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Cost-effectiveness analysis of a system-based approach for managing neonatal jaundice and preventing kernicterus in Ontario

Bin Xie
Western University

Orlando Da Silva
Western University, odasilva@uwo.ca

Greg Zaric
Western University

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OBJECTIVE: To evaluate the incremental cost-effectiveness of a system-based approach for the management of neonatal jaundice and the prevention of kernicterus in term and late-preterm (≥35 weeks) infants, compared with the traditional practice based on visual inspection and selected bilirubin testing.

STUDY DESIGN: Two hypothetical cohorts of 150,000 term and late-preterm neonates were used to compare the costs and outcomes associated with the use of a system-based or traditional practice approach. Data for the evaluation were obtained from the case costing centre at a large teaching hospital in Ontario, supplemented by data from the literature.

RESULTS: The per child cost for the system-based approach cohort was $176, compared with $173 in the traditional practice cohort. The higher cost associated with the system-based cohort reflects increased costs for predischarge screening and treatment and increased postdischarge follow-up visits. These costs are partially offset by reduced costs from fewer emergency room visits, hospital readmissions and kernicterus cases. Compared with the traditional approach, the cost to prevent one kernicterus case using the system-based approach was $570,496, the cost per life year gained was $26,279, and the cost per quality-adjusted life year gained was $65,698.

CONCLUSION: The cost to prevent one kernicterus case using the system-based approach is much lower than previously reported in the literature.

Key Words: *Comparative effectiveness research; Jaundice; Kernicterus; Neonatology*

L'analyse coût-efficacité de l'approche systémique pour prendre en charge la jaunisse néonatale et prévenir l'ictère nucléaire en Ontario, au Canada

OBJECTIF : Évaluer le rapport coût-efficacité incrémentiel d'une approche systémique de prise en charge de la jaunisse néonatale et de prévention de l'ictère nucléaire chez les nourrissons à terme et peu prématurés (au moins 35 semaines d'âge gestationnel) par rapport à la pratique classique fondée sur l'inspection visuelle et des tests de bilirubine sélectionnés.

MÉTHODOLOGIE : Les chercheurs ont utilisé deux cohortes hypothétiques de 150 000 nouveau-nés à terme et peu prématurés pour comparer les coûts et les issues associés à l'utilisation d'une approche systémique ou classique. Les données d'évaluation étaient tirées du centre de coûts des cas d'un grand centre universitaire de l'Ontario, et complétées par des données extraites de publications.

RÉSULTATS : L'approche systémique coûtait 176 $ par enfant, comparativement à 173 $ dans la cohorte de pratique classique. Le coût dans la cohorte d'approche systémique reflète les coûts plus élevés du dépistage et du traitement avant le congé et le plus grand nombre de rendez-vous de suivi après le congé. Il est partiellement compensé par la réduction des coûts attribuable au moins grand nombre de consultations à l'urgence, de réhospitalisations et de cas d'ictère nucléaire. Par rapport à l'approche classique, le coût pour prévenir un cas d'ictère nucléaire au moyen de l'approche systémique s'élève à 570 496 $, le coût par année de vie gagnée, à 26 279 $, et le coût par année de vie pondérée par la qualité, à 65 698 $.

CONCLUSION : Le coût pour prévenir un cas d'ictère nucléaire au moyen de l'approche systémique est beaucoup moins élevé que ce que révélaient les publications auparavant.

Neonatal jaundice is a common condition among neonates, affecting approximately 60% of otherwise healthy newborn infants (1). It is caused by the inability of the infant body to quickly excrete bilirubin in the blood, with symptoms including yellowing of the skin and other tissues. In otherwise healthy term or near term (gestational age ≥ 35 weeks) infants without known risk factors and whose bilirubin levels indicate low or intermediate risk of developing hyperbilirubinemia, the condition usually resolves spontaneously without the need for treatment (2-4). For patients with one or more known risk factors and/or patients with very high bilirubin levels, prolonged hyperbilirubinemia can result in bilirubin-induced neurological dysfunction (BIND) or, in the most severe cases, kernicterus (2-4). In these patients, timely treatment with phototherapy or exchange transfusions is crucial (5).

