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ORIGINAL ARTICLE

Maternal and neonatal factors affecting the incidence of bronchopulmonary dysplasia in very low birth weight newborns

Gicelle S. Cunha,[1] Francisco Mezzacappa Filho,[2] José D. Ribeiro[3]

Abstract

Objective: To determine the incidence of bronchopulmonary dysplasia, to identify maternal and neonatal factors associated with the disease, and to determine the correlation between bronchopulmonary dysplasia and the progress of newborns.

Methods: Data were prospectively collected on 153 infants born in Campinas (state of São Paulo, Brazil) from September 2000 to April 2002 weighing less than 1,500 g and treated at the University Hospital. The ratio of incidence rates with 95% CI, Breslow-Cox regression, Student's *t* test, linear regression and the Fisher's exact test were utilized.

Results: Among the 124 babies who survived until 28 days of age, 33 (26.6%) developed bronchopulmonary dysplasia. Birthweight $\leq$ 1,000 g (5.6; 95% CI 3.0, 10.4) and gestational age $\leq$ 30 weeks (4.0; 95% CI 2.1, 7.2) were correlated with increased incidence of bronchopulmonary dysplasia. Breslow-Cox regression showed that other factors including gender, Apgar score, hyaline membrane disease, antenatal steroid therapy, pregnancy-induced hypertension, delivery route and maternal age were not associated with bronchopulmonary dysplasia. Mean duration of hospitalization and ventilator therapy in newborns with and without bronchopulmonary dysplasia was 78.8 days (SD = 26.67) vs. 43.0 days (SD = 14.49) ($p < 0.01$) and 27.2 days (SD = 21.26) vs. 3.7 days (SD = 3.02) ($p < 0.01$), respectively. Mean weight gain per day was lower in newborns with bronchopulmonary dysplasia ($p < 0.01$). Mortality in newborns with bronchopulmonary dysplasia was 21% ($p < 0.00005$).

Conclusions: Gestational age and birthweight were inversely proportional to incidence of bronchopulmonary dysplasia. After the onset of bronchopulmonary dysplasia, newborns with the disorder required longer periods of ventilator therapy and hospitalization, and presented inadequate weight gain and higher mortality rates than newborns without bronchopulmonary dysplasia.

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1. MSc. Postgraduate student, School of Medicine, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil.
2. Assistant professor, Department of Pediatrics, School of Medicine, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil.
3. PhD. Assistant professor, Department of Pediatrics, School of Medicine, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil.

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Introduction

Recent advances in perinatal care have improved the survival of very low birth weight infants (VLBWI). The development of new treatments over the last few decades has reduced mortality, but their efficacy in reducing the occurrence of bronchopulmonary dysplasia (BPD) remain controversial.[1] The incidence of BPD varies in published studies from 23 to 83%.[2] This can be explained by the acute respiratory insufficiency of the populations studied, the type of care afforded the newborn (NB), or the diagnostic criteria employed.

Bronchopulmonary dysplasia is the most common obstructive lung disease among premature NBs. Its incidence increases as birth weight (BW) and gestational age (GA) decrease.[3-6] Northway et al.[7] and later Bancalari et al.[8] described BPD defining the disease according to oxygen requirements at 28 days.

Bronchopulmonary dysplasia is a disease whose etiology has not yet been fully established, being the result of multiple factors that act on the immature pulmonary system, subject to aggression from many different sources and, at the same time, having defense mechanisms that have not yet developed.[9] In contrast, the only unanimous consensus is that pulmonary immaturity is a risk factor for the development of BPD.

In addition to prematurity, low BW, male sex, low Apgar scores and Hyaline membrane disease (HMD)[10-12] have all been associated with BPD. In contrast, the use of prenatal corticoids has been associated with a reduced BPD incidence.[13]

As BPD is associated with increased morbidity and mortality during the neonatal period and is also often the cause of prolonged hospitalization with serious social and economic consequences,[14] deeper understanding of the disease will contribute to future preventative measures aimed at reducing its incidence, minimizing complications, diminishing hospital costs and improve infant health. This research aimed to discover the incidence of bronchopulmonary dysplasia among very low birth weight infants, to assess the maternal and neonatal factors that are associated with the disease and to determine the correlation between bronchopulmonary dysplasia and the progress of these infants.

