A Comissão Científica do **XV Congresso Mineiro de Terapia Intensiva** se empenhou para compor uma programação científica variada, com temas relevantes e atuais, também em pediatria.

Separamos alguns artigos de dois dos expositores do congresso para você se preparar para o evento. Veja nossas recomendações:

1. Alexandre Rotta

Alexandre Rotta é brasileiro radicado nos Estados Unidos há 25 anos. Formado em medicina na Universidade Federal do Rio Grande do Sul (UFRGS), fez residência médica em pediatria no Children's Hospital of Michigan, e fellowship em Terapia Intensiva Pediátrica no Children's Hospital of Buffalo. Ele é membro da Society of Critical Care Medicine e Fellow do American College of Critical Care Medicine (FCCM). Atualmente é o chefe das Divisões de Terapia Intensiva Pediátrica e de Medicina de Emergência Pediátrica no Rainbow Babies & Children's Hospital. Professor titular de pediatria na Case Western Reserve University School of Medicine, em Cleveland Ohio, onde também é o Endowed Linsalata Chair in Pediatric Critical Care and Emergency Medicine. Publicou mais de 70 artigos, 150 trabalhos e 30 capítulos de livro, e é Editor Associado do livro texto de Terapia Intensiva Pediátrica Fuhrman and Zimmerman."

Lista Seletiva de Publicações:

Critical Care After Sugery for Congenital – Pg 447

Abstract

Critical illness hyperglycemia (CIH) is common in pediatric and adult intensive care units (ICUs). Children undergoing surgical repair or palliation of congenital cardiac defects are particularly at risk for CIH and its occurrence has been associated with increased morbidity and mortality in this population. Strict glycemic control through the

use of intensive insulin therapy (IIT) has been shown to improve outcomes in some adult and pediatric studies, yet these findings have sparked controversy. The practice of strict glycemic control has been slow in extending to pediatric ICUs because of the documented increase in the incidence of hypoglycemia in patients treated with IIT. Protocol driven approaches with more liberal glycemic targets have been successfully validated in general and cardiac critical care pediatric patients with low rates of hypoglycemia. It is unknown whether a therapeutic benefit is obtained by keeping patients in this more liberal glycemic control target. Definitive randomized controlled trials of IIT utilizing these targets in critically ill children are ongoing.

Ventilator-Induced Lung Injury – Pg 636

Jean-Damien Ricard, Didier Dreyfuss, Alexandre T. Rotta, Georges Saumon

Pearls

• Although essential to the support of patients with respiratory failure, mechanical ventilation can be associated with the development of pulmonary tissue injury, termed ventilator-induced lung injury (VILI).

• The concept of VILI has been elegantly tested in the research laboratory in both normal and diseased lungs, where the individual contribution of various factors, such as tidal volume, positive end-expiratory pressure, and overall state of lung distension can be determined. Lung volume at the end of inspiration (i.e., the overall degree of lung distension) probably is the main determinant of VILI severity.

• One must take the magnitude of the loss of aerated lung volume and alterations in lung mechanics into account to assess the risk of VILI.

• Experimental and clinical data support the idea that reasoned tidal volume reduction designed to prevent volutrauma can be advantageous in the management of these patients.

Mechanical ventilation is essential to life support of patients with respiratory failure. Several potential drawbacks to mechanical ventilation were identified early in its history.[1] More recent experimental studies have showed that certain ventilation modalities may produce subtle tissue damage similar to that seen in early acute respiratory distress syndrome (ARDS) and termed ventilator-induced lung injury (VILI). This issue has recently received much attention in the clinical field.[2,3] The purpose of this chapter is to describe pathophysiological events leading to VILI and to place these observations into a clinical perspective of ventilatory management of patients with ARDS.