In response to evidence that kernicterus cases may be on the rise (6-7), a system-based approach to manage neonatal jaundice and prevent kernicterus (8) was recommended by several professional agencies, including the American Academy of Pediatrics (2) and the Canadian Paediatric Society (3). Key elements of this approach include universal bilirubin screening and individualized postdischarge follow-up care based on results of such screening. Although this approach seems intuitive, acceptance is not universal. The growing, but still limited, evidence to support its efficacy and cost-effectiveness have led to legitimate debate (4,9,10). For example, while there are a few cost-effectiveness studies evaluating various elements of the management of neonatal jaundice (11) and the prevention of kernicterus (11-12), we are not aware of any direct economic evaluation comparing the system-based approach with the traditional approach.

In the present study, we present an economic evaluation of the cost-effectiveness of a system-based approach for the management of neonatal jaundice and the prevention of kernicterus compared with the traditional approach. The evaluation includes all major components of the system-based approach and offers a direct comparison

University of Western Ontario, London, Ontario

Correspondence: Dr Bin Xie, Universtiy of Western Ontario, Room E5-319, London Health Sciences Centre - Victoria Hospital, 800 Comissioners Road East, London, Ontario N6A 4G5. E-mail bxie5@uwo.ca

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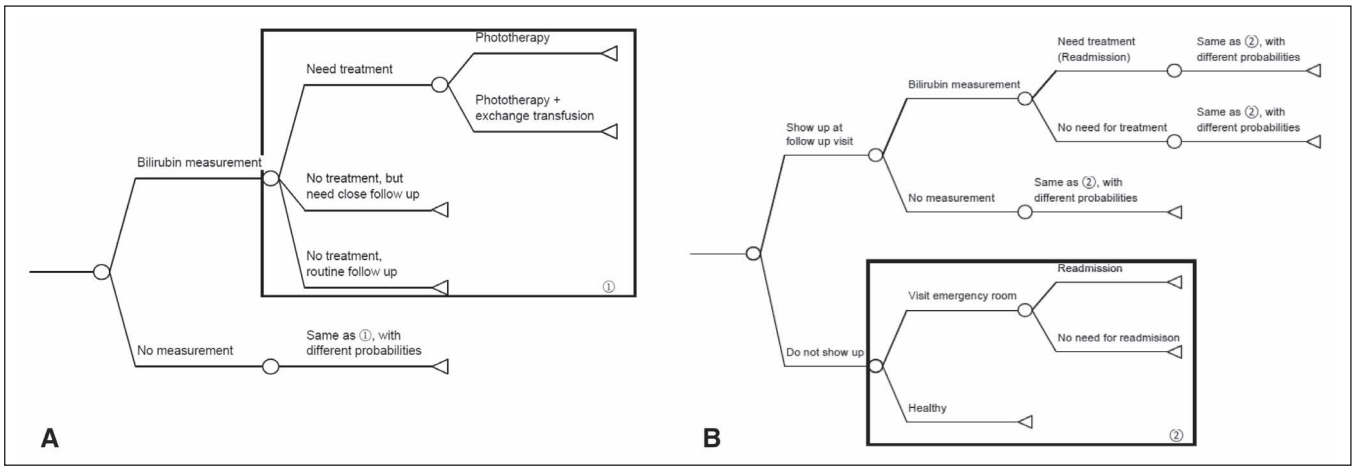

Figure 1) A *Schematic illustration of the two approaches (before discharge).* **B** *Schematic illustration of the two approaches (after discharge)*

