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COMPARISON OF THE INTUBATION RATE IN BRONCHIOLITIS PATIENTS WITH NAVA AND NON-INVASIVE VENTILATION VERSUS PATIENTS WITH EXCLUSIVE NON-INVASIVE VENTILATION

A MULTICENTRED, RANDOMIZED CLINICAL TRIAL

FINAL DEGREE PROJECT

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ABBREVIATIONS

Abbreviation	Meaning
AI	Asynchrony index
ARDS	Acute respiratory distress syndrome
BiPAP	Bilevel Positive Airway Pressure
CPAP	Continuous Positive Airway Pressure
CRP	C-reactive protein
EPAP	Expiratory Positive Airway Pressure
Esens	Expiratory sensitivity
Eadi	Electrical activity of the diaphragm
FiO_2	Fraction of inspired oxygen
HR	Heart rate
ICU	Intensive Care Unit
IPAP	Inspiratory Positive Airway Pressure
NAVA	Neurally Adjusted Ventilator Assist
NIV	Non-invasive ventilation
PCO_2	Partial pressure of carbon dioxide
PICU	Paediatric Intensive Care Unit
PO_2	Partial pressure of oxygen
PVA	Patient-ventilator asynchrony
RR	Respiratory rate
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SaFi	SaO_2/FiO_2
SaO_2	Oxygen saturation
TEn	Expiratory neural time
TIn	Inspiratory neural time
TI	Inspiratory time

ABSTRACT

BACKGROUND: Acute RSV bronchiolitis is a lower respiratory tract infection. It is a common pathology, causing many admissions to the PICU every fall-winter season and high mortality worldwide. No effective treatment has been demonstrated for this pathology, so the treatment nowadays is based on supportive therapy, such as non-invasive ventilation. The issue is that current machines do not detect well the air volumes that infants under one year of age mobilize, causing patient-ventilator asynchrony. NAVA can reduce these asynchronies, improving the patient's symptoms.

OBJECTIVES: This clinical trial aims to analyse the intubation rate of children under 12 months with RSV+ bronchiolitis, comparing both the non-invasive ventilation system with NAVA and the exclusive non-invasive ventilation system without NAVA. The second objective is to compare the days of hospitalization in PICU.

DESIGN: Randomized, controlled, multicentred, open-label, prospective clinical trial. It will be performed among Catalan hospitals that have a PICU service.

PARTICIPANTS: Participants included in this study are infants under 12 months with RSV+ bronchiolitis, who are admitted to the PICU and need non-invasive ventilation. The sample size will be 522 patients, 261 in each group, who meet inclusion criteria.

METHODS: The primary dependent variable will be the intubation rate and the secondary, the length of hospitalization. We will include the following covariables: age, sex, weight, ethnicity, bacterial infection and history of prematurity. The patients will be randomized and assigned in two different groups: exclusive non-invasive ventilation and non-invasive ventilation with NAVA. We will follow-up these patients during their stay at the PICU, taking into account dependent variables and covariables. The results will be analyzed and compared in the two different groups.

KEYWORDS: Neurally adjusted ventilator assist (NAVA), Non-invasive ventilation, bronchiolitis, infant, PICU, intubation

INTRODUCTION

1. Bronchiolitis

1.1. Definition

Bronchiolitis is a lower respiratory tract infection that was defined by McConnochie in 1993 as the first acute episode of wheezing in children under 24 months, with expiratory dyspnoea and proceeded by cold-like symptoms. There are other definitions that limit even further the affected group to 12 months of age (1,2).

1.2. Epidemiology

Bronchiolitis is the most common lower respiratory tract infection in children under one year-old and causes 18% of all paediatric hospitalizations. It has a clearly seasonal distribution, affecting mostly in cold months, during fall and winter (1,2).

Regarding hospitalization, it has a peak incidence in children between two and six months of age, and it is an important cause of respiratory disease until 5 years old. It is the leading cause of hospitalization in infants under 2 years old worldwide, so it has a high economic cost. In Spain, the annual rate of hospitalization is 24/1000 children under 12 months (3–6).

1.3. Aetiologies

Acute bronchiolitis is usually caused by viruses and the most common is the respiratory syncytial virus (RSV), followed by metapneumovirus (hMPV), rhinovirus, bocavirus (HboV), adenovirus, enterovirus, parainfluenza and influenza.

Metapneumovirus belongs to the family of *Paramyxoviridae* and it is the second cause of bronchiolitis after RSV (1,2).

1.3.1. RSV

RSV is a RNA myxovirus, of the genus *Pneumovirus*, which belongs to the family of *Paramyxoviridae* (1,7).

It is the most frequent aetiology of acute bronchiolitis, and it causes about 70-80% of acute bronchiolitis. Its incidence is highly seasonal, with annual epidemics, being its peak of maximum incidence between November and February (1,7).

RSV is a highly contagious virus, which can survive up to 7 hours on non-porous surfaces. It is transmitted by nasopharynx secretions of infected individuals, and it is usually by direct contact or droplet transmission, but it is also possible through the hands or contaminated objects. The virus gateways to the organism are the ocular conjunctiva, nasal and oral mucosa (7).

During their first year of life, RSV infects 75% of the children; especially between 2 and 3 months. Around 2-3% of children with a primary RSV infection in the first 12 months of life require hospitalization and 2-6% of them are admitted to the PICU.

In Spain, every year, between 15,000 and 20,000 paediatrics visits in emergencies department and about 7,000-14,000 hospitalizations are caused by RSV infections (1,7).

Regarding mortality, every year 66,000-199,000 children around the world die from RSV infections, due to its high frequency. It is the second cause of death, after malaria, of children between 1 and 12 years old.
In developed countries, mortality is very low, as it's easy to access ICU and mechanical ventilation (1).

1.4. Risk factors

Several risk factors for developing bronchiolitis and its exacerbations, with the subsequent transfer to the ICU and/or use of mechanical ventilation, have been described (6,8).

- Prematurity (2,9)
- Low birth weight (10)
- Tachypnoea on the first day of admission (10)
- Hemodynamically important congenital heart disease (2,6,11,12)
- Chronic lung disease (cystic fibrosis, bronchopulmonary dysplasia) and anatomic defects of the airways. (2,11)
- Primary (congenital immunodeficiency disease) or secondary (chemotherapy, bone marrow transplant recipients, organ transplantation) immunodeficiency (2,11,13)
- Neurologic disease, neuromuscular disorders (6,10)
- Exposure to the air pollution (14,15)
- Passive smoking (16,17)
- High altitude (>2500 meters) (18)
- Older siblings (17)

1.5. Pathophysiology

The infection causes a direct cytopathic effect of the virus (usually RSV), binding to the toll-4 receptor (TLR-4) in the epithelial cells of the respiratory tract, fusing its membrane with the epithelial cell membrane and consequently causing direct cellular and ciliary damage. Moreover, it also causes an immune response of the host, in which different cytokines are released (IL-6, tumour necrosis factor alpha, chemokines ...) (1,2,6).

The replication of the virus causes epithelial necrosis and ciliary destruction. This triggers an inflammatory response and infiltration of the submucosa with neutrophils, polymorphonuclear cells and lymphocytes (1,2,6).