Methods

A prospective study was performed of a cohort of 153 NBs, treated at the Center for Integral Women's Health Care (CAISM- Centro de Atenção Integral à Saúde da Mulher) at the Universidade Estadual de Campinas (UNICAMP). All infants with a BW of less than 1,500 g, born live during the period between September 2000 and April 2002. Infants with major malformations or chromosomal syndromes were excluded. Infants that died or were transferred to other sectors with resultant loss of monitoring before the 28th day were not included in the analysis as not satisfying the time period established for the diagnostic criteria employed.

The clinical diagnosis of BPD was defined as the need for supplementary oxygen at 28 days in order to maintain arterial oxygen pressure (PaO_2) > 50 mmHg[8] in association with consistent radiological findings. Chest x-ray was used between the 4th and 5th weeks of life for infants dependant upon oxygen. Radiographs were evaluated by a neonatologist and a pediatric radiologist. Variables related to the mother (age, number of consultations, prenatal care, hypertensive disorders of pregnancy, type of delivery and prenatal corticoid used), to the infant (BW, GA, Apgar score, type of respiratory disorder, sex, normality of weight/age ratio) and to the progress of the infant (weight/day gain, period of hospitalization, period of mechanical ventilation and mortality) were all analyzed.

Maternal age was banded into $\leq$ 19 and > 19 years. These age bands were chosen for study based on their difference as representing a group of adolescents compared with a group of mature women.[15] For prenatal care the study employed a cut-off point of: < 3 and > three consultations. Prenatal corticoid use was defined as at least one corticoid dose at least 24 hours at most seven days prepartum.

Gestational age was established for all NB by the method established by Ballard et al.[16] and confirmed by reference to last menstrual cycle. In cases in which the clinical examination did not agree with the date of amenorrhea by more than two weeks, amenorrhea was used. The normality of weight/age was classified in accordance with the Battaglia & Lubchenco growth curves.[17] Apgar scores were grouped into two categories: NBs with an Apgar < 7 and NBs with an Apgar $\geq$ 7.[11] Hypertensive disorders of pregnancy were defined as arterial pressure levels of 140/90 mmHg or more after the 20th week of gestation. The type of respiratory disease was taken to be the acute pulmonary disease that the NB developed during its first 72 hours of life. The criteria for HMD diagnosis included increased oxygen dependency during the first 24 hours confirmed by radiological patterns typical of diffuse "ground-glass" infiltration and with air bronchograms.

Weight/day gain was defined as the average obtained by subtracting birth weight from weight on discharge and dividing the result by the number of days of hospitalization. Mechanical ventilation duration was measured in days for NB that used neonatal respirators with any combination of parameters. Incomplete days were categorized as follows: 0 < x < 6h = 0.25 day; 6 < x < 12h = 0.5 day; 12 < x < 18h = 0.75 day; 18 < x < 24h = 1 day. Bronchopulmonary dysplasia was considered an independent variable in analyzing the infant progress variables.

All of the NB were maintained in incubators under a radiant heat source. Surfactant (Survanta®) was used as a salvation therapy for HMD in cases where ventilated NBs required oxygen supplementation at FiO2 levels greater than 40% with $PaO_2 < 50$ mmHg or $PaCO_2 > 55$ mmHg and x-rays were typical of HMD. Ventilation therapy respirators were pressure-limited, time-cycled and continuous flow (Sechrist Model IV-100B, Sechrist and Inter 3, Intermed). Mechanical ventilation was indicated for NBs with inadequate gas exchange, hypercapnia ($PaCO_2 > 55$ mmHg) and hypoxemia ($PaO_2 < 50$ mmHg) when on supplementary oxygen. Ventilators were adjusted to maintain $PaO_2 > 50$ mmHg, $PaCO_2 < 55$ mmHg and oxygen saturation, by pulse oximetry, between 87% and 96%.

