First line oxygen therapy with high-flow in bronchiolitis is not cost saving for the health service

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Short title: Economic evaluation of high-flow therapy

Abstract

Background: Bronchiolitis is the most common reason for hospital admission in infants. High-flow oxygen therapy has emerged as a new treatment; however, the cost-effectiveness of using it as first-line therapy is unknown.

Objective: To compare the cost of providing high-flow therapy as a first-line therapy compared to rescue therapy after failure of standard-oxygen in the management of bronchiolitis.

Methods: A within-trial economic evaluation from the health service perspective using data from a multicentre randomised controlled trial for hypoxic infants (≤12 months) admitted to hospital with bronchiolitis in Australia and New Zealand. Intervention costs, length of hospital and intensive care stay and associated costs were compared for infants who received first-line treatment with high-flow therapy (early high-flow, n=739) or for infants who received standard-oxygen and optional rescue high-flow (rescue high-flow, n=733). Costs were applied using Australian costing sources and are reported in 2016-17 AU$.

Results: The incremental cost to avoid one treatment failure was AU$1778 (95% Credible Interval [CrI]: 207 to 7096). Mean cost of bronchiolitis treatment including intervention costs and costs associated with length of stay was AU$420 (95% CrI: -176 to 1002) higher per infant in the early high-flow group compared to the rescue high-flow group. There was an 8% (95% CrI: 7.5 to 8.6) likelihood of the early high-flow oxygen therapy being cost saving.

Conclusions: The use of high-flow oxygen as initial therapy for respiratory failure in infants with bronchiolitis is unlikely to be cost saving to the health system, compared to standard-oxygen therapy with rescue high-flow.

Introduction

Bronchiolitis is one of the most common illnesses affecting infants, with 2-3% of all children requiring hospital admissions during their first year of life, and globally represents a major cause of infant morbidity and mortality.(1-3) In high-income countries, approximately one in eight infants hospitalised with bronchiolitis requires admission to an intensive care unit (ICU).(4) In the United States bronchiolitis accounts for 21% of hospital admissions for infants, with an estimated annual hospitalisation cost of US$1.7 billion.(5, 6) In Australia and New Zealand, there has been an increase in ICU admissions. Between 2002 and 2014, 28% of non-elective paediatric ICU admissions were due to bronchiolitis, and the annual cost of bronchiolitis admission requiring intensive care increased by US$30 million over the past decade.(4)

Hospital management of infants with bronchiolitis focuses on maintenance of hydration and respiratory support(2) with a trend towards reduced intubation and ventilation, and increased use of non-invasive ventilation.(7) High-flow is a rapidly emerging therapy providing non-invasive respiratory support both within and outside ICU. It delivers heated and humidified air blended with oxygen via the nasal passages, providing positive pressure, reducing the infant's work of breathing, and providing dead space washout of CO_2 in the upper airway.(5) Over the last decade, high-flow has gained popularity in clinical practice, particularly in Europe, North America and Australasia.(8, 9) Observational and randomised trials of high-flow compared to standard oxygen therapy indicated a good safety profile.(10, 11) While initial non-experimental studies suggested a reduction in ICU admission rates,(10) this finding was not replicated in two recent randomised controlled trials (RCTs) which reported no difference in ICU admission or hospital length of stay.(11, 12) In the absence of evidence suggesting superior long-term clinical or patient-relevant outcomes associated with high-flow in bronchiolitis, its implementation in clinical practice should be guided by its comparative

efficiency in managing an acute bronchiolitis episode. Little is known about the costs and cost-effectiveness of high-flow compared to standard-oxygen in infants with bronchiolitis.

We recently published the findings of the Paediatric Acute Respiratory Intervention (PARIS) trial, which compared initial high-flow oxygen therapy to initial standard-oxygen with the option to use rescue high-flow in infants with bronchiolitis.(11, 13) The present paper reports a pre-planned economic evaluation based on data collected alongside the PARIS trial, which aims to compare the cost of providing of these therapies for infants with bronchiolitis.

