

Direct medical costs of neonatal respiratory distress syndrome in two specialized public hospitals in Mexico

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 Costo médico directo del síndrome de dificultad respiratoria neonatal en dos hospitales públicos de alta especialidad en México.
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Abstract

Objective. To estimate direct medical costs (DMC) associated with treatment of Respiratory Distress Syndrome (RDS) in newborns (NB) in two specialized public hospitals in Mexico. **Materials and methods.** The perspective used was health care payer. We estimated DMC associated with RDS management. The pattern of resource use was established by reviewing clinical records. Microcosting and bootstrap techniques were used to obtain the DMC. Estimated costs were reported in 2011 US dollars. **Results.** Average DMC per RDS event was 14 226 USD. The most significant items that account for this cost were hospitalization (38%), laboratory and diagnostic exams (18%), incubator time (10%), surfactant therapy (7%), and mechanical ventilation (7%). **Conclusion.** Average DMC in NB with RDS fluctuated in relation to gestational age weight at birth and clinical complications presented by patients during their hospitalization.

Key words: costs and cost analysis; respiratory distress syndrome, newborn; newborn; Mexico

Resumen

Objetivo. Determinar los costos médicos directos (CMD) asociados con el tratamiento del síndrome de dificultad respiratoria (SDR) en recién nacidos pretérmino en dos hospitales públicos de alta especialidad de México. **Materiales y métodos.** Se utilizó la perspectiva del pagador de servicios de salud. El uso de recursos se estimó mediante la revisión de expedientes clínicos. Se empleó la técnica de microcosteo y de bootstrap para la obtención de los CMD. Los costos fueron reportados en dólares estadounidenses de 2011. **Resultados.** El CMD por evento de SDR promedio fue de 14 226 dólares distribuidos entre los costos de hospitalización (38%), laboratorio y exámenes de diagnóstico (18%), tiempo en incubación (10%), terapia con surfactantes (7%) y ventilación mecánica (7%). **Conclusión.** Los CMD promedio en recién nacidos pretérmino con SDR están relacionados con la edad gestacional, el peso al nacer y las complicaciones clínicas que presentan los pacientes durante su hospitalización.

Palabras clave: costos y análisis de costos, síndrome disneico respiratorio del recién nacido; neonato; México

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In general, neonatal mortality accounts for ~40% of deaths in children under five years of age.¹ After 28 weeks of gestation (WG), neonatal mortality rates are closely linked with prematurity.² The risk of premature births in the general population is estimated at ~6 to 10%.³

Respiratory distress syndrome (RDS) is a clinical condition seen almost exclusively in preterm newborns (NB) characterized by respiratory distress, cyanosis, and tachypnea, beginning after birth and increasing in severity during the first two days of life.⁴ The presence of RDS is inversely proportional to gestational age and birth weight; thus, it is estimated that in NB <30 WG, the condition occurs in ~60%, in NB between 32 and 36 WG it occurs in 15 to 20%, and at >37 WG the condition is seen in 5% of NB.⁵

In addition to prematurity, other risk factors associated with the development of RDS are male gender, Caucasian, history of maternal diabetes, perinatal asphyxia due to hypothermia, multiple pregnancy, or cesarean birth.⁶⁻¹⁰

Treatment of RDS is multidisciplinary and should preferably be carried out in the neonatal intensive care unit (NICU). Basic care must focus on minimizing stress and maintaining the NB under the most optimal physiological conditions. To accomplish this, adequate oxygenation (with or without mechanical ventilation [MV]) and normal temperature must be maintained (use of incubators), as well as maintaining cardiac and renal function within normal limits. Specifically, use of exogenous surfactant is currently recommended.¹¹

In economic terms, patients with RDS represent a major burden within the health system because their management requires a substantial amount of resources.¹² A follow-up study of 117 patients in Canada reported the cost of care required by NB with RDS over a two year period. The study found that a high proportion of costs accounted for the initial episode of hospitalization (82%), whereas 76% of costs were due to hospital management in the NICU.¹³

As a reference for Mexico, for the population covered by the Mexican Social Security Institute (IMSS, for its Spanish acronym) in 2008, the unit cost based on diagnosis related groups (DRG) for an RDS event or for an extremely premature neonate was 8 449 USD. In the case of patients who developed major complications, the costs were 31 478 dollars per case and for NB without major complications, cost were 2 700 USD (updated to 2011 prices).¹⁴⁻¹⁶