Infants that developed BPD were classified according to the severity of the disease as mild, moderate and severe, according to criteria formulated by Jobe & Bancalari.[18]

Sample size was calculated as 103 VLBWI for an α of 5% and a ß of 20%. The study was approved by the Committee for Ethics in Research of the Medical Sciences Faculty at UNICAMP.

For each infant a form was filled out that had been designed for the study. Data was entered into a database using Epi-Info 6.0. Data was input twice in order to perform a consistency test and any inconsistencies corrected.

For the statistical analysis BPD incidence rates (IR) were calculated according to maternal and neonatal variables. For each of these variables, IR were compared between categories to give incidence rate ratios (IRR) with 95% confidence intervals (CI). The IRR for each variable was adjusted for BW, GA and, when necessary, according to HDP and type of delivery, by means of the Breslow-Cox regression model.[19] The Student *t* test was used for continuous variables, with a 5% significance level ($p < 0.05$). These variables were adjusted for BW and GA via a linear regression model.[20] Fisher's exact test was used to compare mortality between groups. All statistical analysis was performed using the software SAS, version 8.2.

Results

The study began with 153 NB of whom 29 died before the 28th day of life and were excluded from the analysis. The causes of death were heart disease (three), otitis media (four), supra-renal failure (one), pulmonary hemorrhage (four), extreme prematurity (two), cardiogenic shock (one) and 14 cases of sepsis.

Average weight and standard deviation (SD) and average GA (SD) of the NB that died were 833.8 (253.3 grams) and 27.9 (2.3 weeks) respectively. Of the 124 NB that survived, 33 (26.6%) developed BPD. All of the NB that developed BPD had gestational ages of less than 32 weeks. Four NB (12.1%) developed mild BPD, 16 (48.5%) moderate and 13 (39.4%) severe.

Average BW and GA were significantly lower for the group with BPD compared with those without the disease: 913.3±199.4 as against 1.242.1±181.6 g and 28.9±2.0 against 31.8±2.0 weeks, respectively. Table 1 shows that GA and BW are strongly and independently associated with developing BPD.

Data on sex, intrauterine growth and first minute Apgar score were not associated with BPD incidence. The fifth minute Apgar score showed an association with increased BPD incidence which did not remain after adjustment for BW and GA. Hyaline membrane disease was the primary respiratory disorder in 71.4% of the NB that developed BPD, giving a significantly higher gross IRR amongst these NB. However, when the confounding variables, BW and GA were controlled, the adjusted IRR showed that HMD did not directly influence the incidence of BPD (Table 1).

The results in Table 2 indicate that the BPD IR is greater among NB whose mothers did not receive corticoid, with a gross IRR that double for untreated mothers. However, when this variable was adjusted for BW and GA, while the adjusted IRR was still higher for mothers that hadn't received corticoid, this difference was no longer statistically significant. It can be observed that HDP was initially a variable statistically correlated with BPD, presenting gross BPD IR and IRR significantly lower for NB whose mothers presented the disease. However, the fact that the mother presented HDP taken as a factor independently of BW and GA in the NB revealed an adjusted IRR below the 5% significance level. All 8 HDP cases that developed BPD were the children of mothers that presented preeclampsia. In terms of type of delivery, a gross IRR of 0.4 demonstrated a protective effect for NB whose mothers underwent caesarians. However, when the confounding variables, HDP, BW and GA were controlled, the adjusted BPD IRR differences were not significant. The effect of maternal age was not sustained when the variables BW, GA, HDP and type of delivery were controlled. Similarly, prenatal care and number of consultations did not influence BPD incidence.

Averages for days hospitalized and weight gain for the NB with and without BPD were: 78.8±26.67 versus 43.0±14.49 days ($p < 0.01$) and 13.3±6.12 versus 18.5±4.25 g/kg/day ($p < 0.01$), respectively. This association was maintained when the regression model was used to exclude the confounding variables, BW and GA ($p < 0.01$). The period of mechanical ventilation was significantly shorter for NB without BPD compared with NB with BPD 3.7±3.02 as against 27.2±21.26 days, respectively ($p < 0.01$). At 28 days of life, 7/33 (212%) of the NB in the BPD group had died and none had died in the group without BPD ($p < 0.00005$).