Evidence for Ventilator-Induced Lung Injury

Ventilation of Intact Lungs

High Lung Volume Ventilator-Induced Lung Injury

Webb and Tierney[4] found that pulmonary edema rapidly developed in rats subjected to 45 cm H_2O peak airway pressure ventilation, whereas it did not develop in rats

undergoing ventilation for a longer time with 14 cm H_2O peak airway pressure. Edema severity and rate of development increased with peak airway pressure magnitude. It was later confirmed that such a ventilation modality produces endothelial and epithelial cell damage and lung capillary permeability changes that result in nonhydrostatic pulmonary edema.[5] This edema formation is now generally believed to be the hallmark of VILI.

The respective roles of increased airway pressure and increased lung volume in this injury were clarified when mechanical ventilation at high and low tidal volume (V_T) were compared at identical (45 cm H_2O) peak airway pressures.[6] The injury was found only in rats subjected to high V_T and not in those undergoing ventilation at high airway pressure in which lung distention was limited by thoracoabdominal strapping (Figure 51-1).[6] Furthermore, in animals undergoing ventilation at high V_T by negative external distending pressure, pulmonary edema still developed, confirming that excessive airway pressure is not the causal factor of this type of injury.[6] This VILI that depends mostly on end-inspiratory volume has been called volutrauma.[7,8] The alveolar pressure corresponding to end-inspiratory volume is the "plateau" airway pressure (measured at no-flow), and its clinical importance has been emphasized in a Consensus Conference on mechanical ventilation.[9] Several investigators reached the same conclusions in other species using different protocols.[10–12]

Figure 51–1 Comparisons of the effects of high-pressure–high-volume ventilation *(HiP-HiV)* with those of negative inspiratory airway pressure high tidal volume ventilation (iron lung ventilation, *LoP-HiV)* and of high-pressure–low-volume ventilation (thoracoabdominal strapping, *HiP-LoV). Dotted lines* represent the upper 95% confidence limit for control values. See Figure 51-3 for details on edema indices. Permeability edema occurred in both groups receiving high tidal volume ventilation. Animals undergoing ventilation with a high peak pressure and a normal tidal volume had no edema. *BW,* Body weight; *DLW,* dry lung weight; *Qwl,* extravascular lung water.

(From Dreyfuss D, Soler P, Basset G et al: High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure, Am Rev Respir Dis 137:1159-1164, 1988.)

Taken together, these experimental studies have shown that large tidal volumes are more critical than high intrathoracic pressures in the genesis of ventilator-induced lung edema in intact animals.

Low Lung Volume Ventilator-Induced Lung Injury

Unlike volutrauma, ventilation at low lung volumes does not seem to injure healthy lungs. Intact animals tolerate mechanical ventilation with physiologic V_T and low levels of positive end-expiratory pressure (PEEP) for prolonged periods of time without any apparent damage. Taskar and colleagues[13] have shown that the repetitive collapse and reopening of terminal units during 1 hour of mechanical ventilation does not result in appreciable lung damage, although it does alter gas exchange and reduce compliance, as does spontaneous (low V_T) ventilation under deep anesthesia.

Ventilation of Damaged Lungs

High-Volume Lung Injury

Several investigators have evaluated the effect of overdistension on damaged lungs. These studies consistently demonstrated the increased susceptibility of diseased lungs to the detrimental effects of some modalities of mechanical ventilation.

The first studies were performed on isolated lungs. Bowton and Kong[14] showed that isolated perfused rabbit lungs injured by oleic acid gained significantly more weight when ventilated with 18 mL/kg V_T than with 6 mL/kg V_T. Hernandez and colleagues[15] compared the effects of oleic acid alone, mechanical ventilation alone, and their combination on lung capillary filtration coefficient and wet-to-dry weight ratio (which reflects lung protein accumulation) in young rabbits. Filtration coefficient and wet-to-dry weight were not significantly affected by low doses of oleic acid or by mechanical ventilation at a peak inspiratory pressure of 25 cm H_2O for 15 minutes. However, the filtration coefficient increased significantly when oleic acid injury was followed by mechanical ventilation at these pressures. Wet-to-dry weight ratio was also significantly higher than in lungs subjected to oleic acid injury or ventilation alone. The same team also showed that inactivating surfactant with dioctyl-succinate aggravates the filtration coefficient increase produced by ventilating isolated blood-perfused rabbit lungs at 30 to 45 cm H_2O peak pressure.[16] Whereas light microscope examination showed only minor abnormalities (minimal hemorrhage and vascular congestion) in the lungs of animals subjected to ventilation or surfactant inactivation alone, their combination caused severe damage (edema and flooding, hyaline membranes, and extensive alveolar hemorrhage).