Methods

Participants and Trial Design

PARIS was an open label, non-blinded multicentre RCT in hypoxemic infants with bronchiolitis, less than 12 months of age, admitted to hospital.(11, 13) 1472 infants were randomly allocated (1:1 ratio) a treatment; either high-flow as initial therapy (early high-flow group) or standard-oxygen with the option to escalate to high-flow (rescue high-flow group). In the early high-flow group, infants received heated and humidified nasal high-flow delivered by the Optiflow system (Fisher and Paykel Healthcare, New Zealand; n=739) at a rate of 2L/kg/min. Infants started on standard-oxygen received oxygen via nasal cannula up to 2L/min (n=733). Escalation to rescue high-flow was permitted when infants failed standard-oxygen. The study took place in emergency departments and general paediatric wards in 17 hospitals in Australia and New Zealand between October 2013 and August 2016. Ethics approval was granted by the Children Health Services Queensland Human Research Ethics Committee (HREC/13/QRCH/93). The trial was registered prospectively on the Australian New Zealand Clinical Trials Registry (ACTRN12613000388718).

The primary outcome of the clinical trial was the proportion of infants in each group with treatment failure. Treatment failure of either standard-oxygen or high-flow therapy arm is

defined as meeting three out of four specified failure criteria requiring escalation of treatment or high level of care such as high acuity or intensive care.(13) Secondary outcomes included the intubation rates and length of hospital stay. The trial reported an 11% decrease (95% confidence interval (CI), -15% to -7%) in the escalation of care due to treatment failure when high-flow was used early during admission compared to standard-oxygen, but no significant difference was observed in some of the secondary outcomes.(11)

Estimating Resource Use and Costs

The resources costed included resources used to deliver high-flow, the treatment of bronchiolitis for the hospital length of stay (disaggregated by ICU and ward stay) and retrieval and transport events observed in the trial. Costs were measured from the healthcare service perspective in 2016-17 Australian Dollars (AU$). Given the short time horizon, costs were not discounted.

Intervention Costs

The intervention resources included capital equipment and consumables (online supplementary table S1). Quantities of consumables used were multiplied by unit costs (Table 1), summed to generate a total consumables cost and divided by the number of infants who received high-flow to generate a weighted cost per infant. The capital equipment cost per infant was estimated based on an assumed 5-year equipment lifespan with a machine utilisation rate of 80%. An 80% utilisation rate was assumed based on the rate adopted in a previous economic study.(14) We performed sensitivity analyses around this assumption by varying utilisation rate and equipment lifespan. Infants in standard-oxygen were costed for one paediatric nasal cannula.

We assumed no difference in the time taken to establish an infant onto either early high-flow or standard-oxygen, and the ward nursing-ratio for both arms remained the same throughout

the trial (1:4). Nasogastric tube (NGT) usage and enteral nutrition was not captured, and it was anticipated that there was minimal cost difference between the two groups due to NGT's being a low cost item.

Bronchiolitis Treatment Costs

Infants who remained on high-flow or standard-oxygen in the ward were costed for their length of stay (until the point of hospital discharge) based on assumed Australian Refined Diagnosis Related Group (AR-DRG) prices for Bronchiolitis with Complications (E70A; Table 1).(15) Patient postcodes were used to adjust for remoteness area boundaries.(16) Infants who received standard-oxygen and escalated to high-flow but remained in the ward were costed for high-flow in addition to the cost per general bed-day. Infants who were escalated to ICU were costed for the amount of time in ICU.

Retrieval and Transport Costs

Interhospital transport for infants with bronchiolitis is commonly used in the sites participating in the study.(17) Transport costs were included for infants requiring transfer to a higher level of care. All transfers were by road. Considering most retrievals occurred in South East Queensland, Queensland Health wage rates were used to cost the time taken to retrieve each infant.(18, 19)

Within-trial Economic Analysis

We undertook a cost-minimisation analysis from the healthcare provider perspective using data from the PARIS trial to compare the cost of providing initial high-flow to that of standard-oxygen including the option for rescue high-flow, as detailed in the trial protocol.(13) The analysis estimated the costs for the bronchiolitis episode of care until the point of discharge home. This assumes an equivalent clinical outcome at the point of discharge. To establish within-trial cost-effectiveness, we assessed the direct hospitalisation-

related costs in infants with bronchiolitis and calculated the incremental cost based on the primary outcome i.e. to avoid a treatment failure

We utilised guidelines for performing economic evaluation alongside clinical trials.(20) For the base case analysis, Australian unit costs were applied to all resources used regardless of the trial site. Subgroup analyses were conducted to examine the differential mean cost for pre-specified infant subgroups; born prematurely (<37 weeks gestation), previous hospital admission for respiratory disease, congenital heart defect, age group (≤3, 3-6, >6 months) and infants presenting to hospitals with/without an on-site ICU.(13)

We used non-parametric bootstrapping (10,000 replications) to estimate uncertainty using 95% credible intervals (CrI) around the point estimates and the probability that early high-flow was cost saving compared to standard-oxygen with rescue high-flow.