TABLE 1
Input values used in the evaluation

	Traditional cohort		System cohort	
Resource use	**Value**	**Reference(s)**	**Value**	**Reference(s)**
Predischarge phototherapy	4.25	LHSC,15	4.8	20
Predischarge exchange transfusion	0.03	15	0.035	23
Morbidity from exchange transfusion	5.0	16	5.0	2,24
Predischarge bilirubin measured	25.1	Assumption	100	20
Early and more intensive follow-up scheduled (ie, high risk)	10.0	20	13.0	21
Attend early and more intensive follow-up visits	82.4	8	82.4	13
Number of visits for high risk infants, mean	2	8	2	13
Bilirubin measurement at follow-up visits for high-risk patients	50.0	Assumption	100	13
Attend routine follow-up	53.0	17	53.0	25
Bilirubin measurement at routine follow-up visit	1.3	18, 21	1.3	26,27
Probability of emergency room visit	1.87	LHSC	1.46	20
Probability of readmission	0.49	LHSC	0.38	20
Probability of kernicterus	0.002	8,15,20	0.0014	30
Costs, $				
Predischarge bilirubin measurement	1.11	LHSC	1.11	20
Predischarge phototherapy	2,012.16	LHSC	2,012.16	20
Predischarge exchange transfusion	8,903.50	LHSC	8,903.50	20
Average cost of morbidity from exchange transfusion	29,854.00	LHSC	29,854.00	20
Follow-up visit	56.10	25	56.10	34
Bilirubin measurement at follow-up visit	5.00	25	5.00	34
Emergency room visit	262.36	LHSC	262.36	20
Readmission	3,240.34	LHSC	3,240.34	20
Kernicterus	1,329,388.71	26	1,329,388.71	35

Data presented as % unless otherwise indicated. Costs reported as 2008 Canadian dollars. LHSC London Health Sciences Centre, London, Ontario

between the system-based approach and the traditional approach. We included incremental costs, incremental kernicterus cases, cost per kernicterus cases prevented and cost per life year gained as outcomes. While the main analyses were based on the public payer's perspective, we also reported results based on societal perspective in sensitivity analyses.

METHODS

Patient cohorts

The costs and outcomes of two hypothetical cohorts of 150,000 (the approximate number of newborns each year in Ontario) otherwise healthy, term or near term infants in Ontario, were compared. One cohort experienced the system-based approach to jaundice management and kernicterus prevention (the 'system' cohort), and the other experienced the traditional approach (the 'traditional' cohort). Graphic illustrations of these two approaches are presented in Figures 1A and 1B. Figure 1A illustrates the treatment regimens before discharge for both cohorts, and Figure 1B illustrates the treatment regimens after discharge for both cohorts. The differences between the two approaches lie in the probability values, as presented in Table 1.

In both cohorts, bilirubin measurements and referral of infants for readmission to initiate treatment during follow-up visits were at the discretion of family doctors or paediatricians. Parents could also bring their infants to the emergency room, and infants could be readmitted from the emergency room if necessary.

Data and sources

Parameter estimates and sources are summarized in Table 1. All costs are in 2008 Canadian dollars.

Traditional cohort

Resource use for hospital-related services for the traditional cohort, including bilirubin measurements, treatments with phototherapy or exchange transfusion, emergency room visits and readmissions, were based on a cohort of 2630 healthy term or late-preterm infants delivered at the London Health Sciences Centre (LHSC) in London, Ontario, from January 1, 2008 to December 31, 2008, or were obtained from secondary sources. LHSC is one of two hospitals in the London region that handles the vast majority of deliveries. The system-based approach was not implemented at the time of data collection. LHSC has the only paediatric emergency room in the city and handles readmissions for all infants delivered at the hospital.

An exchange transfusion rate of 0.03%, as reported by Seidman et al (15) was used, and a 5% morbidity rate from exchange transfusion was assumed, as reported in the literature (2). The morbidity due to exchange transfusion was assumed to be short-term only; therefore such morbidity only impacted the costs component of the analysis.

It was further assumed that during these routine follow-up visits, 2.2% of infants would show signs of jaundice, as Bhutani et al (17) reported that 2.2% of infants whose bilirubin level was below the high-risk zone would move to the high-risk zone at follow-up, and that bilirubin measurements would be ordered in 57.7% of these infants (18). This means that the probability of bilirubin measurement for all infants at routine follow-up visits would be 1.3% (57.7% × 2.2%).

There have been no kernicterus cases at LHSC during the period of data collection, so the rate reported in Canada (19), one in 50,000 live births, was used in the evaluation.

System cohort

Resource use data for the system cohort were derived from the literature. For the probability of predischarge treatment, several studies reported an increase in predischarge treatment rate following implementation of a system-based approach. For example, Mah et al (14) reported an increase of 11.3% (from 4.4% to 5.1%). Assuming the same increase from the 4.25% treatment rate in the LHSC cohort, results in a treatment rate of 4.8% (4.25% × 1.113) in the system cohort. This rate is comparable with rates reported elsewhere (17,20).