These results suggested that ventilation at high volume and pressure might favor VILI in abnormal isolated lungs and that it might occur at lower airway pressure than in the normal lung. Whether this could also occur in lungs in situ was investigated by comparing the effects of different modalities of mechanical ventilation in rats with α-naphthylthiourea (ANTU)-injured lungs[17] (Figure 51-2). ANTU infusion alone caused moderate permeability pulmonary edema. Mechanical ventilation alone resulted in a permeability edema of severity related to magnitude of V_T. It was thus possible to calculate the theoretical amount of edema that would result from ventilating ANTU-diseased lungs with a given V_T by summing up the separate effect of mechanical ventilation and ANTU. However, lungs of animals injured by ANTU had more edema than predicted when they underwent ventilation with a high V_T (45 mL/kg body weight), indicating that the two insults acted in synergy. Even slight lung alterations, such as those produced by spontaneous ventilation during prolonged anesthesia (which inactivates surfactant and promotes focal atelectasis[18,19]), are sufficient to exacerbate the harmful effects of high-volume ventilation.[17] The extent to which lung mechanical properties are altered prior to ventilation is a key factor in this synergy. The amount of pulmonary edema produced by high-volume mechanical ventilation in animals given ANTU, or after prolonged anesthesia, was inversely proportional to respiratory system compliance measured at the very beginning of high-volume mechanical ventilation.[17] Thus the more severe the lung abnormalities were before ventilation, the more severe was the VILI.

Figure 51–2 Interaction between previous lung alterations and mechanical ventilation on pulmonary edema. **A,** Effect of previous toxic lung injury. Extravascular lung water *(Qwl)* after mechanical ventilation in normal rats *(orange circles)* and in rats with mild lung injury produced by α-naphthylthiourea (ANTU) *(purple circles).* Tidal volume (V_T) varied from 7 to 45 mL/kg body weight *(bw) Black line* represents the Qwl value expected for the aggravating effect of ANTU on ventilation edema assuming additivity. ANTU did not potentiate the effect of ventilation with V_T up to 33 mL/kg bw. In contrast, ventilation at 45 mL/kg bw V_T resulted in an increase in edema that greatly exceeded additivity, indicating synergy between the two insults. **B,** Effect of lung functional alteration by prolonged anesthesia. Intact rats were anesthetized and breathed

spontaneously for 30 or 120 minutes prior to mechanical ventilation with 7 mL/kg bw *(open bars)* or 45 mL/kg bw *(shaded bars)* V_T in intact rats. Qwl of animals that underwent ventilation with a high V_T was significantly higher than in those that underwent ventilation with a normal V_T. Qwl was not affected by the duration of anesthesia in animals that underwent ventilation with a normal V_T. In contrast, 120 minutes of anesthesia before high V_T ventilation resulted in a larger increase in Qwl than did 30 minutes of anesthesia. $**P < .01$.

(From Dreyfuss D, Soler P, Saumon GL: Mechanical ventilation-induced pulmonary edema. Interaction with previous lung alterations, Am J Respir Crit Care Med 151:1568-1575, 1995.)