The submucosa and adventitial tissues become oedematous, with increased mucus secretion. As a consequence of this, plugs, which are composed of mucus and desquamated epithelial cells, are formed in the airways, causing a narrowing of these, mediated by the release of leukotrienes, prostaglandins, and nitric oxide. All this causes bronchiolar obstruction, which produces air trapping, areas of atelectasis, and areas of hyperinflation (1,2,6).

Finally, these mechanisms cause a ventilation-perfusion mismatch, and ultimately hypoxemia (2).

In summary, bronchiolitis is characterized by extensive inflammation and oedema of the airways, increased mucus production, necrosis of epithelial cells, bronchoconstriction, and air trapping (1,2,6).

1.6. Clinical presentation

The classic presentation of acute bronchiolitis begins, after a short incubation period, with symptoms of a viral infection of the upper respiratory tract, such as rhinorrhoea, sneezing, and nasal congestion with or without fever, for 1-4 days, which resolves gradually (1,6).

After this period, the symptoms progress towards the lower respiratory tract, becoming more persistent cough, irritability, refusal to eat, tachypnoea, and increased work of breathing (sternal retraction, use of accessory muscles, rib pulling, respiratory whining, and nasal flaring) (1,2,4,6).

Cough is the main symptom. It is usually dry, in fits, and paroxysmal. Children under 1-2 months may have apnoea, and it's important to rule out whooping cough. The auscultatory findings include crackles and wheezing (1,3,6).

Fever can be present or not, especially at the beginning of the illness, with a temperature lower than 39ºC (6).

There is minute-to-minute variation in these clinical findings, as they can change quickly with crying, coughing, or agitation. This can confuse the clinical evaluation (4,6).

The duration of acute bronchiolitis depends on its severity, age, risk factors, and the causal agent. The average length of symptoms is two weeks, and it is usually self-limited, so most children do not require hospitalization. Cough is the last symptom to disappear, which can persist up to 3-4 weeks (1,4).

1.7. Complications

Normally, bronchiolitis in previously healthy children, resolves without complications. However, when they have risk factors, they are more likely to suffer complications (4,19).

- **Dehydration**: It is very common, as they have a high demand of fluids due to the clinic with fever, and decreased intake of liquids by food refusal, tachypnoea, and respiratory effort. In addition, they may vomit. For this reason, the signs of dehydration (tachycardia, tachypnoea, parched buccal mucosa, markedly sunken anterior fontanelle and eyes, skin turgor, anuria, conscience level…) should be monitored, in case it is necessary to administer fluids (4,19).

- **Apnoea**: As we have said before, it is more frequent in children under 2 months of age and premature. It is a risk factor for progression to respiratory failure and the need for mechanical ventilation.
  Several pathogens are associated with apnoea, with a similar risk to produce it, so the risk of apnoea isn't increased with RSV (20).

- **Respiratory failure:** Hypoxemia, caused by mucous plugs and atelectasis, is common in bronchiolitis. It normally responds to supplemental oxygen, but sometimes requires additional respiratory support. Furthermore, hypercapnia may also occur, which is associated with fatigue of the respiratory muscles, and

usually requires additional respiratory support (intubation, mechanical ventilation) (4).

- **Secondary bacterial infection:** Approximately 50-60% of children with bronchiolitis may have associated acute otitis media (2). Other secondary infections are uncommon (4).

- **Aspiration pneumonia:** The risk of aspiration increases during active bronchiolitis with cough, and it is higher among children who require admission to the ICU and intubation (21).

1.8. Diagnosis

The diagnosis is based on clinical presentation with anamnesis and physical examination. Additional tests are not usually necessary, only to evaluate complications, comorbid infections, and to do a differential diagnosis with other pathologies (1,4,6).

- **Anamnesis:** We have to insist on factors that have been related to a higher risk of progression to severe disease, such as age under 6 weeks, history of prematurity, underlying diseases (congenital heart diseases, chronic pulmonary diseases, neuromuscular disorders, immunodeficiencies), passive smoking, absence of breastfeeding, evolution of less than 72 h, overcrowding and poverty, or low birth weight.

  It is also important to ask about the evolution of the symptoms, such as nasal congestion, fever, cough, respiratory distress, and apnoea (1,4,6).

- **Physical examination:** A complete examination must be done, especially paying attention to signs of dehydration and respiratory distress, like tachypnoea, nasal flaring, intercostal and subcostal retractions, and expiratory wheezing.

  It's important to notice if the patient presents other indicators of severity as lethargy, refusal to eat or digestive intolerance, history of apnoea or cyanosis

Auscultatory findings may include elongated expiratory phase, wheezing, crackles, and even areas of hypoventilation (1,4,6).

- **Transcutaneous pulse oximetry:** It is a simple method that has a good correlation with blood PaO_2, therefore, it allows us to discern the cases that require oxygen supply, when the saturation is less than 95%, from those that don't. So, it tells us when we have to admit the patient to the hospital.
  It is recommended to perform transcutaneous pulse oximetry in all patients with bronchiolitis on admission, to make an initial assessment, in the control of clinical changes, and before being discharged from the hospital. Its continuous monitoring is not justified (1,6,22).

- **Blood gas test:** Not routinely recommended in bronchiolitis. It might be useful for patients with severe respiratory distress or impending respiratory failure, when it's necessary to know the gas exchange and acidosis, with pCO_2 and pH.
  It is required in patients with $SatO_2 < 90\%$ and $FiO_2 > 40\%$ (1,2,6).

- **Chest radiography:** Not routinely recommended, there is no evidence to do it in all patients. There's low levels of inter-observer agreement and wide variability, making chest radiography and unreliable test. We have to consider using it if severe disease, atypical presentation, bad evolution, or uncertain diagnosis (1,6,23).
  There isn't a single radiological pattern for bronchiolitis. Most of the children present parabronchial thickening, hyperinflation, air trapping, atelectasis, interstitial infiltrates… (6,22)

- **Viral testing, nasopharyngeal aspirate:** It is not routinely recommended. Although knowing the causal virus is epidemiologically interesting, it has not been demonstrated to be useful in the clinical management of patients with acute bronchiolitis.
  Virological testing is not recommended unless the results will change the attitude towards the patient or their contacts.

The indication of these tests to prevent transmission to contacts through isolation measures has been studied, but the evidence has not been sufficient, and it seems more reasonable to apply precautions in all children with bronchiolitis, such as hand washing, separating the children who share a room in the hospital more than 1 meter, and other hygienic and isolation recommendations.

If an etiological diagnosis is needed, the test that we will carry out will be a screening by a rapid antigen test with samples obtained by aspiration or nasal washing. These are usually readily available, easy to use, give results very quickly, and are cost-effective. They also have a sensitivity of 80-90%. There are rapid antigen tests for RSV, parainfluenza, adenovirus, and influenza.

CPR would be an alternative method because it is more expensive, slower, and is not available in all centres (1,2,4,6,22).

- **Blood test:** It is not recommended, because its results are unspecific and has not been shown to be useful in diagnosis or guiding its treatment. CPR and procalcitonin can be helpful when the patient has high fever (1,6,24).

- **Urine test:** Even though it is not routinely recommended in typical acute bronchiolitis, but it may be necessary to exclude secondary bacterial infection in a patient with high fever or symptoms of urinary tract infection (UTI). Infants under 60 days with acute bronchiolitis and fever have a high incidence of UTI, so it is recommended to rule out any urine infections (1,4,25).