The Health Social Protection System (SPSS, for its Spanish acronym) in 2008, through the Fund for Protection against Catastrophic Expenses (FPGC, in Spanish) paid hospitals in 2008 a total of 8 569 379 USD in fees

equivalent to 115 343 838 Mexican pesos (updated to 2011 prices) to manage patients with RDS. Thus, there were 2 485 paid NB cases with RDS with a per capita payment of 3 448 USD (46 416 pesos updated to 2011 prices).¹⁵⁻¹⁷

The large difference between the fees paid by SPSS and the per capita payment (8 449 vs 3 448 USD) shows the need for a detailed cost analysis of the care of these patients and a careful assessment of these variations. Besides, the information reported by the SPSS did not include the detailed use of resources for the different types of patients in terms of gestational age or according to the presence of complications.

This information is relevant to the economic evaluation of interventions and/or health technologies because data for the population of interest is used to extrapolate data for other populations.¹² Faced with the limited information concerning the cost of treating NB with RDS in Mexico, this study was performed to estimate the direct medical costs (DMC) of such treatment.

Materials and methods

We performed a retrospective and descriptive study to assess DMC in NB with RDS treated in two specialized public hospitals in Mexico City and paid through the FPGC.

The perspective used in the study focused on the Public Health Sector, as the health care provider in Mexico. Patients were classified according to gestational age. This was done to identify differences in use of resources because it would be expected that, with greater disease severity, resource allocation would be higher and would correspond with the highest degree of prematurity. In this way, four groups were comprised: a) NB <28 WG; b) NB 28-32 WG; c) NB 33-37 WG, and d) NB >37 WG.

A second classification criterion was the development of clinical complications after RDS resolution. This criterion differentiates the DMC to meet the initial hospitalization event and the cost of follow-up care. Complications of RDS were bronchopulmonary dysplasia (BPD), pneumonia, intraventricular hemorrhage (IVH), hydrocephalus, and apnea.¹⁸

The time horizon analysis applied to the initial hospitalization event is regarded as the time of the patient's hospital admission until discharge (high for either improvement or death). For cases with RDS-associated complications, the time horizon covered up to two years.

Sample selection

The sample comprised patients treated at two specialized public hospitals: Hospital Infantil de México Dr.

Federico Gómez (HIMFG) and Hospital General de México (HGM). Both hospitals treated 43% of paid cases with RDS through FPGC in Mexico City during the year 2008. FPGC pays fees to the service providers so that they are able to provide high specialization medical services to the population not covered by Social Security.¹⁷ The protocol was approved by HIMFG's the institutional Ethics Committee.

Non-probability sampling technique was used to complete a quota of cases with RDS as primary admission diagnosis in the two specialized hospitals. The quota was set at 70 cases based on the sample size for estimating averages in a probabilistic sample,¹⁸ considering 95% confidence interval, 80% sampling power, standard deviation of 54 000 dollars¹⁹ and 15% losses.

Resource use

Identification of resources used in patient management was performed by reviewing clinical files. Data collection instruments were constructed based on clinical guidelines for treatment of patients with RDS¹⁴ and were then adjusted and validated by a panel of experts: department heads and physicians specializing in neonatology and pediatrics at the same hospitals where patients were recruited.

Estimation of direct medical costs

Items included in DMC were hospital bed days, days in NICU, intermediate care days, days with respiratory support, days in an incubator, number of interconsultations, laboratory and diagnostic exams, surgical procedures, blood component transfusions, and use of parenteral nutrition and drug treatment, including the use of surfactant. Estimation of DMC was done by combining the techniques of average costs for services and surgical procedures. For drug prescriptions and surfactant treatment microcosting was applied. Average costs used corresponded to recoverable quotas for medical services of each hospital published for 2009.²⁰

For drug prescriptions and surfactant treatment, costs were estimated according to the presentation and unit purchase price reported for basic drugs and equipment for patient treatment (2009).²¹ Costs were expressed according to October 2011 prices in USD. We applied the inflation factor reported by the Bank of Mexico¹⁶ and used an exchange rate of 1 USD= 13.46 pesos.¹⁵

Statistical analysis

The study population was characterized using frequency tables and simple percentages. We assessed differences

in resource use among the four age groups of children using Wilcoxon and rank-sum test.²²

For the estimation of direct medical costs, we calculated means and confidence intervals adjusted through bootstrapping for mean difference. Bootstrapping has the advantage of avoiding parametric assumptions of normality, allowing more robust inferences about distribution of costs.²³ The nonparametric bootstrap procedure consists of repeated sampling from the observed data; 1 000 resamples were obtained to estimate a bootstrap confidence interval.² The estimation was performed using STATATM software.