The reason for this synergy requires clarification. The presence of zones of alveolar edema in animals given this harmful ventilation was the most evident difference from those that underwent ventilation with lower, less harmful V_T.[17] Because alveolar flooding reduced the number of alveoli available for ventilation, they were more prone to overinflation, more vulnerable, and at greater risk of alveolar flooding. This in turn would further reduce aerated lung volume and result in positive feedback. The same reasoning applies to prolonged anesthesia, during which aerated lung volume was probably gradually reduced by atelectasis.[17] Both flooding and atelectasis decrease lung compliance by a "baby lung" effect, a reduction in the volume of lung available for ventilation. It is not surprising that the lower the compliance before ventilation, the more severe were the lung alterations induced by high-volume ventilation.[17] Thus uneven distribution of ventilation during acute lung injury[20] favors regional overinflation and injury. To substantiate this phenomenon, rats underwent ventilation with V_T of up to 33 mL/kg after alveolar flooding by instillation of saline solution into the trachea. Flooding with saline solution did not significantly affect microvascular permeability when V_T was low. As expected, capillary permeability alterations were more important in animals that experienced alveolar flooding than in intact animals that underwent ventilation at high V_T. Correlations also were found between end-inspiratory (plateau) airway pressure, the pressure at the "lower inflection point" on the pressure-volume (PV) curve, and the capillary permeability changes found in animals that experienced alveolar flooding and underwent ventilation with at high V_T (Figure 51-3).[21] Thus the changes in capillary permeability caused by lung overinflation are more severe in poorly recruitable (and less compliant) lungs.

Figure 51–3 Static volume-pressure relationship for the total respiratory system of a surfactant-depleted juvenile rabbit. *Pflex* indicates the lower inflexion point.

Low-Volume Lung Injury

An increase in trapped-gas volume during pulmonary edema and acute lung injury probably occurs because of airway closure and is worsened by impaired surfactant function.[22] Under such conditions, the slope of the inspiratory limb of the respiratory system PV curve often displays a sharp increase at low lung volume. This change reflects the sudden and massive opening of units previously excluded from ventilation and has been termed the "lower inflection point." This phenomenon often has a dramatic effect on arterial oxygenation, because setting PEEP above the pressure at this inflection point often decreases shunt and increases PaO_2.[23–26]

The possibility that pulmonary dysfunction may be aggravated if this inflection point lies within the V_T has been a recent focus of attention. Experimental evidence for this possibility initially was provided by studies comparing conventional mechanical ventilation with high-frequency oscillatory ventilation in premature or surfactant-depleted lungs. Studies performed on such lungs ventilated at various levels of PEEP

suggest that repeated closure and reopening of terminal units can cause lung injury.[27–29] Argiras and colleagues[27] and Sandhar and associates[28] studied this issue in rabbits with surfactant-depleted lungs. During volume-controlled ventilation, peak inspiratory pressure was initially 15 mm Hg but increased to 25 mm Hg 5 hours later because lung compliance fell. PEEP was then adjusted to be either above (8 to 12 mm Hg) or below (1 to 2 mm Hg) the lower inflection point of the inspiratory limb of the PV curve. Mortality rates in the two groups were identical, but arterial PaO_2 was better preserved and less hyaline membrane formation occurred in the high-PEEP group.[27,28] This lessening of pathologic alterations was observed even when inspiratory/expiratory time ratios were adjusted so that mean airway pressures were the same in the low-PEEP and high-PEEP groups.[28] Muscedere and colleagues[30] reported similar results in isolated, unperfused rabbit lungs lavaged with saline solution and ventilated with a low (5 to 6 mL/kg) V_T and with a PEEP set below or above the inflection point. However, Sohma and colleagues[29] did not find this injury in vivo in rabbits whose lungs had been injured with hydrochloric acid.[29]

It often is argued that the lower inflection point on the PV curve reflects the recruitment of collapsed zones that are found predominantly in dependent areas[31,32] and that this recruitment persists during further lung expansion. Recently Martynowicz and coworkers[33] have questioned the existence of the repetitive collapse-reexpansion phenomenon during tidal ventilation and have reevaluated the significance of the lower inflection point on the PV curve. They studied the regional expansion of oleic acid–injured lungs using the parenchymal marker technique in dogs. They found that the gravitational distribution of volume at functional residual capacity was not affected and not associated with a decreased parenchymal volume of the dependent regions. In addition, they found that the between-region asynchrony of tidal expansion was not influenced by oleic acid injury. Their findings therefore did not support the hypothesis that a more important gravitational gradient during VILI produces atelectasis by compression of the dependent lung, cyclic recruitment and collapse, and ultimately shear stress injury.[33] They propose that the displacement of air-liquid interfaces along the tracheobronchial tree causes the lower inflection point on the PV curve and conclude that this knee on the curve reflects the mechanics of partially fluid-filled alveoli with constant surface tension and not the abrupt opening of airways or atelectatic parenchyma.[34] It therefore remains unsettled whether injury caused by the repetitive reopening of collapsed terminal units and the protective effect of PEEP is restricted to the peculiar situation of surfactant depletion by bronchoalveolar lavage. In the clinical arena, the recent negative results of the ALVEOLI trial[35] and the two other more recent randomized controlled trials[36,37] cast doubt on the clinical existence of repetitive opening and closing lung injury.[38]