1.9. Treatment

Most cases are mild, so they can be treated at home, controlled by primary care, with supportive care and without pharmacologic interventions routinely recommended. It is possible that some infants may progress to several forms, so it is very important to teach parents to recognize signs of clinical deteriorating and measures to take.

Nevertheless, there are some cases that are moderate or severe and require hospitalization (**Table 1**) (1,26).

Table 1. *Criteria to recommend hospitalization adapted from (1).*

Refusal of food or digestive intolerance (intake <50% of usual)
Dehydration
Lethargy
History of apnoea
Tachypnoea
Moderate or severe respiratory distress
Oxygen saturation <92-94% breathing room air
Severe illness
Uncertain diagnosis
Age < 2-3 months
Comorbidities
Beginning of the symptoms <72 h, for the risk of deterioration
Socioeconomical situation, geographic factors and transport difficulties
Low capacity of parents to take care of the patient at home, or to evaluate the severity of the symptoms.

Furthermore, there are some criteria for admitting a patient with bronchiolitis to the PICU (27):

- Severe respiratory failure.
- High O_2 needs: SaO_2 <92% with FIO_2 > 50%.
- Recurrent apnoea episodes, with a decrease in saturation.

The base treatment of acute bronchiolitis in children remains supportive care. Despite there is great variability in treatments and abundant studies, there is much confusion with the management of bronchiolitis (2).

1.9.1. Supportive care

Supportive care is the cornerstone of the treatment, and it is based on:

- **Hydration and nutrition:** Monitoring the fluid intake and output is very important, because children with bronchiolitis have increased fluid needs, due

to fever and tachypnoea, and a decreased intake, so they can be dehydrated quickly (2,26).

In mild cases, we have to try oral intake, and if the infant is breastfeeding to maintain it if it is possible. Has been shown that breast milk has neutralizing activity against RSV (1,2).

Nasogastric enteral feeding is necessary when the child has reduced oral intake, but if the respiratory rate exceeds 60-70 breaths per minute it may be necessary to administrate intravenous fluids because there is an elevated risk of aspiration. When we use intravenous fluids, it is recommended to use isotonic fluids to avoid hyponatremia (1,2,6,26).

- **Nasal aspiration or lavage:** It is essential to do abundant lavage and nasal aspirations with physiological saline, to ensure the patency of the upper airway (1).

- **Postural treatment:** It is recommended to elevate the head of the crib (1,25).

- **Supplemental oxygen:** It is important to correct hypoxia in children with bronchiolitis, providing oxygen. It is recommended to supplement with oxygen to patients with $SatO_2$ <90-92%, depending on the guidelines. It can be administered with a nasal cannula, face mask, or headbox.

  When $SatO_2$ > 90-92%, it is suggested to discontinue oxygen therapy, administering it intermittently (1,26).

- **Non-invasive ventilation:** We have to consider this option in impending respiratory failure, severe respiratory distress, or recurrent apnoea (1,25).

  There are different types of non-invasive ventilation (*See 2. Non-invasive ventilation).*

- **Endotracheal intubation:** It may be necessary if non-invasive ventilation fails, and the patient still has severe respiratory distress and hypoxemia with oxygen supplementation. (*See 5. Invasive ventilation*) (25,26).

- **Chest physiotherapy:** It is not routinely recommended, because there is no evidence of clinical benefit. It may be necessary for children with associated pathologies that difficult the breathing (1,6).

1.9.2. Pharmacologic treatment

The use of drugs is controversial, as there is no evidence to justify their use routinely (1,19).

- **Bronchodilators:** These are the most used and may be necessary for infants and children with bronchiolitis and severe disease or respiratory failure, despite they are not routinely recommended. The effects must be monitored, evaluating the child's condition before and after treatment (1,26).
    - **β_2-agonists (Salbutamol):** In some studies, certain clinical improvement has been shown, but they do not affect the resolution of the process, they do not reduce the rate of admission or the days of hospitalization. So, the evidence is not very strong.

      If the use of these is considered appropriate, it is recommended to carry out a therapeutic test before, and only continue with the treatment if there is a clinical response (1,2,25).
    - **Nebulized epinephrine:** It is also not used routinely, as there is not enough data to support its use. Some studies have shown some clinical improvement and a slight decrease in the rate of admission, but there are no differences in terms of the length of hospital stay.

      Adrenaline is not available for use in the home setting, therefore β_2-agonists are preferred (1,2,25).

- **Corticosteroids:** They can be administered inhaled or systemically and are used for many respiratory diseases because they reduce air obstruction. But, like all drugs in bronchiolitis, their use is controversial as it has not shown efficacy (1,2,26).

A study shows that treating children with nebulized epinephrine and dexamethasone reduces the admission rate significantly, although more studies still need to be done, because these results are considered exploratory (6,28).

- **3% Nebulized hypertonic saline:** Its use remains controversial. The first studies showed certain efficacy, reduction of hospital stay, and improvement of the clinic, but later more studies have been done that do not indicate the same.
  Its use is currently recommended, with or without bronchodilators, in patients with stays longer than 72 hours, in whom it has been seen that the duration of admission can be reduced by one day (1,26).

- **Antibiotics:** Bronchiolitis is almost always caused by viruses; therefore, antibiotics are not routinely recommended. If a concomitant or secondary infection occurs, we will treat it with antibiotics, as well as if there was no bronchiolitis.
  We must remember that in patients with severe acute bronchiolitis who require intubation, there is a risk of pulmonary bacterial coinfection, and we should consider in these cases the use of antibiotics.
  We will also have to contemplate its use if the child has a high fever, severe clinical signs and/or alterations in the blood count (1,2,25).

- **Antivirals (Ribavirin):** It is not used routinely, but it may be considered in severe cases of bronchiolitis or in severely immunosuppressed patients with RSV infection (1,25,26).

- **Heliox:** It is a mixture of helium and oxygen, with a lower density than room air. It is not recommended, but it can be used in severe bronchiolitis in the ICU, although there is no evidence that it reduces the need for intubation (1,2,26).

- **Leukotriene modifiers (Montelukast):** They are not suggested for the treatment of bronchiolitis. Although leukotrienes contribute to the inflammatory response

of the airway, no clear effect has been found to improve the clinical situation or reduce days of hospitalization (2,26).

- **Surfactant:** In some studies, it has been shown that when surfactant is administered in mechanically ventilated patients, it decreases the duration of intubation and the length of hospitalization in the ICU. However, additional studies are needed (1,26).

1.10. Prevention

Hygiene measures are the base for the prevention of bronchiolitis, as the viruses that cause it are transmitted through secretions, contact with the hands, and fomites, where they can survive for several hours. Therefore, hands must always be disinfected before and after being in contact with a patient, and after touching contaminated objects. (1,2)

In addition, it is important to remember the parents or caregivers the importance of hygiene measures (1).

Another measure for prevention is the administration of Palivizumab, a humanized monoclonal antibody, which provides passive immunization. It reduces RSV hospitalization rates but does not reduce hospital stay, mortality, requirements of oxygen or mechanical ventilation.
The problem is that Palivizumab is very expensive, so it is only recommended in some cases (*See* ***Table 2***) (1,2,26).