It was assumed that earlier and more intense follow-up would be arranged for 13% of infants (20). It was also assumed that bilirubin levels would be measured in all infants with early and intense follow-up because such measurements can be used with predischarge measurements to accurately assess the risk for hyperbilirubinemia or kernicterus. The probability of actually being followed-up for these high- or intermediate-to-high-risk patients was assumed to be the same as the traditional cohort. The remaining infants would receive routine follow-up, with the same probability of actually being followed-up as in the traditional cohort.

For resource use of emergency room visits and hospital readmissions, several studies reported a decrease in hyperbilirubinemia-related readmissions. For example, Eggert et al (21) reported a 21.8% decrease in readmission rate (from 0.55% to 0.43%) after the implementation of a universal screening program. An emergency room visit rate of 1.46% (1.87% × [1−0.218]) and a readmission rate of 0.38% (0.48% × [1−0.218]) in the system cohort was assumed. This readmission rate is similar to those reported in the literature (9,21).

TABLE 2
Kernicterus reduction rate calculations

	Hyperbilirubinemia	Bilirubin level below hyperbilirubinemia	Total
Traditional cohort			
Kernicterus	0.00125* (0.002%×62.5%)	0.00075	0.002†
Normal	6.09875	93.89925	99.998
Total	6.1	93.9	100
System cohort			
Kernicterus	0.00072 (0.00125%× [1-42.3%])	0.00075	0.00147
Normal	3.519	96.479	99.9985
Total	3.52	96.48	100
Reduction rate	26.4‡		

*Data presented as %. *The percentage of infants in the traditional cohort who had both kernicterus and hyperbilirubinemia; †The percentage of infants in the traditional cohort who developed kernicterus; ‡The reduction rate is calculated as (0.002%-0.00147%)/0.002%*

There is no evidence that directly links the system-based approach to a reduction in the rate of kernicterus cases. The conservative assumption was made that the system-based approach reduces the kernicterus case rate only through reducing hyperbilirubinemia cases. More specifically, it was assumed that 62.5% of all kenircterus cases would have bilirubin levels above the 95th percentile (13). A further assumption that the system-based approach would reduce the incidence of hyperbilirubinemia by 42.3% was made (14). Assuming a hyperbilirubinemia rate of 6.1% (17), this would translate into a 26.4% reduction in the rate of kernicterus cases (see Table 2 for details).

Due to the very limited survival data for kernicterus patients, life expectancy was approximated using survival data for cerebral palsy (CP) patients (22). A Gompertz function was fitted (23) using these survival data and the life tables for Ontario (24). Utilities for CP patients reported in the literature (25) were also used to calculate quality-adjusted life years (QALYs).

Possible negative consequences of the system-based approach include potential harm from phototherapy such as weight loss, gastrointestinal problems, interruption of breastfeeding and disruption of the maternal-infant relationship, possible growth of melanocytic nevi and significant morbidity due to exchange transfusion (4). Only the costs due to morbidity from exchange transfusion were included in the analysis, becasue a public payer perspective was taken and it was assumed that the potential harm from phototherapy would be temporary and would not cost the public payer.

Costs

Cost data for predischarge bilirubin measurements, predischarge hospital treatments, exchange transfusion-related morbidity, emergency room visits and readmissions were obtained from the case costing centre at LHSC. The costs for predischarge treatment include costs due to prolonged hospital stay. Costs for follow-up visits and laboratory tests were obtained from the 2008 Ontario Health Insurance Plan (OHIP) fee schedule (26). The lifetime medical cost for kernicterus was obtained from the literature (27).

RESULTS

Base case analysis

Results for the base case analysis are presented in Table 3.

Overall, the system-based approach was more costly (total cost was $452,000 higher for the entire cohort, or $3 per child).