Table 1 - Ratio of incidence of BPD according to neonatal variables

	n	BPD	IR (%)	Whole RIR (95% CI)	Adjusted RIR (95% CI)
Gestational age					
> 3 weeks	86	12	14.0	ref.	
≤ 30 weeks	38	21	55.3	4.0 (2.1-7.2)	
Birthweight					
> 1.000 g	93	11	11.8	ref.	
750 - 1,000 g	27	18	66.7	5.6 (3.0-10.4)	
< 750 g	4	4	100	8.4 (4.8-14.7)	
Sex					
Female	61	14	23.0	ref.	
Male	63	19	30.2	1.3 (0.7-2.4)	
Weight/age adjustment					
SGA	64	16	25.0	ref.	
AGA	60	17	28.3	1.1 (0.6-2.0)	
Apgar index					
1 min					
≥ 7	54	11	20.4	ref.	ref.
< 7	70	22	31.4	1.5 (0.8-2.9)	1.0 (0.4-2.3)
5 min					
≥ 7	109	25	22.9	ref.	ref.
< 7	15	8	53.3	2.3 (1.3-4.1)	1.1 (0.4-2.6)
Type of respiratory disorders					
Others	27	4	14.8	ref.	ref.
HMD	28	20	71.4	4.8 (1.8-12.2)	2.1 (0.6-6.7)

n: number of children; IR: incidence rate; RIR: ratio of incidence rate; ref.: reference; CI: confidence interval; BPD: bronchopulmonary displasia; HMD: hyaline membrane disease; SGA: small for gestational age; AGA: adequate for gestational age.

Discussion

As a result of its status as a tertiary center of excellence, the CAISM concentrates a large proportion of the obstetric and neonatal risk of the city of Campinas and the surrounding region. These characteristics explain the elevated incidence of VLBWI (4.3% - 213/4,897) observed during the period under study.

In a recent prospective study the incidence of BPD defined by the need for O2 at 28 days in VLBWI was 23% and 62% for those whose BW was < 1,000 g,[21] while, in our study, these values were 26.6 and 71%, respectively.

The findings of this study confirm expectations to the extent that it confirmed that more premature and lower BW were the independent factors most strongly associated with the incidence of BPD. This data emphasizes that BPD as a complication of prematurity will continue to be a common cause of morbidity and a significant public health problem since the rates of VLBWI survival continue to rise.

In contrast with previous studies,[11,22] we did not find as association between first and fifth minute Apgar scores below 7 and BPD. These studies, however, presented serious methodological problems. It should also be pointed out that a premature NB may have a low Apgar score because of its neurological development. This fact may explain the result of our research that suggests that an association between the fifth minute Apgar score and BPD was confounded by BW and GA.

A number of different authors relate BPD with DMH.[12,23] The absence of a direct association between HMD and BPD when IRR was adjusted for BW and GA in these results attracts attention. Knowing that these two variables constitute an approximation of an expression

Table 2 - Ratio of incidence rate for BPD according to maternal variables

	n	BPD	IR (%)	Whole RIR (95% CI)	Adjusted RIR (95% CI)
Prenatal corticoid					
Yes	110	26	23.6	ref.	ref.
No	13*	7	53.9	2.3 (1.2 - 4.2)	1.5 (0.6 - 3.6)
HDP					
Yes	55	8	14.6	ref.	ref.
No	69	25	36.2	0.4 (0.1 - 0.8)	0.4 (0.2 - 1.1)
Type of delivery					
Vaginal	30	14	46.7	ref.	ref.
Cesarean	94	19	20.2	0.4 (0.2 - 0.7)	1.1 (0.4 - 3.3)
Mother's age					
> 19 years	103	20	19.4	ref.	ref.
≤ 19 years	21	13	61.9	3.2 (1.9 - 5.3)	1.7 (0.7 - 3.7)
Prenatal care					
Yes	119	31	26.1	ref.	
No	5	2	40.0	1.5 (0.5 - 4.7)	
Number of prenatal consultations					
> 3	82	19	23.2	ref.	
≤ 3	42	14	33.3	1.4 (0.8 - 2.6)	