Results

The sample consisted of 71 NB (29 from HIMFG and 42 from HGM) diagnosed with RDS and treated at either hospital. NB showed an average weight of 1.670 kg (95% CI 1.50-1.83). Mean gestational age was 33.5 WG (95% CI 32.6-34.5), whereas length at birth was 41.7 cm (95% CI 40.6-43.0). Of the total sample, 52% were females; 86% were treated in the NICU and 14% required only intermediate care. Due to the severity of cases, 83% required mechanical ventilation (MV) (both high-frequency mode and continuous positive pressure). Of all the patients, 14% died during hospitalization (table I).

Overall average hospital stay was 36 days (95% CI 29.8-42.7), whereas average incubator days was 23 days (95% CI 5.17-29.6), 13.5 days on oxygen (95% CI 10.1-16.9) and 23.5 days with MV (95% CI 8.4-16.6). Table II depicts the detailed use of resources according to gestational age.

Average DMC per RDS event was 14 226 USD (95% CI 11 627-16 823 USD), where the most significant component was hospitalization with 38% (5 444 USD), followed by laboratory and diagnostic exams with 18%

Table I
DESCRIPTION OF SAMPLE.
CASES OF NEWBORNS WITH RDS. MEXICO

<i>Patients' characteristics</i>	<i>n = 71</i>	<i>%</i>
Female	37	52
Average gestational age - mean (25-75%)	33.5 weeks	(32.6-34.5)
Average weight at birth - mean (SD)	1 670 g	(1 500-1 830)
Complications during hospitalization	11	15.5
Neonatal intensive care unit required	61	86
Mechanical ventilation required	59	83
Death during hospitalization	10	14

Table II
UTILIZATION OF RESOURCES OF NEWBORNS WITH RDS ACCORDING TO GESTATIONAL AGE

Weeks of gestation	<28 WG n = 5			28-32 WG n = 26			33-37 WG n = 30			>37 WG n = 10			p>
	AV	95%CI		AV	95%CI		AV	95%CI		AV	95%CI		
Weight (g)	1 079	893	1 265	1 168	1 069	1 268	1816	1 652	1 980	2 837	2 495.5	3 179	0.0001*
	Freq	Med	IR	Freq	Med	IR	Freq	Med	IR	Freq	Med	IR	
Days of hospitalization	5	22	42	26	60	63	30	32	16	10	10	10	0.0014‡
Days in incubator	5	8	41	26	61	77	30	13	19	10	6	11	0.0069‡
Days with mechanical ventilation	5	5	7	26	30	72	30	7	9	10	3	5	0.0308‡
Laboratory studies	5	8	2	26	10	4	29	9	4	10	6	1	0.0025‡
Biochemistry panel	5	17	34	24	44	48	30	16	24	10	4	3	0.0001‡
Determination of serum electrolytes	5	10	13	20	21	30	27	10	22	8	3	5	0.0066‡
Blood gases	5	30	27	22	37	66	27	21	66	0	0	0	0.0140‡
Blood chemistry	5	10	34	23	45	58	30	14	26	10	3	6	0.0001‡
Liver function tests	0	0	0	20	6	6	28	1	1	8	5	5	0.0312‡
Others	5	2	2	20	4	4	24	3.5	4	7	1.5	1	
Surgical procedures	5	2	1	26	3	2	25	3	1	10	1.5	1	0.0016‡
Pleural catheter	1	1	0	1	1	0-	3	1	0-	0	0	0	0.0001‡
Catheter for venodissection	1	1	0	4	1	0	8	1	0	0	0	0	0.0001‡
Umbilical catheter	5	1	0	23	1	0	25	1	0	3	1	0	0.0001‡
Others Surg. Proc.	3	1	4	18	12.5	9	20	3	7	3	13	10	0.0001‡

NB= newborns
 RDS= respiratory distress syndrome
 PDA= patent ductus arteriosus
 AV= average
 Freq= frequency
 IR= interquartile range
 Med= median
 * Anova test
 ‡ Rank-sum test

(2 529 USD), surfactant treatment 7% (1 078 USD), days in an incubator with 10% (1 377 USD), mechanical ventilation with 7% (1 003 USD) and oxygen use with 5% (792 USD) (figure 1).