Roles of Tidal Volume, Positive End-Expiratory Pressure, and Overall Lung Distention

The influence of PEEP on acute lung injury (and more specifically on ventilator-induced pulmonary edema) must be studied in the context of the level of V_T. Indeed, PEEP increases functional residual capacity (FRC) and recruits the lung but also increases end-inspiratory volume when V_T is kept constant, thus possibly favoring overinflation. PEEP application also may depress hemodynamics and affect lung fluid balance. Therefore close analysis of the numerous studies that have been done to clarify the relationships between PEEP, oxygenation, and extravascular lung water accumulation during hydrostatic or permeability type edema must take into account the experimental approach used, that is, intact animals or isolated lungs (for which lung water content will differ), and whether or not V_T is reduced (thus increasing or not increasing end-inspiratory lung volume).

Effects of Positive End-Expiratory Pressure When Tidal Volume Is Kept Constant

Application of PEEP may result in lung overinflation if it is followed by a significant change in FRC because of the increase in end-inspiratory volume. Overinflation will affect preferentially the more distensible areas that receive the bulk of ventilation, which may explain the lack of reduction or even the worsening of edema reported following PEEP application in most experiments.[39] PEEP does not affect the severity of hydrostatic[40] or permeability[40,41] edema in intact animals, although it improves oxygenation[40] because of the recruitment of flooded alveoli (Figure 51-4). In isolated ventilated-perfused lungs, PEEP rather aggravates edema fluid accumulation[42](Figure 51-5). Thus when V_T is left unchanged, increasing FRC with PEEP affects edema differently in isolated lungs or in intact animals. In the latter, the lack of effect of PEEP depends on the balance between PEEP-induced increase in end-inspiratory lung volume, which decreases interstitial pressure and increases filtration pressure in extra-alveolar vessels, and the hemodynamic depression due to elevated intrathoracic pressure that, in the opposite, decreases filtration pressure. In contrast, preservation of perfusion rate in isolated-perfused lungs favors edema formation.[42]

Figure 51–4 Change in arterial oxygen tension (ΔPaO_2, mm Hg) during 1-hour period between the initial and final measurements for groups I (control), II, and III (severe hydrostatic pulmonary edema, without and with positive end-expiratory pressure [PEEP], respectively), and IV and V (moderate pulmonary edema, without and with PEEP, respectively). The difference between ΔPaO_2 for groups II and III is significant ($P < .01$).

(From Hopewell PC, Murray JF: Effects of continuous positive-pressure ventilation in experimental pulmonary edema, J Appl Physiol 40:568-574, 1976.)

Figure 51–5 Effect of three levels of positive end-expiratory pressure (PEEP) on water accumulation in hydrochloric acid–injured ventilated-perfused dog pulmonary lobes. The highest PEEP resulted in a further increase in pulmonary edema.

(From Toung T, Saharia P, Permutt S, et al: Aspiration pneumonia: beneficial and harmful effects of positive end-expiratory pressure, Surgery 82:279-283, 1977.)