Table 2. *Recomendations for bronchiolitis profilaxis with pavilizumab (adapted from Sociedad Española de Neonatologia, 2014 (1))*

Chronic lung disease (CLD)	Children under 2 years of age with bronchopulmonary dysplasia who have required treatment (supplementary oxygen, bronchodilators, diuretics or corticosteroids) in the 6 months prior to the start of the RSV season or who are discharged during it
Congenital heart disease	Children under 2 years of age with congenital heart disease with significant hemodynamic alteration (uncorrected or with palliative surgery), under treatment for heart failure, moderate or severe pulmonary hypertension or cyanogenic heart disease.
History of prematurity	Preterm under 28+6 weeks of gestation, who are 12 months of age or younger at the beginning of the RSV season or are discharged during it.
	Preterm between 29 and 32 weeks of gestation, who are 6 months of age or younger at the beginning of the RSV season or are discharged during it.
	Preterm between 32+1 and 35 weeks of gestation, who are 6 months of age or younger at the beginning of the RSV season or are discharged during it, who has two or more risk factors for hospitalization due to RSV infection: chronological age less than 10 weeks at the beginning of the season, lack of breastfeeding or duration less than two months (for medical indication), having at least one school-age brother (<14 years), day-care attendance, family history of wheezing, overcrowded conditions at home (4 adults) or airway malformations or neuromuscular disease.

2. Non-invasive ventilation

Non-invasive ventilation (NIV) is a respiratory support technique, in which an artificial airway is not required through intubation or tracheostomy. Its aim is to reduce respiratory work, improve gas exchange and decrease the frequency of intubation and its complications. It is recommended in the treatment of acute respiratory failure.

2.1. Acute respiratory failure

Respiratory failure is the inability to maintain oxygenation, ventilation, or both. It can be classified into two groups, due to the physiopathology (29–31):

- **Hypoxemic respiratory failure (type I):** Gas exchange failure occurs due to lung parenchymal involvement, causing oxygenation problems. The collapse of the alveoli produces a decrease in ventilation/perfusion (V/Q) rate, being able to behave like a shunt, with hypoxemia.
  It can be caused by bronchiolitis, asthma, pneumonia, pulmonary oedema, cystic fibrosis, aspiration, etc.

- **Hypercapnic respiratory failure (type II):** It is caused by a failure of the ventilatory pump, i.e., the musculature. There is hypercapnia in addition to hypoxemia. It can be caused by neuromuscular diseases, defects in the diaphragm, the involvement of the central nervous system, congenital or traumatic chest abnormalities, etc.

It is important to emphasize that most of the time we find type I and II mixed respiratory failure.

2.2. Modes of ventilation

Continuous Positive Airway Pressure (CPAP): It is a spontaneous ventilation modality, controlled by pressure and cycled by the patient. It consists of applying continuous positive pressure in the airway at a single level, maintaining a constant pressure throughout the respiratory cycle, both inspiration and expiration. The patient breathes spontaneously within a pressure level higher than atmospheric.

CPAP produces rapid relief from dyspnoea and improves gas exchange, as it improves oxygenation. On the other hand, it does not improve hypercapnia, because this modality does not increase ventilation.

It is especially useful to reduce the intrapulmonary shunt, reclining the collapsed alveolar units. Therefore, it is used in type I respiratory failure, because they need to improve oxygenation (30–32).

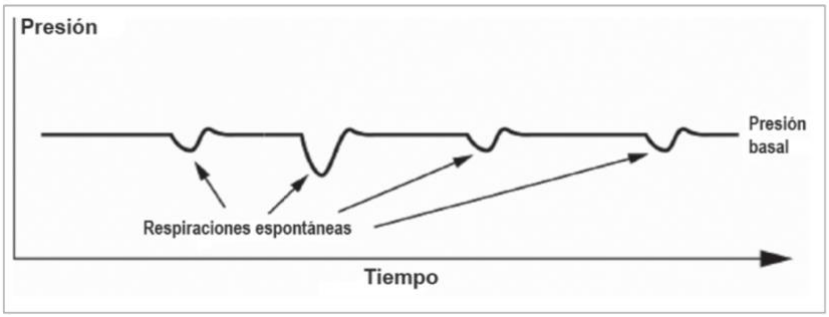

Figure 1. *CPAP. The pressure drop during the inspiratory phase is dependent on the inspiratory effort of the patient within a system of high pressure above atmospheric pressure* (32).

Bilevel Positive Airway Pressure (IPAP/EPAP): The patient breathes spontaneously, applying pressure to the airway at two levels, one inspiratory and the other expiratory. The difference between inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) is the effective pressure support. It is used in type II respiratory failure because they have ventilatory problems. The main objective is to relieve the load on the respiratory muscles to increase alveolar ventilation, decrease PaCO2 and stabilize arterial pH (30–32).

It is divided into three modes:

- **S mode (Spontaneous):** The ventilator cycles between IPAP and EPAP following the patient's respiratory rhythm. The ventilator activates IPAP in response to

spontaneous inspiratory effort and cycles EPAP during expiration. Therefore, the patient is the one who sets the respiratory rate (RR), since the ventilator is only activated if the patient is able to activate the trigger (31,32).

- **ST mode (Spontaneous/timed):** It is the most used. It is similar to S mode, but if the patient does not breathe spontaneously within a pre-set time, it will cycle to IPAP and initiate a breath. A rescue frequency must be established.
  This mode guarantees a minimum safety respiratory rate (RR) (31,32).
- **T mode (timed):** The ventilator cycles IPAP and EPAP based on the RR programmed in the ventilator and the selected inspiratory time proportion. It is purely machine-triggered (31,32).

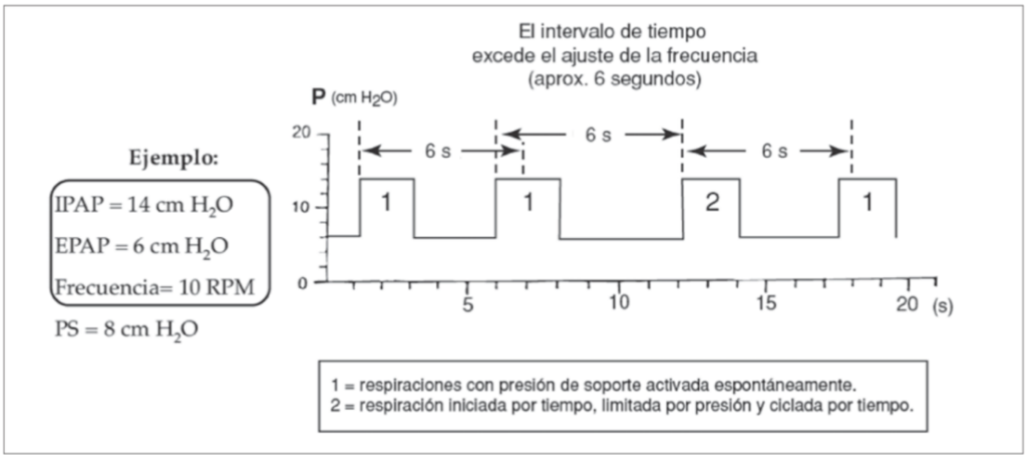

Figure 2. *Spontaneous and spontaneous-time-cycled modes of bilevel pressure ventilation* (32).