TABLE 3
Results of the base case analysis

Item	Traditional cohort	System cohort	Difference
Cost per kernicterus case prevented, $	–	570,496	–
Life years gained	–	17.2	–
Cost per life year gained	–	26,279	–
Total cost	25,897,000	26,349,000	452,000
Cost per child	173.00	176.00	3.00
Per child cost before discharge	101.50	89.10	12.40
Per child cost in follow-up visits	39.00	36.40	2.60
Per child cost in emergency room visit	3.80	4.90	–1.10
Per child cost in readmission	12.30	16.00	–3.70
Per child cost in kernicterus	19.40	26.60	–7.20

Data reported as 2008 Canadian dollars unless otherwise indicated. Cohort size is 150,000

However, the system-based approach prevented 0.8 kernicterus cases and gained 17.2 life years or 6.88 QALYs, resulting in a cost per kernicterus case prevented of $570,496, a cost per life year gained of $26,279 and a cost per QALY gained of $65,698.

Sensitivity analysis

The analyses were performed from a societal perspective, using the economic cost to society for a child with kernicterus (28) and other nonmedical costs such as transportation and lost productivity of the parents (29). The system-based approach would achieve a cost-savings of $597,527 per kernicterus case prevented, compared with the traditional approach. The main driver is the high societal cost for kernicterus cases. Given the lack of data, the potential costs associated with the transmission of bilirubin results and arranging for a follow-up are not included in the analysis.

Several costs were varied, including costs for biliburin measurements, follow-up visits, emergency visits, hospital treatments, readmissions and the lifetime costs of kernicterus, in the sensitivity analysis. Key effectiveness data, including reduction rates in treatment, readmission and kernicterus cases due to the system-based approach, were also varied. One-way and multiway sensitivity analyses for these variables were performed.

Results for one-way sensitivity analysis are presented in Table 4. The analysis found that the cost per kernicterus case prevented was very sensitive to the cost of bilirubin measurement, the rate of change in treatment rate, and baseline kernicterus case rate or kernicterus case reduction rate.

Results of the multiway sensitivity analysis are presented in Table 5. The analysis found that the system-based approach would achieve cost-savings under a wide range of values for other parameters if the reduction rate for kernicterus cases was above 50%.

TABLE 4
Selected results for one-way sensitivity analysis

	Cost per kernicterus case prevented, $
Treatment rate of the traditional cohort*	
3.0%	5,332,970
4.0%	1,522,061
5.0%	–2,288,847
6.0%	–6,099,756
Rate of increase in treatment rate with system approach	
0%	–1,525,503
10%	94,133
20%	1,713,769
Cost per bilirubin measurement	
$1	553,105
$5	1,143,256
$10	1,880,945
$20	3,356,324
Kernicterus rate in the traditional cohort	
1 in 27,000	–303,450
1 in 40,000	190,519
1 in 80,000	1,710,428
1 in 100,000	2,470,382
Reduction rate in kernicterus cases	
10%	3,686,309
40%	–75,464
70%	–612,860
100%	–827,818

*Costs reported as 2008 Canadian dollars. *Assuming that the treatment rate of the system-based approach would remain constant*

DISCUSSION

The advantages of the system-based approach lie in its ability to timely and accurately identify, treat and follow up infants at high risk of developing hyperbilirubinemia, therefore reducing the number of cases of BIND or kernicterus (8). Apart from reducing kernicterus cases, the system-based approach may also reduce emergency room visits and readmissions (21). However, the system-based approach can be costly because it involves more bilirubin measurements, more aggressive treatment and more follow-up visits.

In the present study, we found that the system-based approach was more costly than the traditional approach, but also more effective in preventing kernicterus. The cost per life year gained was $26,279, and the cost per QALY gained was $65,698, which is well within the range accepted for screening tests in the perinatal period (30). The cost to prevent one case of kernicterus is $570,496, which is lower than the lifetime medical cost of caring for a child with kernicterus (27).