Cost of RDS according to gestational age

Table III presents the main costs according to age group. These are 19 182 USD for the group of NB of ≤28 WG. For the second group (28-32 WG) the cost was 20 265 USD, for the third (32-37 WG) it was 12 193 USD, and for the group of >37 WG it was 3 332 USD.

Costs according to patients who died and survived

Subsequently, DMC were disaggregated into two groups according to patient outcome: the first group represents

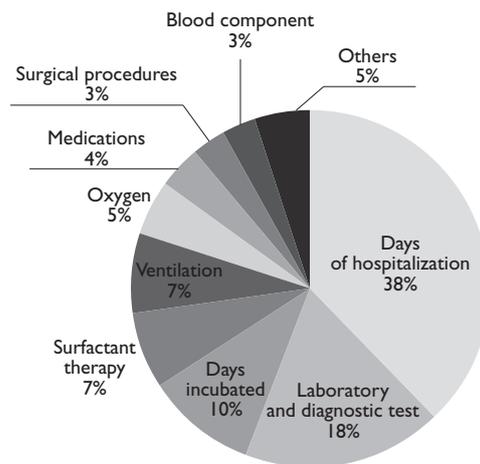


FIGURE I. PARTICIPATION OF DIRECT MEDICAL COSTS FOR TREATING RESPIRATORY DISTRESS SYNDROME (RDS) IN MEXICO

Table III
DIRECT MEDICAL COSTS OF CARE OF NEWBORNS WITH RDS ACCORDING TO GESTATIONAL AGE

Weeks of gestation	<28 WG			28-32 WG			33-37 WG			>37 WG			p>
	Mean cost	SD	Part	Mean cost	SD	Part	Mean cost	SD	Part	Mean cost	SD	Part	
Days of hospitalization	8 815	3 551	46%	7 673	1 465	38%	4 325	461	35%	1 322	362	40%	0.0404*
Laboratory and diagnostic exams	2 347	830	12%	3 768	538	19%	2 070	321	17%	778	366	23%	0.0240*
Incubator days	1 295	594	7%	2 046	352	10%	1 162	217	10%	327	173	10%	0.0172*
Surfactant	3 325	2 248	1%	1 737	423	9%	493	186	4%	0	0	0%	0.0078*
Mechanical ventilation	1 079	659	6%	1 473	371	7%	796	145	7%	362	213	11%	0.0174*
Surgical procedures	351	57	2%	622	152	3%	372	27	3%	188	39	6%	0.0900*
Blood components	647	208	3%	608	109	3%	229	61	2%	38	27	1%	0.0006*
Others	1 323	N.A	7%	2 338	N.A	12%	2,747	N.A	23%	317	N.A	10%	N.A
Total costs	19 182	5 750	100%	20 265	2 688	100%	12 193	1,431	100%	3 332	1 150	100%	0.0030*0
Daily cost	31 669	18 308	-	16 255	8 204	-	4 142	266	-	3 132	397	-	0.0000*

Exchange rate: 1 USD= 13.46 Mexican pesos. Prices updated for inflation to October 2011

NB= newborns

RDS= respiratory distress syndrome

SD= standard deviation

Part= participation

WG= weeks of gestation.

* Anova test

patients who survived the event and the second group represents patients who died. Average DMC of surviving NB with RDS, regardless of complications during hospitalization, was 27 579 USD in those <28 WG, for those with 28-32 WG the cost was 21 759 USD, for those with 33-37 WG the cost reached 11 897 USD and for NB >37 WG the cost was 2 195 USD. For patients who died, the cost was 6 587 USD in NB <28 WG, 15 282 USD for NB 28-32 WG, 20 477 USD for NB 33-37 WG and 13 558 USD for NB >37 WG (data not shown).