Sensitivity analyses

We performed sensitivity analyses for the different health care systems, in which we computed costs for the two New Zealand (NZ) study sites using price weights based on NZ's case-mix framework for publicly funded hospitals for 2016-17 (online supplementary table S2).(21) Costs (NZ$) were then converted to Australian dollars (AU$0.95=NZ$1 based on average exchange rates in 2016-17).(22) There were no hospital transfers in the NZ. We explored the impact of assumptions made related to high-flow equipment by varying the equipment utilisation rates between 10% to 100% (base case 80%) and the lifespan between 2 to 10 years (base case 5 years).

Results

Resource Use

Of the 1472 infants enrolled, 739 were randomised to early high-flow with 87 of these receiving escalation of care (all to ICU; Figure 1). A further 733 infants were randomised to

initially receive standard-oxygen, with 167 of these receiving escalation of care, 165 of whom received rescue high-flow as part of the escalation. Baseline demographic and physiological characteristics of the infants were similar between study groups.(11) There was no significant difference in total hospital stay between groups across the whole trial cohort or in infants who failed their initial treatment and received escalated care (Table 2).(11) However, in infants who did not require escalation of care, those receiving early high-flow had a longer hospital stay (0.41 days) than those on standard-oxygen ($p<0.001$). No significant difference in length of stay in ICU between groups was shown for infants admitted to ICU as part of the escalation of care (Table 2). Standard-oxygen group who received rescue high-flow were treated with high-flow for a mean of 0.41 (95% CI, 0.11-0.71, $p=0.008$) days longer than those who received early high-flow.

Within trial Economic Analyses

Initial intervention costs were higher for the early high-flow (AU$139.21 per infant) than for initial standard-oxygen prior to escalation (AU$2.64 per infant; Table 3). The mean cost of oxygen therapy overall was higher per infant for early high-flow (AU$139.21±11.73) compared to standard-oxygen with the option of rescue high-flow (AU$33.79±58.54; $p<0.001$). Thirty-five infants required a transfer from regional hospitals to tertiary centres. Mean retrieval time was 5.46±1.55 hours in early high-flow (20 infants) and 5.21±1.0 hours in standard-oxygen with rescue high-flow group (15 infants, $p=0.59$).

The incremental cost to avoid one treatment failure amounted to AU$189 (95% CrI, 67 to 311). This relates to total per person cost of each intervention arm from enrolment to discharge for responders and from enrolment to escalation of care for non-responders. Overall, the early high-flow group cost a mean of AU$420 (95%CrI,-176 to 1,002) more per infant. There was an 8% (95% CrI: 7.5% to 8.6%) likelihood of early high-flow being less costly than standard-oxygen with rescue high-flow.

The absolute mean cost differed across subgroups defined by infant age, prematurity, history of a congenital heart defect and level of the hospital but not by the previous admission for respiratory disease (Table 4). No significant differences in mean cost per infant between study groups within any one subgroup were evident.

Sensitivity Analysis

The mean costs for both early high-flow and standard-oxygen with rescue high-flow were slightly lower when NZ sites were costed using NZ prices (online supplementary table S3). The mean differential costs were similar (AU$435; 95% CrI, -110 to 967). As the capital costs associated with the high-flow machine were low (AU$3.53 per infant assuming an 80% utilisation rate) compared to overall costs, changes in high-flow machine utilisation rates had minimal impact on the differential cost between the groups (online supplementary table S4).