In paediatric patients with both type I and type II respiratory failure, it seems appropriate to start with a BIPAP with a low-pressure difference (the difference between IPAP and EPAP). This support it is then modified depending on the blood gas results.

In patients with bronchiolitis, acute lung oedema, or apnoea, it may be reasonable to start treatment with CPAP instead of BIPAP (30).

2.3. Interfaces

There are different types of interfaces to use on the NIV (30): Nasal, nasal prongs, oronasal mask, facial, and helmet.

3. Patient-ventilator asynchrony (PVA)

Patient-ventilator asynchrony (PVA) is defined as the mismatch between the breaths delivered by the ventilator and those required by the patient at that moment, regarding the demand of time, flow, volume, or pressure.

The incidence of PVA is highly variable, with published ranges from 10 to 80%, as it depends on many factors (ventilatory modes, ventilator settings, observation time, level of sedation, length of the observation periods, detection method, type of patients, type of PVA…). It is more frequent in NIV due to the existence of leaks (30,33).

The asynchrony index (AI) is defined as the quotient between the number of breaths with PVA and the number of total breaths. It is considered serious when AI exceeds 10% (30,33,34).

PVA has consequences, such as increased work of breathing, increased time on mechanical ventilation, more days in the PICU, and the development of muscle dysfunction. Although, it is not so clear if all PVAs lead to ventilatory failure, or simply if the existence of PVA is nothing more than the translation that patients are more serious (30).

In patients older than 3-6 months with BIPAP, the inspiratory trigger is sufficiently sensitive, which makes the synchronization better, that is why the rescue frequency should be kept to a minimum, to diminish the asynchrony.
In contrast, children younger than 3-6 months are more likely to present asynchrony in non-invasive mechanical ventilation. This occurs because there is a lack of sensitivity to the triggers of current respirators (30).

Therefore, in children younger than 3-6 months it is reasonable to start NIV with CPAP, thus avoiding the risk of asynchrony from the beginning.
If it is necessary to put a BiPAP, we have to try to have a good synchronization, increasing the expiratory trigger to values greater than 60% to shorten the inspiratory time (30).

It is very difficult, despite all measures, to achieve adequate inspiratory timing in such young children. In case we have NAVA, it could be useful to reduce asynchronies. (*See 4. Neurally adjusted ventilator assist*). (30)

3.1. Types of PVA

There are different types of patient-ventilator asynchrony (30,33–35):

Table 3. *Types of patient-ventilator asynchronies, own source.*

Type		Definition and cause	Solution
Triggering PVA	**Auto-triggering**	The ventilator is triggered in the absence of effort from the patient, as it receives a "false" signal, as a consequence of artifacts in the ventilator circuit (water in the circuit, vibrations, leaks, or cardiac oscillations). It can also be produced due to a very sensitive trigger.	- Optimize the sensitivity setting - Remove artifacts
	Ineffective triggering	The patient's muscular efforts do not trigger the ventilator. Causes are common with delayed triggering and may be patient or ventilator related. Patient - Dynamic hyperinflation - Muscular weakness - Low central respiratory drive Ventilator: - High levels of assistance - Inspiring trigger not very sensitive	- Optimize inspiratory trigger - Decrease instrumental dead space - Minimize hyperinflation - Reduce sedation
	Delayed triggering	Delay time from patient effort until ventilator delivers the gas flow. Causes are common with ineffective triggering.	
Cycling PVAç	**Premature cycling and double triggering**	Premature cycling occurs when the patient's inspiratory neural time is greater than the ventilator's inspiratory time. It can be caused by high inspiratory flow (short pressure ramp) or high expiratory sensitivity (Esens) [low inspiratory time (Ti)]. The ventilator ends the delivery of flow, but the patient continues to inhale. In the event that the inspiratory trigger is exceeded, a double triggering may occur, and the ventilator administrates another breath.	- Increase Ti of ventilator and decrease Esens, to not cycle so fast. - Increase pressure ramp time

	Delayed cycling	The mechanical inspiratory time exceeds the neural inspiratory time. The most frequent causes are air leaks. The patient struggles against the respirator.	- Eliminate or reduce leaks. - Increase Esens so cycling occurs earlier or program a maximum Ti.
Flow PVA	**Excessive flow**	It can be caused due to the flow setting of the ventilator is too high or the applied pressure is too high.	- Adjust flow level - Modify pressure ramp time.
	Insufficient flow	It can be caused because the flow setting is too low, the applied pressure is too low, or an excessive ventilatory demand by the patient.	

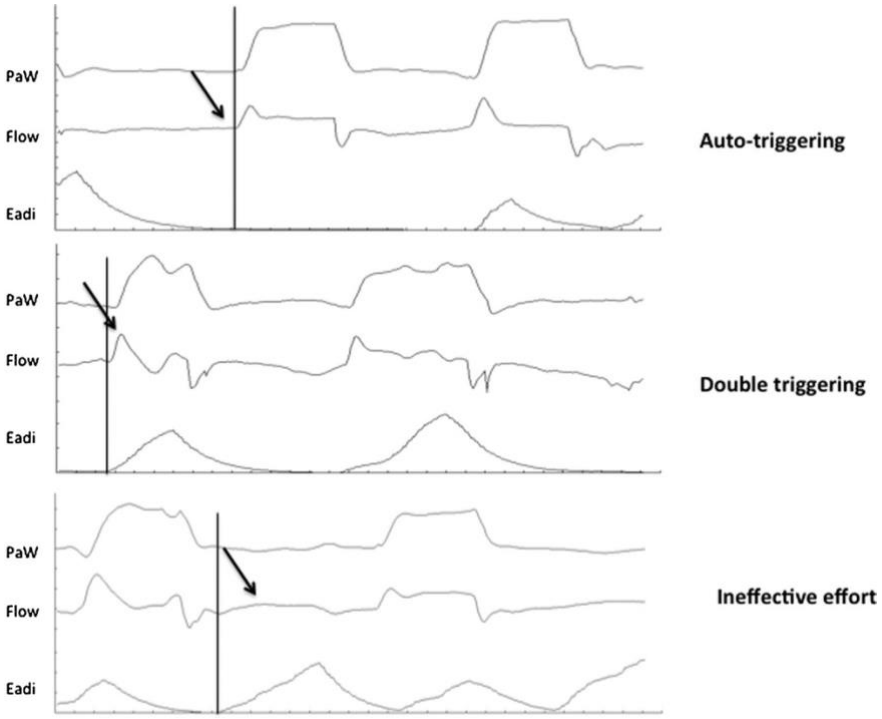

Figure 3. *Examples of the three main asynchronies in a child on non-invasive ventilation. Arrow indicates abnormal events and vertical lines indicate the beginning of the cycle. Paw, airway pressure; Eadi, electrical activity of the diaphragm* (36).

4. Neurally adjusted ventilator assist (NAVA)

NAVA is a mechanical assisted ventilation mode that detects and measures the electrical activity of the diaphragm (Eadi) for ventilator control. Variable pressure support proportional to the intensity of Eadi is administered (30,37).

Eadi is measured by 10 oesophageal electrodes positioned by a conventional nasogastric tube that has them incorporated (**Figure 4**). It is very important to position the electrodes correctly on both sides of the diaphragm, using the oesophageal electrocardiographic signal as a reference, recorded by the same electrodes (30,37).