Additional cost of RDS-associated complications

Of all patients, 15.5% (11 NB) were reported to have complications associated with RDS. In these patients, costs included up to two subsequent years. Average DMC of NB with complications was 3 035 USD. Patients who incurred higher costs were those with hydrocephalus (10 546 USD) and intraventricular hemorrhage (4 168 USD), whereas those patients with BPD (2 101 USD), pneumonia (1 738 USD) and apnea (2 469 USD) had lower costs (data no shown).

Discussion

In our study, average DMC for an event of NB with RDS was 14 226 USD, we found differences in terms of

gestational age and weight at birth of the NB, as well as in the presence of complications and death during hospitalization.

Based on our results, neither IMSS DRG's cost nor SPSS fees cover the DMC. The fees paid by FPGC covers only 25% of the DMC according to our estimates, although the concepts covered by the amount paid by SPSS are not known (whether such amount was intended to cover only the cost of surfactant treatment, or other costs).

In the analysis by age group, the amount paid by the FPGC covered only the cost of premature to term (>37 WG) babies. So it would be advisable to know the methodology used by SPSS for the calculation of payments and the concepts covered by these resources, to ensure a proper care of patients.

Previous studies have reported the main factors that affect the cost of patients with DRS, which agree with our results.

First, as reported by Zupancic and colleagues,²⁴ some variability exists in costs according to WG. There is a higher cost in those NB who survived and represented the shorter gestational age groups. Second, DMC of patients who died were lower compared to the costs for survivors. Third, as reported by Neil,²⁵ we found differences in terms of weight of the NB. Neil reported an inverse relationship between DMC of the initial hospitalization and NB survivors and

their weight: for NB weighing 500-1 000 g, the cost is 101 887 USD; for NB weighing 1 000-1 500 g the DMC is 85 524 USD and for NB weighing >1 500 g the cost was 27 224 USD. In our study we found a similar relation: in NB weighing 500-1 000 g, the cost of care was 23 684 USD; in NB weighing 1 000-1 500 g the cost decreased to 19 834.12 USD, whereas in NB >1500 g, the cost was 7 294.63 USD.

Using the above information it can be demonstrated that DMC in NB with RDS is multifactorial. Factors identified here are WG at birth, weight of the child at birth, the presence of complications, and death.

Disease management require large resources utilization, which was intensively established by the fact that 86% of patients required management in the NICU; 56% of costs comprised components such as lengthy hospitalization (up to 36 days), use of a large number of laboratory and diagnostic exams, and high number of consultations, as well as the need for surfactant treatment and MV. The cost predictive model of Zupancic and colleagues²⁴ reported that the main factors that explain the daily cost of care of premature infants are surfactant therapy, x-ray studies, blood transfusions, surgeries, and echocardiography. Although the cost items identified in this study are different from those used by Zupancic and colleagues,²⁴ results of their model are similar except that the costs of MV and medication outweigh surgical procedures or blood component products.

Regarding the limitations of our study, we found that the sample was not selected randomly, so the representativeness for the nationwide population requiring RDS treatment could not be warranted. However, as mentioned these two hospitals treated >43% of RDS cases paid for and reported by the FPGC in the year of analysis.

Another limitation is the small number of patients who presented complications, a larger number would have been useful for more accurate results, although the actual limitation was the incidence of cases in the population.

In other countries, DMC due to complications in patients who died may also lead to underestimation of costs; however, no information is available on the subject in our country.

Conclusion

Average DMC for NB with RDS presents important fluctuations (23-142%) because the use of resources is relative to gestational age, birth weight and clinical conditions of patients during hospitalization.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