TABLE 5
Selected results for multiway sensitivity analysis

Treatment rate of the traditional cohort	Rate of change in treatment rate	Readmission rate of the traditional cohort	Rate of change in readmission rate	Kernicterus rate in the traditional cohort	Reduction rate in kernicterus case	Cost per kernicterus case prevented, $
3.0	0	0.3	0	1 in 2,7000	30	–1,101,788
4.0	10	0.4	10	1 in 4,0000	50	–586,877
6.0	10	0.6	20	1 in 6,0000	60	–258,044
4.0	10	0.3	20	1 in 10,0000	70	–96,056
3.0	20	0.6	5	1 in 4,0000	40	33,586
4.0	20	0.5	10	1 in 6,0000	60	371,211
6.0	20	0.4	10	1 in 8,0000	90	926,493
5.0	15	0.5	15	1 in 8,0000	50	1,100,984
5.0	20	0.5	25	1 in 10,0000	30	4,870,632

Data reported as % unless otherwise indicated. Costs reported as 2008 Canadian dollars

The cost to prevent one case of kernicterus in our study was much lower than those reported in the literature. For example, Suresh et al (12) reported a cost of more than $5 million to prevent one case of kernicterus. There are three main reasons for the dramatic differences between our results and those from Suresh et al (12).

First, we included the costs of subsequent emergency room visits and readmissions, whereas Suresh et al did not. We believe that including the costs of emergency room visits and readmissions can provide a more comprehensive evaluation because hyperbilirubinemia is the most common cause of neonatal readmission to hospitals in North America (31), and the system-based approach has been shown to reduce emergency room visits and readmissions (21). Given the high costs of such readmissions, the impact on the incremental cost-effectiveness would be significant. This is demonstrated by Paul et al (11), who reported significant cost-savings using a home nurse visit program, which was largely driven by the reduction in emergency room visits and readmissions.

Second, our analysis used costs from a Canadian institution, which may be lower than the United States institution used in Suresh et al (12). For example, the cost for predischarge bilirubin measurment was only $1.11 in our analysis, based on data provided by the LHSC case costing group, but was assumed to be $20 in Suresh et al (12). Given that this test would be performed for every neonate in the system-based approach, a difference of this magnitude would have major implications for the result. When we changed the cost to $20 in the sensitivity analysis, the cost to prevent one kernicterus case increased to approximately $3 million, which is more in line with the estimate of Suresh et al (12).

Third, some of the probabilities in our analysis were different from those in Suresh et al (12). For example, the reduction rate of kernicterus cases used in our analysis was much lower than the 70% reduction rate used in Suresh et al (12). Another example is that we used one in 50,000 as the prevalence of kernicterus cases, based on the most reliable study in Canada, whereas they used one in 100,000, based on United States data.

We used total serum biliburin measurements in the main analyses; another possible measurement of biliburin level is transcutaneous bilirubin measurement (TcB), whose properties are well established and considered to be suitable for screening purposes. Given that TcB is more costly than total serum biliburin measurements (32), the cost per kernicterus case prevented would be $1,544,559, assuming that using TcB will not result in any change in other parameter values in the model. While it is currently more costly to use TcB, it is more convenient, and if the cost of TcB goes down, it may become an even more appealing option.

It has been suggested that one of the reasons for the rise in kernicterus cases or jaundice-related emergency room visits was the reduced length of stay after delivery (31). The older 'traditional' approach, in which babies were kept in hospital throughout most of the risk period for jaundice (and kernicterus), would be very effective in managing neonatal jaundice and preventing kernicterus; however, the medical costs would also be significantly higher given the high cost of hospital stays. Given the trend of decreasing length of stay after birth (33), it is especially important to have an effective strategy, such as the system-based approach, to manage neonatal jaundice and prevent kernicterus.

There are some limitations to the present study. Our analysis was based on Canadian data, so our results may not apply to other countries. The fact that the data for the system cohort were taken from the literature and not from the same institution where the data for the traditional cohort were taken, leaves open the possibility that the cost-effectiveness of the system-based approach would be different from that reported in our analysis if the experiences of the system-based approach at LHSC are different.

Another limitation was the exclusion of some elements of the management of neonatal jaundice that are practiced with varying degrees in some communities, such as home phototherapy (34). Due to the lack of data on the prevalence, efficacy and costs of such treatments, they were excluded in the analysis. Our results may not be applicable to communities where these alternative treatment options are widely practiced.

CONCLUSION

Given that kernicterus is a preventable disease, we believe that it is economically justifiable to implement the system-based approach in communities with similar cost structures as presented in our analysis.

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