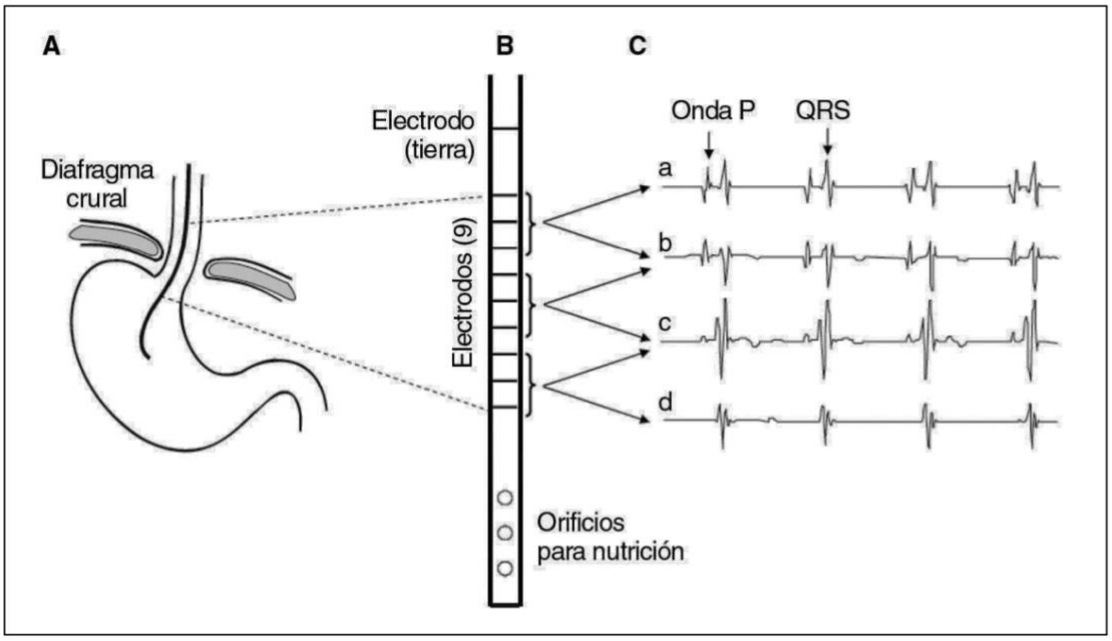

Figure 4. *NAVA system: catheter positioning. A) Anatomical positioning: The region of the electrodes (delimited by the dotted line) must be on both sides of the diaphragm for a correct registration. B) The Eadi catheter is a modified conventional nasogastric tube to which 10 electrodes have been added in series, included concentrically in the tube wall. C) With the oesophageal electrocardiographic recording using the system's own electrodes, correct positioning can be verified; the upper leads (a and b) record the activity of the proximal electrodes, closer to the cardiac region, and the P wave is more prominent; the lower leads (c and d) record the activity of the distal electrodes, which show a progressive decrease in the P wave. The ventilator has a positioning tool that shows the electrocardiographic record and facilitates its positioning* (37).

The respiratory cycle originates in the respiratory centre, the efferent impulse travels through the motor neurons of the phrenic nerve, and this initiates the electrical activation of the diaphragm, causing its mechanical contraction (37,38).

The NAVA uses the Eadi signal to control the ventilator, allowing the respiratory centre to modulate mechanical ventilatory assistance in a more direct way, measuring the inspiratory (TIn) and expiratory (TEn) neural time directly. TIn begins with the increase of the Eadi above the expiratory value and ends when the inspiratory peak is reached, and then the TEn begins (37,38).

The difference that NAVA has with conventional pneumatic triggering modes is that they use the pressure and/or flow signal in the airway, so it requires that the neuronal impulse is first translated into an effective diaphragmatic contraction, depending on an adequate neuromechanical coupling. This contraction must be capable of producing the effective intrathoracic pressure or flow changes that must be efficiently transmitted to the ventilator.

In conventional modes, Tin and TEn can only be estimated indirectly by recording changes in airway pressure and flow (37).

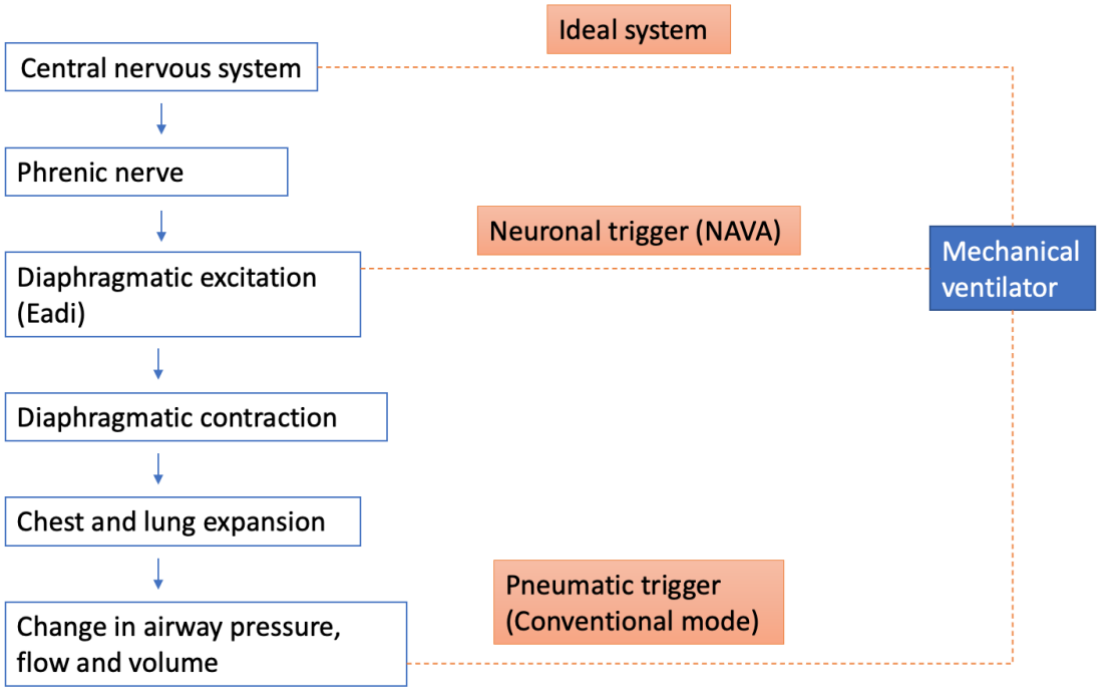

Figure 5. *Central ventilatory impulse path. The diaphragmatic electrical activity (Eadi) used by NAVA system is the closest signal to the genesis of the central respiratory impulse that current technology allows us to use to control the ventilator. The ideal system would be a signal from the central nervous system directly to the ventilator. Adapted from* (37,38).

NAVA reduces patient-ventilator asynchrony and is very useful in children younger than 3-6 months because, as we have said previously (*See 3. Asynchrony patient-ventilator*), there is a lack of sensitivity of conventional ventilator triggers (30,37).

Furthermore, another advantage of the NAVA is that it provides a discharge from muscular work, reducing exhaustion or excessive inactivity, facilitating the withdrawal of mechanical ventilation (37).

5. Invasive ventilation

Tracheal intubation consists of the placement of a tube into the trachea, either through the mouth (orotracheal intubation) or through the nose (nasotracheal intubation) (39).