References

1. Goldenberg RL, Culhane JF, Lams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371(9606):75-84.
2. Yost CC, Soll RF. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *The Cochrane Library* 2000;(2):1-11.
3. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 1997;4:CD000511.
4. Sweet D, Bevilacqua G, Carnielli V, Greisen G, Plavka R, Saugstad OD, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome. *J Perinat Med* 2007;35(3):175-186.
5. López NL, Rodríguez JJ, Zavala A, Mendoza DS, Torres PC. Administración de surfactante exógeno en el tratamiento del síndrome de dificultad respiratoria neonatal, en su modalidad de rescate. *Rev Mex Pediatr* 1999;66(1):5-8.
6. Pérez JJ, Blancas O, Ramírez JM. Enfermedad de membrana hialina: mortalidad y factores de riesgo maternos y neonatales. *Ginecol Obstet Mex* 2006;74(7):354-359.
7. Fraser J, Walls M, McGuire W. Respiratory complications of preterm birth. *BMJ* 2004;329:962-965.
8. Zanardo V, Simbi AK, Francio M, Soldà G, Salvadori A, Trevisanuto D. Neonatal respiratory morbidity risk and model of delivery at term: influence of timing of caesarean delivery. *Acta Paediatr* 2004;93(5):643-647.
9. Hansen AK, Wisborg K, Ulbjerg N, Henriksen TB. Elective caesarean section and respiratory morbidity in the term and near-term neonate. *Acta Obstet Gynecol Scand* 2007;86(4):389-394.
10. Jain L, Dudell GG. Respiratory transition in infants delivered by cesarean section. *Semin Perinatol* 2006;30(5):296-304.
11. Mazzi GE. Síndrome de dificultad respiratoria en el recién nacido (SDR). *Rev Soc Bol Ped* 1995;34(2):68-74.
12. Profit J, Lee D, Zupancic JA, Papile L, Gutierrez C, Goldie SJ, et al. Clinical benefits, costs, and cost-effectiveness of neonatal intensive care in Mexico. *PLoS Med* 2010;7(12):e1000379. Doi:10.1371/journal.pmed.1000379
13. Cheung AM, Tansey CM, Tomlinson G, Díaz-Granados N, Matté A, Barr A, et al. Two years outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;173(5):538-544.
14. Instituto Mexicano del Seguro Social. Guía de práctica clínica. Diagnóstico y tratamiento del síndrome de dificultad respiratoria en el recién nacido [internet document]. México: IMSS, 2009 [accessed on: December 20, 2011]. Available at: http://www.imss.gob.mx/.../GuíasClínicas/GPC_SDRRecienNacido.pdf
15. Banco de México. Mercado cambiario nacido [internet document]. 2011 [accessed on: December 31, 2011]. Available at: <http://www.banxico.org.mx/portal-mercado-cambiario/index.html>
16. Banco de México. Inflación 2009-2011 [internet document]. [accessed on: November 12, 2011]. Available at: <http://www.banxico.org.mx/portal-inflacion/index.html>
17. Comisión Nacional de Protección Social en Salud. Registros pagados por el Fondo de Gastos Catastróficos. México: CNPSS, 2008.
18. Meinert CL. Clinical trials: design, conduct and analysis. In Lilienfeld AM, ed. *Monographs in epidemiology and biostatistics*, vol. 8. New York: Oxford University Press, 1986:71-88.
19. Thomas NJ, Hollenbeck CS, Lucking SE, Willson DF. Cost-effectiveness of exogenous surfactant therapy in pediatric patients with acute hypoxemic respiratory failure. *Pediatr Crit Care Med* 2005;6(2):160-165.
20. Hospital Infantil de México Federico Gómez. Dirección de Finanzas. Cuotas de recuperación de servicios de Atención Médica 2009. México: HIMFG, 2009.
21. Hospital Infantil de México Federico Gómez. Dirección de Finanzas. Precios Unitarios de compra de medicamentos 2009. México: HIMFG, 2009.

22. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. Regression methods in biostatistics: Linear, logistic, survival, and repeated measures models. New York: Springer, 2005:157-209.
23. Glick H, Doshi J, Sonnad S, Polsky D. Economic evaluation in clinical trials (handbooks in health economic evaluation). New York: Oxford University Press, 2007:101.
24. Efron B, Tibshirani RJ. An introduction to the bootstrap. Vol. 57, Monographs on Statistics and Applied Probability. New York: Chapman and Hall/CRC, 1993.
25. Zupancic JA, Richardson DK, O'Brien BJ, Schmidt B, Weinstein MC. Daily cost prediction model in neonatal intensive care. *Int J Technol Assess Health Care* 2003;19(2):330-338.
26. Neil N, Sullivan SD, Lessler DS. The economics of treatment for infants with respiratory distress syndrome. *Med Decis Making* 1998;18(1):44-51.