n: number of children; IR: incidence interval; RIR: ratio of incidence rate; ref.: reference; CI: confidence interval; BPD: bronchopulmonary displasia; HDP: hypertensive disorders of pregnancy; *1 ignored case

of the level of prematurity, the results permit the inference that association with them eliminates any independent effect in the genesis of BPD, thus remaining BW and GA as the greatest determinants of BPD in NB that develop HMD; a fact that is confirmed by the majority of work to be found in literature published to date.

Our findings in terms of the prenatal use of corticoid agree with the extensive meta-analysis by Crowley,[24] but are in contrast with a study by van Marter et al.[13] In the current study, those mothers who did not receive treatment were those whose delivery was vaginal, who were admitted at an advanced stage of labor and gave birth to NB with lower BW and GA. This immaturity could have predisposed them to develop BPD.

In relation to HDP, results are conflicting. Kim et al.[25] found a lower incidence of BPD (11% versus 58%, $p < 0.04$) for NB whose mothers had moderate HDP compared to NB whose mothers had severe HDP (preeclampsia). It was shown that initially HDP behaved in a protective manner against the incidence of BPD, which could reflect a less severe disease in which NB are more mature and there is a lower incidence of BPD. However, when confounding variables were controlled, the protective effect remained, but was no longer statistically significant. In a more detailed analysis it was found that all of the mothers whose children developed BPD had presented preeclampsia, and, due to compromised fetal or maternal conditions, the pregnancy had been interrupted, increasing prematurity and, consequentially, the risk of BPD.

In this study the protective effect of caesarian deliveries can be explained by the choice of this type of delivery because of diagnoses of maternal or fetal complications that may correlate with a more rigorous control of the pregnancy. This having been known to be the case, these mothers were better monitored and it was possible to use corticoid and/or other measures in order to prolong gestation and deliver their NB with greater GA and BW. Indeed, the type of delivery did not influence BPD incidence when controlled by BW and GA.

The greatest morbidity with NB is associated with neonatal care, which can be measured in terms of period

of hospitalization.[14] There is an association between average hospitalization durations and the presence of BPD; it is significantly longer among NB with BPD.[22] Rationally, it is to be expected that younger GA and also low BW would be factors leading to increased NB hospitalization periods.[14] Notwithstanding, it became clear that, excluding both GA and BW, BPD was responsible for increasing the hospital stays of these NB.

As has been demonstrated by Korhonen et al.[12] our NB with BPD require significantly more time on mechanical ventilation than NB without BPD. The mortality of the group of NB with BPD was 21.2%. These results are similar to those published by Hakulinen et al.[22] who found 22.8% among VLBWI with BPD and by Farstad & Bratlid[23] who published 17.4% and above those of Kornhauser et al.[26] who found 11%. However, in this last study, the NB had higher GA, a fact that greatly reduced mortality. In the present population, all deaths occurred in the group of NB with BPD.

The results of this study allow for the conclusion that the most effective means of reducing the incidence of BPD is to reduce the incidence of prematurity. Prospective work, involving risk factors should be stimulated as it reaps benefits in terms of improved health for specific populations. However, such work should concern itself with assessing confounding variables to check the independent contribution of each of the risk factors.