In children under 2 years of age, the tongue is relatively large compared to the mandible, which facilitates the obstruction of the upper airway and makes it difficult to visualize the larynx, which is in a higher and anterior position than in the adult. The infant's epiglottis is flexible and attached to the pharyngeal wall at a 45 ° angle, so visualization of the larynx may require an elevation of the epiglottis with a straight laryngoscope blade, which provides a direct view of the larynx.
Therefore, in children younger than 2 years, more often under one year, we use a straight laryngoscope blade to intubate rather than a curved blade as in older children or adults (39,40).

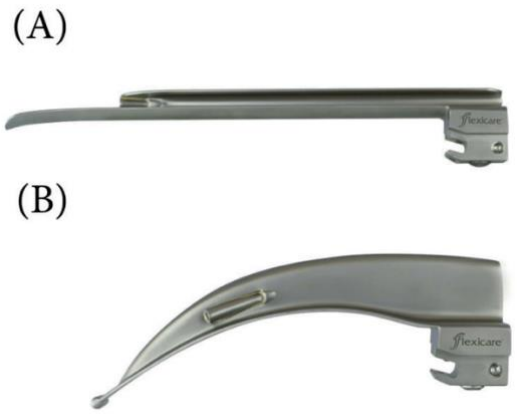

Figure 6. *Laryngoscope blades: (A) Straight blade (Miller); (B) Curved blade (Macintosh)* (41).

5.1. Indications for intubation

Indications for intubation in bronchiolitis are (27):

- Increased respiratory distress (often associated with agitation or reduced level of consciousness), with the risk of stopping due to muscle fatigue.
- CPAP / BiPAP failure (need for FIO2 ≥ 0.6, S / F ≤ 150-200)
- Recurrent apnoea

5.2. Non-invasive ventilation failure criteria

Once non-invasive ventilation has started, we will monitor the patient to see if at any time we have to intubate.

For this, we will use SaFi, which is the correlation between the transcutaneous oxygen saturation (SaO_2) and the inspired fraction of oxygen (FiO_2). A SaFi below 270 is considered a hypoxemic failure (30).

$$SaFi = \frac{SaO_2}{FiO_2}$$

The patient needs immediate intubation when, with non-invasive ventilation, he has moderate/severe ARDS and a SaFi less than or equal to 150.

If the patient has a SaFi of 150-200, we increase the EPAP, to keep the alveolus open and improve oxygenation. And we re-evaluate in 1-2 hours. If he does not improve, since his SaFi continues to be below 200 and there is no decrease in HR and RR, which indicates that he has a high respiratory effort, we will proceed to intubate.

If the SaFi is above 200 with non-invasive ventilation, we also need a new evaluation in 1-2 hours and we will proceed according to the improvement or not (as in the previous case) (30).

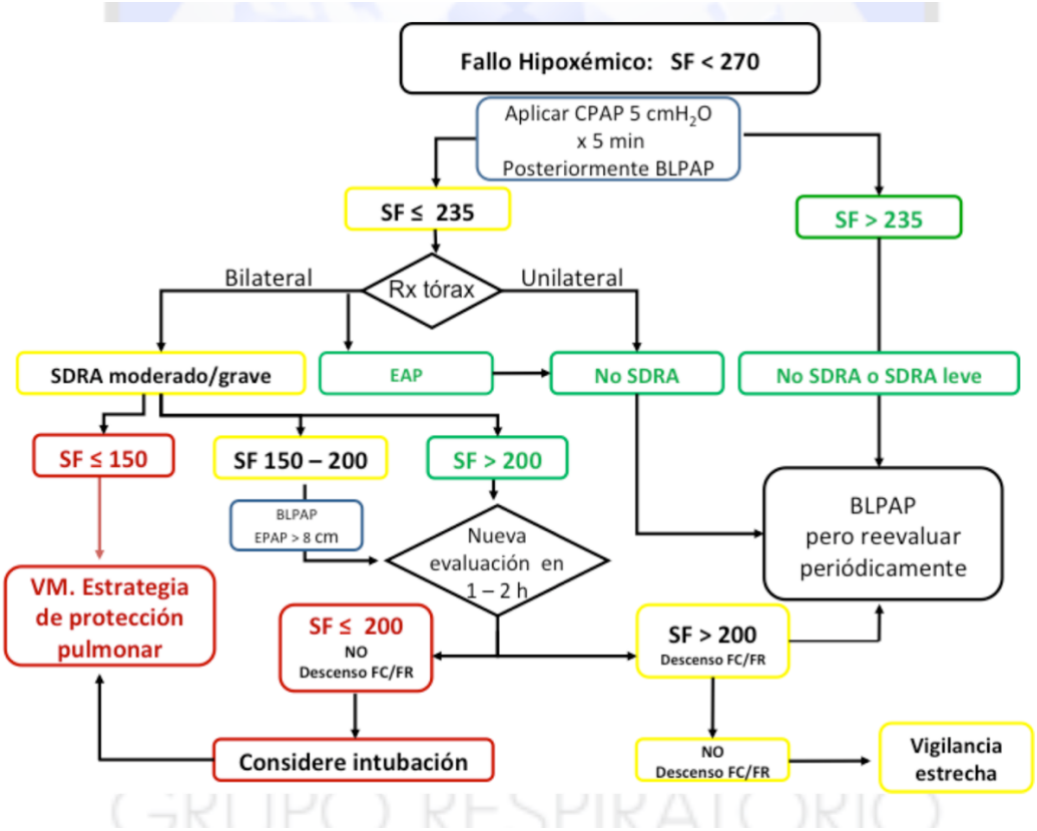

Figure 7. *Non-invasive ventilation failure analysis algorithm in respiratory failure with hypoxemia (from Manual de VM Pediatrica y neonatal* (30)*).*

JUSTIFICATION

Bronchiolitis has a high incidence in cold months, and it is the most common cause of hospitalization in infants under two years of age, with high mortality and morbidity worldwide. Moreover, no specific treatments have been demonstrated to improve symptoms and reduce hospitalization length, so it is based on support measures. Therefore, this disease consumes many resources in hospitals, producing a high economic cost.

In children under one year of age, especially in those under 3-6 months, there is a large percentage of patient-ventilator asynchronies (PVA). That increases the duration of hospitalization and produce larger respiratory dysfunction, causing more intubations. As a result, complications and sequelae in children can be produced, so, the less we intubate the better.

NAVA is a system that improves patient-ventilator asynchronies, consequently decreasing respiratory effort, days on mechanical ventilation, days of hospitalization, and decreasing muscle dysfunction. In addition, NAVA adapts very well to the needs of the patient, as its support pressure varies depending on the intensity of the Eadi.

This research is relevant because there are few studies about NAVA, which demonstrate in some infant patients that it reduces PVA. However, there are no investigations that directly relate the use of NAVA in bronchiolitis with the number of subsequent intubations and length of hospitalization.

The aim of this study is important because, as we said before, it is a very prevalent clinical problem, and there is no single respirator (both invasive and non-invasive ventilators) that is well suited for such small patients. For the machine to adapt to the patient it needs a minimum degree of respiratory effort, and none of them detects well the small volumes of air that infants mobilize. This problem could be solved with the use of NAVA.