Discussion

This economic analysis used data from the PARIS trial and found higher costs per infant treated with high-flow compared with the standard-oxygen with rescue high-flow, this difference did not reach statistical significance at conventional 5% levels. Nevertheless, early high-flow provided as first-line therapy for hypoxic infants with bronchiolitis had a very low likelihood (8%) of being a lower cost therapy. The sub-group analyses showed that costs for the management of bronchiolitis in infants differ slightly across patients, but early high-flow was not proven to be cost-saving for any subgroup. Moreover, relaxing assumptions made around the use of country-specific costs or the utilisation rate of the high-flow equipment did not substantially impact findings.

The costs associated with length of hospital stay dominated the overall cost per infant. Previous cost estimates in larger bronchiolitis cohorts were based on summary data from large healthcare databases.(4, 6) We used individual patient-level data to estimate the cost of

bronchiolitis. Since total hospital length of stay was similar between the groups in the PARIS trial, it is not surprising that this evaluation was unable to show that the additional intervention costs of high-flow, though small, would be offset by any savings associated with the reduced escalation rate that was reported by the PARIS trial in the early high-flow group (compared to standard-oxygen). Likewise, the mean length of ICU stay for those who failed initial treatment (high-flow or standard-oxygen) was similar between the groups. There may be benefits for patients and their families associated with high-flow that has not been considered in this analysis. The patient and family experience with high-flow is an important area for future research.

A recent trial(12) found that high-flow was cost-saving compared to standard-oxygen in bronchiolitis. However, the study recruited infants aged up to 24 months in contrast to 12 months in this study, and the analysis assumed similar hospitalisation costs (emergency department, ward and ICU) per patient. Our analysis included a much larger sample of sicker patients from 17 sites in two countries, and we include other costs such as retrievals. In a further study, Heikkila(23) used data from a retrospective case-control study to estimate the cost-effectiveness of high-flow in infants with bronchiolitis, compared to standard-oxygen. Using a decision model, the authors found that high-flow was cost-saving. This was contributed by lower ICU admission rates and consequential costs in the high-flow group. However, these lower rates of ICU admission have not been found in the two RCTs conducted to date.(10, 11)

Strengths and Limitations

Our study investigated costs to the point of hospital discharge and assumed no difference in long-term outcomes irrespective of the treatment received. As bronchiolitis is a self-limiting illness without long-term sequelae, we consider this approach reasonable. Our analysis did not consider family or community costs associated with the illness. Retrieval costs were

comparatively low as transfer did not require any rotary or fixed-wing retrievals. Likewise, the analysis assumed similar medical and nursing care per patient ratios.

The primary outcome of the clinical trial was defined as an escalation of therapy, whereas the cost-minimisation analysis encompassed the entire stay in the hospital, including the crossover from standard-oxygen to high-flow. The clinical trial(11) reported high-flow to be associated with a lower escalation rate compared to initial standard-oxygen. We did not collect data on patient-reported outcomes, and we cannot comment on whether the quality of life or satisfaction may be perceived to be better with high-flow or standard-oxygen. Long term outcome data in infants with bronchiolitis is only available in patients who received mechanical ventilation and impaired neurodevelopment in these infants was related to the sedation used during PICU (24).

The PARIS trial on which this analysis is based was large, recruiting over 1,400 infants; and yet the findings related to costs are inconclusive. A study with a sufficient sample size to be powered to show a difference in costs at conventional significance levels is likely to be prohibitively expensive to run. It shows that the costs associated with high-flow constitute a small proportion of the overall costs of hospitalisation for bronchiolitis.

Implications for Practice

It is unlikely that early high-flow represents value for money compared to standard-oxygen with rescue high-flow when it is used as a first-line treatment for infants admitted to hospital with bronchiolitis. Higher costs for the high-flow stem to a lesser extent from equipment costs, but more from a longer length of stay in the hospital, particularly for those who did not require escalation of care.

Conclusions

Routine implementation of early high-flow as first-line therapy for the management of bronchiolitis in infants under 12 months cannot be recommended from a health care cost perspective. Future studies should investigate if provision of high-flow to selected patient groups at higher risk of requiring intensive care would be cost-effective as second-line therapy.

What is already known on this topic?

- The use of high-flow oxygen therapy has increased in infants with bronchiolitis to provide humidified oxygen.
- Little is known about the costs and cost-effectiveness of high-flow as initial therapy compared to standard-oxygen therapy in infants with bronchiolitis.

