombin time and partial thromboplastin time	13.44	
Erythrocyte sedimentation rate	1.55	
Serum amino acids	105.47	
Bilirubin	2.59	
Thyroid-stimulating hormone/thyrotropin	9.48	
γ-Glutamyl transpeptidase	2.59	
Aspartate aminotransferase	2.59	
Alanine transaminase	2.59	
Electrolytes	7.93	
Urea	2.59	
Creatinine	2.59	
Glucose	2.59	
Phosphate	2.59	
Albumin	2.59	
Magnesium	2.59	
Transferrin	12.25	
Ferritin	9.31	

APPENDIX Continued

Item	Cost per Visit/Test, $	Reference
Total iron-binding capacity	17.93	
Calcium	2.59	
Blood gas	10.54	
Phenobarbital level	18.46	
Urine tests		
Urine routine and microscopic	2.89	
Urine culture	12.93	
Cultures/screening		Ontario Schedule of Benefits 2008
Nasal swab for methicillin-resistant *Staphylococcus aureus*	12.93	
Swab for culture (eye)	12.93	
Stool culture for bacteria	17.58	
CSF bacterial culture (including Gram-stain)	14.48	
Stool culture for rotavirus	70.00	
Stool culture for vancomycin-resistant *Enterococcus*	12.93	
Polymerase chain reaction testing for pertussis	60.00	
CSF analysis		Ontario Schedule of Benefits 2008
CSF cell count	9.31	
CSF protein, glucose	2.59	
CSF Gram-stain	2.59	
Radiologic investigations		Ontario Schedule of Benefits 2008
Radiograph, abdomen (≥2 views)	32.90	
Radiograph, soft tissue of neck (2 views)	22.25	
Computed tomography of the head	650.00	
Cranial ultrasound	78.95	
Other investigations		
Electrocardiogram	16.50	
Procedure costs		
Lumbar puncture	77.25	
Travel-related costs		
Kilometers traveled	0.45	Canadian Automobile Association, Driving costs 2008
Ambulance	75.00	Ontario Health Insurance Plan

CSF indicates cerebrospinal fluid.

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