Effects of Positive End-Expiratory Pressure when Tidal Volume Is Reduced

Edema is less severe during high-volume ventilation (even though FRC is increased by PEEP) when end-inspiratory lung volume is kept constant by decreasing V_T(Figure 51-6). Webb and Tierney[4] showed that less edema developed during ventilation with 45 cm H_2O peak airway pressure when 10 cm H_2O PEEP was applied. The authors attributed this beneficial effect of PEEP to the preservation of surfactant activity. It was later shown that, although PEEP decreased the amount of edema, it did not prevent alteration of capillary permeability.[6] However, animals undergoing ventilation with PEEP had no alveolar damage in contrast with those that underwent ventilation without PEEP. The only cellular alterations found in animals that underwent ventilation with PEEP consisted of capillary endothelial blebs.[6] No satisfactory explanation has been found for this preservation of the epithelial layer. It may be that PEEP prevented fluid movement in terminal units, thereby decreasing shear stress at this level. Similar observations have been made by other investigators in intact animals[43,44] and in isolated perfused canine lobes.[45] The hemodynamic alterations induced by PEEP probably play an important role in lessening the severity of edema. Application of PEEP

produces an increase in mean intrathoracic pressure that adversely affects cardiac output.[46,47] For example, in rats subjected to high peak airway pressure and 10 cm H_2O PEEP, edema was more severe when the hemodynamic alterations induced by PEEP were corrected with dopamine infusion.[48] The amount of extravascular lung water was correlated with systemic blood pressure, suggesting that restoration of cardiac output increased filtration pressure and was responsible for aggravation of edema. The reduction of edema and of the severity of cellular damage by PEEP during ventilation-induced pulmonary edema may be linked to reduced tissue stress by decreasing volume-pressure excursion, movement of foam in distal airways, preservation of surfactant activity, and a decrease in capillary filtration.

Figure 51–6 Effect of increasing positive end-expiratory pressure (PEEP) from 0 to 15 cmH_2O during ventilation with two different tidal volume (V_T) values (7 mL/kg body weight *[BW]*: LoV_T and 14 mL/kg BW: $MedV_T$). Pulmonary edema (as evaluated by increases in extravascular lung water [Qwl]) occurred when PEEP was increased. PEEP required to produce edema varied with V_T: 15 cmH_2O PEEP during ventilation with low V_T and 10 cmH_2O PEEP during ventilation with moderately increased V_T. $*P < .05$; $**P < .01$ vs. zero end-expiratory pressure (ZEEP) and the same V_T.

(From Dreyfuss D, Saumon G: Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation, Am Rev Respir Dis 148:1194-1203, 1993.)

Asthma – Pg 646

http://www.scielo.br/pdf/rbti/2016nahead/en_0103-507X-rbti-20160020.pdf

Pediatric Critical Care:

https://books.google.com.br/books?id=g86fDQAAQBAJ&pg=PR26&lpg=PR26&dq=publica%C3%A7%C3%B5es+alexandre+rotta&source=bl&ots=D5NdyE_GYR&sig=ooioNcHguhiUzFCIacrAyqQvCVo&hl=pt-BR&sa=X&ved=0ahUKEwiT4Or6ycXSAhWDgpAKHXcgDQ8Q6AEISDAL#v=onepage&q=publica%C3%A7%C3%B5es%20alexandre%20rotta&f=false

2. Orlando da Silva

Dr. Orlando da Silva recebeu seu diploma de medicina da Universidade Federal do Estado de Minas Gerais (UFMG), Brasil, em dezembro de 1981. Ele completou sua residência de Pediatria geral na Universidade de Queen's em Kingston, Ontário, e sua especialização em Neonatologia pelo Hospital for Sick Children em Toronto, Ontário.

Ele também recebeu o grau de Mestre em Epidemiologia Clínica pela Universidade de Toronto, em Novembro de 1996.

Dr. da Silva é atualmente professor catedrático titular do Departamento de Pediatria (Divisão de medicina neonatal), Epidemiologia e Bioestatística da Western University, London, Ontario, Canada. Como pesquisador na área de Neonatologia e epidemiologia perinatal, ele é cientista membro do Instituto de Saúde e Pesquisa Infantil no Canada.

Dr. da Silva tem mais de 150 artigos e apresentações cientificas em revistas e congressos nacionais e internacionais. Ele é membro de vários comitês locais, regionais e nacionais na área de neonatologia e perinatologia.