What this study adds?

- The analysis used data from the PARIS trial in bronchiolitis and provides a comprehensive analysis of costs related to bronchiolitis management in infants.
- High-flow oxygen therapy as initial therapy for respiratory failure in infants with bronchiolitis is unlikely to be cost saving to the health system compared to standard-oxygen with the option of rescue high-flow.

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Contributors

VG acquired health economic data, performed the economic analysis, drafted the manuscript; DF provided trial data and their interpretation; JW conceptualized and designed the economic analysis, and supervised the economic analysis; SD, FB, LS, JF, SC, JN, and EO contributed to the interpretation of the data; AS provided trial data and their interpretation. All authors critically revised and approved the final manuscript.

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Tables

Table 1. Unit costs used to value resource use measured in the main trial analysis

Resource item	Unit	Unit cost (AU$)	Source
High-flow capital equipment (AIRVO™2 system)	Item	2795.00	Manufacturer
Consumables for high-flow therapy			
Pediatric circuit	Item	55.50	Manufacturer
Pediatric nasal cannula (Optiflow™)	Item	25.00	Manufacturer
Oxygen tubing	Item	7.50	Manufacturer
Wiggle pads	Item	3.00	Manufacturer
Consumables for standard-oxygen therapy			
Pediatric nasal cannula	Item	2.64	Manufacturer
Bronchiolitis treatment			
Bronchiolitis treatment and LoS	Episode of care (AR-DRG code E70A)[a]	Varies	National Efficient Price Determination[14]
Retrieval and transfer costs			
Road transfer in Queensland (fixed)	Retrieval	832	Queensland Health Ambulance
Nurse time (grade 6.4)	Hour	61.64	Queensland Health[17]
Medical practitioner time (L8)	Hour	80.94	Queensland Health[18]

[a] AR-DRG is Australian Refined Diagnosis Related Group; Code E70A is Bronchiolitis with Complications. Price determination varies dependent on the length of stay (disaggregated by hospital and ICU), indigenous status and remoteness of the patient; LoS: length of stay

Table 2 Key resource (hospital length of stay) measured in the trial [11]

Item of resource use	Early High-flow Group	Standard-Oxygen +/- Rescue High-Flow Group	Mean Difference (95% CI)[a]
Total HLoS in days	(n=739)	(n=733)	
Mean (SD)	3.12 (2.43)	2.94 (2.73)	0.18 (-0.09 to 0.44)
Median (IQR)	2.50 (1.71-3.90)	2.20 (1.48-3.55)	–
HLoS for those who failed treatment and received escalation of care (days)	(n=87)	(n=167)	
Mean (SD)	5.82 (2.77)	4.95 (4.13)	0.87 (-0.09 to 1.85)
Median (IQR)	5.37 (3.71—7.31)	4.0 (2.69—5.81)	–
HLoS for those who did not require escalation of care (days)	(n=652)	(n=566)	
Mean (SD)	2.76 (2.14)	2.35 (1.75)	0.41 (0.18 to 0.63; p<.001)
Median (IQR)	2.23 (1.60—3.37)	1.88 (1.36—2.81)	–
HLoS for those who failed treatment and transferred to ICU (days)	(n=87)	(n=65)	
Mean (SD)	5.82 (2.77)	6.19 (5.30)	-0.36 (-1.67 to 0.95)
Median (IQR)	5.37 (3.71—7.31)	4.66 (3.06—6.88)	–
ICU length of stay (days)	(n=87)	(n=65)	
Mean (SD)	2.63 (1.70)	2.72 (2.31)	-0.09 (-0.74 to 0.55)
Median (IQR)	2.22 (1.50—3.54)	2.02 (1.34—2.98)	–
Duration of high-flow therapy (days)[b]	(n=728)	(n=162)	
Mean (SD)	1.85 (1.70)	2.26 (2.09)	-0.41 (-0.71 to -0.11; p=0.008)
Median (IQR)	1.38 (0.74—2.40)	1.62 (1.04—2.70)	

HLoS = total hospital length of stay – i.e., in general ward and intensive care unit (ICU); IQR = interquartile range; SD = standard deviation

[a] Student's t-test of independent samples was used.