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References

1. Manktelow BN, Draper ES, Annamalai S, Field D. Factors affecting the incidence of chronic lung disease of prematurity in 1987, 1992, and 1997. Arch Dis Child Fetal Neonatal. 2001; 85: 33-5.
2. Kraybill EN, Runyan DK, Bose CL, D'ercole AJ. Chronic lung disease in infants with very low birth weight. Am J Dis Child. 1987;141:784-8.
3. Corcoran JD, Patterson CC, Thomas PS, Halliday HL. Reduction in the risk of bronchopulmonary dysplasia from 1980-1990: results of a multivariate logistic regression analysis. Eur J Pediatr. 1993;152:667-81.
4. van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M, et al. Do clinical markers of barotrauma and toxicity explain interhospital variation in rates of chronic lung disease? Pediatrics. 2000;105:1195-201.
5. Todd DA, Jana A, John E. Chronic oxygen dependency in infants Born at 24-32 weeks gestation: the role of antenatal and neonatal factors [abstract]. J Paediatr Child Heath. 1997;33: 402-7.
6. Fitzgerald DA, Mesiano G, Brosseau L, Davis GM. Pulmonary outcome in extremely low birth weight infants. Pediatrics. 2000;105:1209-15.
7. Northway WH, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease: bronchopulmonary dysplasia. N Engl J Med. 1967;276:357-68.
8. Bancalari E, Abnenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. J Pediatr. 1979;95(5 Pt 2):819-23.
9. Northway WHJR. An introduction to bronchopulmonary dysplasia. Clin Perinatol. 1992;19:489-95.
10. Kraybill EN, Runyan DK, Bose CL, Khan JH. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. J Pediatr. 1989;115:115-20.
11. Palta M, Gabbbert D, Weinstein MR, Peters ME. Multivariate assessment of traditional risk factors for chronic lung disease in very low birth weight neonates. J Pediatr. 1991;119:285-92.
12. Korhonen P, Tammela O, Koivisto AM, Laippala P, Ikonen S. Frequency and risk factors in bronchopulmonary dysplasia in a cohort of very low birth weight infants. Early Hum Dev. 1999; 54:245-8.
13. van Marter LJ, Leviton A, Kuban KCH, Pagano M, Allred EN. Maternal glucocorticoid therapy and reduced risk of bronchopulmonary dysplasia. Pediatrics. 1990;86:331-6.
14. Barton L, Hodgman JE, Pavlova Z. Causes of death in the extremely low birth weight infant. Pediatrics. 1999;103:446-51.
15. Scholl TO, Hediger ML, Belsky DH. Prenatal care and maternal health during adolescent pregnancy: a review and meta-analysis. J Adolesc Health. 1994;15:444-56.
16. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119:417-23.
17. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr. 1967; 71:159-63.
18. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723-9.
19. Skov T, Deddens J, Petersen MR, Endahl L. Prevalence proportion ratios: estimation and hypothesis testing. Int J Epidemiol. 1998; 27:91-5.
20. Drapper NR, Smithy H. Applied regression analysis. New York: John Wiley & Sons; 1998.
21. Collaborative Neocosur Multicenter Study Group. Very low birth weight infant outcomes in 11 South American NICUs. J Perinatol. 2002;22:2-7.
22. Hakulinen A, Heinonen K, Jokela V, Kiekara O. Occurrence, predictive factors and associated morbidity of bronchopulmonary dysplasia in a preterm birth cohort. J Perinatol Med. 1998;16: 437-46.
23. Farstad T, Bratlid D. Incidence and prediction of bronchopulmonary dysplasia in a cohort of premature infants. Acta Paediatr. 1994;83:19-24.
24. Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trial, 1972 to 1994. Am J Obstet Gynecol. 1995;173:322-34.

25. Kim CR, Vohr BR, Oh W. Effects of maternal hypertension in very low birth weight infants. Arch Pediatr Adolesc Med. 1996; 150:686-91.

26. Kornhauser M, Cullen JA, Baumgart S, Mckee LJ, Gross GW, Spitzer AR. Risk factors for bronchopulmonary dysplasia after extracorporeal membrane oxygenation. Arch Pediatr Adolesc Med. 1994;148:820-5.

Corresponding author:
José Dirceu Ribeiro
Depto. Pediatria da Faculdade de Ciências Médicas - UNICAMP
Área de Imunologia-Alergia e Pneumologia
Centro de Investigação em Pediatria - CIPED
Rua Osório Alves, 612
CEP 13084-020 – Campinas, SP, Brazil
Tel.: +55 (19) 3788.8970 – Fax: +55 (19) 3289.8638
E-mail: dirceu@fcm.unicamp.br / ribeiroj@lexxa.com.br