Como epidemiologista e intensivista neonatal seus interesses de pesquisa provem de vários problemas clínicos comuns nas unidades de tratamento intensivo neonatal.

Lista Seletiva de Publicações

1. Asztalos, EV, Campbell-Yeo M, **da Silva OP**, Ito Shinya, Kiss A and Knoppert. Enhancing human milk production with domperidone in mothers of preterm infants: Results from the EMPOWER trial. J Human Lact, 2017 Jan; 33 (1): 181-187, **Co-Principal Author**, DOI: 10.1177/0890334416680176.

2. King CP, **da Silva O**, Filler G, Lopes LM. Online calculator to improve counseling of short-term neonatal morbidity and mortality outcomes at extremely low gestational age (23-28 weeks). Am J Perinatol, 2016 Jul; 33 (9): 910-7, **Co-Principal Author**, DOI: 10.1055/s-0036-1581131.

3. Karel O'Brien, Marianne Bracht, Kate Robson, Xiang Y. Ye, Lucia Mirea, Melinda Cruz, Eugene Ng, Luis Monterrosa, AmuchouSoraisham, Ruben Alvaro, Michael Narvey, **Orlando Da Silva**, Kei Lui, William Tarnow-Mordi and Shoo K. Lee. Evaluation of the Family Integrated Care model of neonatal intensive care: a cluster randomized controlled trial in Canada and Australia. BMC Pediatrics, 2015 Dec 1; 15:210, **Coauthor**, Available from: http://www.biomdcentral.com/1471-2431/15/210

4. Shah J, Singhal N, **da Silva O**, Rouvinez-Bouali N, Seshia M, Lee S and Shah P. Intestinal perforation in very preterm neonates: Risk factors and outcomes. Journal of Perinatology, 2015 Aug; 35 (8): 595-600, **Coauthor**

5. Geoghegan-MorphetN,Yuen D, Rai E, Angelini M, Christmas M, and **da Silva O**. Development and Implementation of a Novel Online Breastfeeding Support Resource: the Maternal Virtual Infant Nutrition Support (MAVINS) Clinic. Breastfeeding Medicine,

2014 Dec 1; 9 (10): 520-523, **Senior Responsible Author**, DOI: 10.10891bfm.2014.005.

6. Knoppert DC, Page A, Warren J, Seabrook J, Carr M, Angelini M, Killick D, **da Silva OP**. The effect of two different domperidone doses on maternal milk production. J of Human Lactation 2013, 29(1):38-44, **Senior Responsible Author**

7. Ng GY, **da Silva O**, Ohlsson A. Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants (full review). The Cochrane Library Published online: 13 June 2012, **Coauthor**

8. KW Coughlin, L Hernandez, BS Richardson, **OP da Silva**. Life and Death Decisions in the Extremely Preterm Infant: What happens in a level III Perinatal Centre. Paediatric and Child Health, 2007; 12

9. Zaw W, Gagnon R, **da Silva O**. The risks of adverse neonatal outcome among preterm small for gestational age infants according to neonatal versus fetal growth standards. Pediatrics 2003;111:1273-1277. **Coauthor**

10. **da Silva O**, Knoppert D, Forret P, Angelini M. Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial. Can Med Assoc J, 2001; 164 (1): 17-21, **Principal Author**

11. H Salama, **da Silva O**. Neonatal enterocolitis with portal vein gas. New England Journal of Medicine (Images in Clinical Medicine, 2001; 344 (2): 108, **Senior Responsible Author**

12. **da Silva O**, Stevens D. Complications of airway management in very low birth weight infants. Biology of the Neonate 1999;75:40-45. **Principal Author**

13. **da Silva O**, Ohlsson A. How accurate are leukocyte indices and C-reactive protein for diagnosis of neonatal sepsis? Paediatrics and Child Health, 1998; 3 (3): 158-159, **Principal Author**

14. **da Silva O**, Gregson D, Hammerberg O. The role of Ureaplasmaurealyticum and Chlamydia trachomatis in development of bronchopulmonary dysplasia in very low birth weight infants. Pediatric Infectious Disease Journal 1997;16:364-9. **Principal Author**