[b] Data on the duration of high-flow therapy were missing for three patients in the standard-oxygen group and eleven in the high-flow group.

Table 3. Comparison of costs and effects per infant between high-flow and standard-oxygen therapy (AU$)

	Early High-Flow Group (n=739)	Standard-Oxygen +/- Rescue High-Flow Group (n=733)
A. Initial intervention cost per infant		
Capital cost of high-flow equipment, mean (SD)	3.53 (3.23)	—
Consumables, mean (SD)	136.61 (0.00)	2.64
(A) Total intervention cost per infant (capital + consumables), mean (SD)	139.21 (11.73)	2.64
B. Costs for rescue high-flow therapy (n=165)		
Capital (high-flow equipment) for those receiving rescue high-flow, mean (SD)	—	4.32 (3.97)
Consumables for those receiving rescue high-flow, mean (SD)	—	136.61 (0.00)
(B) Total costs associated with rescue high-flow therapy, mean (SD)	—	141.01 (19.30)
C. Costs associated with length of stay for bronchiolitis episodes of care, mean (SD)		
Cost of hospital length of stay – non-ICU stay, mean (SD)	5552 (1593)	5596 (1970)
Cost of ICU stay for those with an ICU stay, mean (SD, n)	13415 (8679, n=87)	13889 (11823, n=65)
(C) Total costs associated with bronchiolitis episode of care, mean (SD)	7131 (5469)	6827 (5701)
D. Hospital transfer and retrieval cost, mean (SD, n)	2442 (221, n=20)	2406 (142, n=15)
E. Total cost per infant (A+B+C+D)		
Mean (SD)	7314 (5586)	6893 (5809)
Median (IQR)	5568 (5567—5572)	5431 (5431—5569)
Differential mean cost (95% CrI)*	420 (-176 to 1002)	
F. Total cost up to treatment failure or until discharge if responder		
Mean (SD)	5681 (1575)	5492 (584)
Median (IQR)	5568 (5567—5572)	5431 (5431—5569)
Differential mean cost (95% CrI)*	189 (67 to 311)	
G. Effectiveness		
Treatment failure rate	0.118 (0.094 to 0.141)	0.228 (0.197 to 0.258)
Differential treatment effect (95% CrI)*	-0.118 (-0.072 to -0.148)	
H. Cost-effectiveness ratio i.e. mean incremental cost per treatment failure avoided, F/G (95%CrI)	1778 (207 to 7096)	

SD = standard deviation; IQR = interquartile range;

* 95% non-parametric credible interval based on 10,000 bootstrap replications

The incremental cost per treatment failure avoided in the table is close to but not exactly equal to the difference in cost divided by the difference in effectiveness, due to the bootstrapping method employed and rounding error.

Table 4. Variation in mean total costs (AU$) per infant treated by subgroups

Subgroup	Early High-Flow Group	Standard-Oxygen +/- Rescue High-Flow Group	Mean Cost Difference (95% CrI)[a]
Prematurity <37 weeks			
Yes	8233 (n=137)	7519 (n=128)	714 (-1025 to 2278)
No	7104 (n=602)	6761 (n=605)	343 (-267 to 951)
Age group			
≤ 3 months	8285 (n=211)	8196 (n=186)	89 (-1438 to 1570)
> 3 to 6 months	7172 (n=187)	6395 (n=170)	777 (-75 to 1669)
> 6 months	6790 (n=341)	6475 (n=377)	315 (-415 to 1008)
Hospital levels			
Onsite ICU	7578 (n=469)	7089 (n=486)	489 (-271 to 1208)
No onsite ICU	6854 (n=270)	6508 (n=247)	345 (-638 to 1253)
Previous hospital admission for respiratory disease			
Yes	7558 (n=187)	6792 (n=225)	766 (-467 to 1953)
No	7231 (n=552)	6938 (n=508)	293 (-394 to 949)
Congenital heart defect			
Yes	9538 (n=8)	10394 (n=16)	-855 (-9816 to 8066)
No	7289 (n=731)	6815 (n=717)	474 (-86 to 1040)

[a] 95% non-parametric credible interval based on 10,000 bootstrap replications

Figures

Figure 1: Flow diagram of the randomisation trial from enrollment till hospital discharge.