HYPOTHESIS

Primary hypothesis

- The non-invasive ventilation with NAVA (Neurally Adjusted Ventilator Assist) reduces the intubation rate in children under 12 months with RVS + bronchiolitis versus the patients using the exclusive non-invasive ventilation without NAVA.

Secondary hypothesis

- The non-invasive ventilation with NAVA reduces the days of hospitalization in pediatric ICU in children under 12 months with RVS + bronchiolitis versus the patients using the exclusive non-invasive ventilation without NAVA.

OBJECTIVES

Primary objective

- To analyze the intubation rate using the non-invasive ventilation system with NAVA (Neurally Adjusted Ventilator Assist) compared to using the exclusive non-invasive ventilation system without NAVA, in children under 12 months with RSV+ bronchiolitis.

Secondary objective

- To compare the days of hospitalization in pediatric ICU between patients using non-invasive ventilation with NAVA and patients using exclusive non-invasive ventilation.

METHODOLOGY

1. Study design

Randomized, controlled, multicentred, open-label, prospective clinical trial that compare to the use of NAVA in non-invasive ventilation versus to the use of exclusive non-invasive ventilation without NAVA, in infants under 12 months with RSV+ bronchiolitis that require mechanical ventilation.

Hospital Universitari Doctor Josep Trueta will be the reference centre. Each participating hospital will have an assigned principal investigator.

The centres that will be asked to participate in the study are the Catalan hospitals that have paediatric ICU:

- Hospital Universitari Doctor Josep Trueta (HUDJT), in Girona
- Hospital Sant Joan de Déu, in Barcelona
- Hospital Universitari Vall d'Hebron, in Barcelona
- Hospital Universitari Parc Taulí, in Sabadell
- Hospital de la Santa Creu i Sant Pau, in Barcelona
- Hospital Joan XXIII, in Tarragona

2. Study population

The study subjects will be patients admitted to the PICU of each participating hospital, under 12 months of age, with a diagnosis of RSV+ bronchiolitis.

2.1. Inclusion and exclusion criteria

Infants of our study population from participating centres who meet inclusion and exclusion criteria will be selected (*See **Table 4.*** Inclusion and exclusion criteria).

Table 4. *Inclusion and exclusion criteria*

Inclusion criteria:	Exclusion criteria
- Age under 12 months - RSV+ bronchiolitis - Requirement of non-invasive ventilation. - Admitted in the PICU	- Airway malformations - Metabolism disease - Neuromuscular disease - Congenital heart disease - Congenital syndrome - Patients who are admitted to the ICU and are directly intubated

2.2. Withdrawal criteria

Reasons for patient removal from the study include:

- Request of the parents/legal tutor (revocation of the informed consent)
- The patient meets exclusion criteria at some point in the clinical trial (either newly developed or previously unrecognised)

As study includes patients through consecutive non-probabilistic sampling, they can be replaced during the time of recruitment in order to have enough people.

3. Sampling

It is not predictable when an infant will suffer bronchiolitis, since it is an acute disease, there is no sampling frame. So, we will do a consecutive non-probabilistic sampling.

4. Sample size

We used the program GRANMO to calculate the size of our sample for the clinical trial. The difference indicated concerns the intubation rate in each patient group.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **261** subjects are necessary in first group and **261** in the second to find as statistically significant a proportion difference, expected to be of 0.25 in group 1 and 0.15 in group 2. It has been anticipated a drop-out rate of 5%. The ARCSINUS approximation has been used.

5. Time of recruitment

To find out the recruitment time, we rely on data from the Doctor Josep Trueta University Hospital.

- In 2019, 31 patients were admitted to the PICU for a one-year debate with acute bronchiolitis RSV + that required non-invasive ventilation.
- The population under 12 months in the health area of Girona that covers this hospital in the 2019 data is 6,688 infants.

In Catalonia, according to data from 2019, there were 62,576 infants under 12 months. So, if we extrapolate, we expect to have 290 patients admitted to the PICUs of Catalonia with RSV + bronchiolitis that requires NIV in one year.

Therefore, we estimate to obtain enough sample for our clinical trial in two years. As the appearance of bronchiolitis has a seasonal distribution, with two seasons of bronchiolitis we will have enough to collect the sample (October-March).

6. Study variables and measuring instruments

6.1. Independent variable

The use of NAVA with non-invasive ventilation.

It is a dichotomous nominal qualitative variable, expressed by yes or no (applying NAVA or not).

- **Control group:** Using exclusive non-invasive ventilation, without NAVA.
- **Experimental group:** Using non-invasive ventilation with NAVA.

6.2. Dependent variable

Primary dependent variable: Intubation rate.

We will measure the ratio of infants who need intubation, because we cannot stabilize them with non-invasive ventilation.

It is a dichotomous nominal qualitative variable, expressed by yes or no (intubated or not).

Secondary dependent variable: Length of hospitalization in the ICU.

It is a discrete quantitative variable. It will be measured in days from the day of admission to the day of discharge. We will record the admission data and the discharge data in the case report form.

6.3. Co-variables

We are going to take in to account some covariables, that could be cofounding factors:

- **Age**: It is a discrete quantitative variable. It will be measured in months.
- **Sex**: Male or female. It is a dichotomous nominal qualitative variable.
- **Weight:** It is a continuous quantitative variable. It will be measured in kilograms with a weighing machine.
- **Ethnicity:** It is a polychotomous nominal qualitative variable divided into 5 groups: Caucasian, African, Latin-American, Asian and Other. It will be asked to the parents of the patient.
- **Bacterial infection:** Yes or no. It is a dichotomous nominal qualitative variable. We will do a blood culture if there are bacterial infectious clinic signs and analytical markers.
- **History of prematurity**: Yes or no. It is a dichotomous nominal qualitative variable.

Table 5. *Variables summary*

	Variable	Description	Measure instruments	Categories or values
Independent variable	**Use of NAVA**	Dichotomous nominal qualitative variable	Case report form	Yes / No
Primary dependent variable	**Intubation rate**	Dichotomous nominal qualitative variable	Case report form	Yes / No
Secondary dependent variable	**Length of hospitalization in the ICU**	Discrete quantitative variable	Case report form	Days
Covariables	**Age**	Discrete quantitative variable	Medical history Case report form	Months
	Sex	Dichotomous nominal qualitative variable	Medical history Case report form	Male / Female
	Weight	Continuous quantitative variable	Weighing machine Case report form	Kilograms
	Ethnicity	Polychotomous nominal qualitative variable	Asked to the parents Case report form	- Caucasian - African - Latin – American - Asian - Other
	Bacterial infection	Dichotomous nominal qualitative variable	Clinic and blood culture Case report form	Yes / No
	Prematurity	Dichotomous nominal qualitative variable	Medical history Case report form	Yes / No

7. Measure instruments

Bronchiolitis will be diagnosed based on the clinic by a paediatrician, and we will make a viral test to confirm the RSV+ cases.

We will have to have the patients monitored and measure HR, RR, pH, PO2, PCO2, and SaFi to see how they evolve with non-invasive ventilation, and to know if we have to intubate them.

Measure instruments required for this study include:

- Weighing machine
- Pulse oximetry
- Vital signs monitor
- Arterial blood gas measurements, to adjust ventilatory support
- Case report form (*See Annex 8)*

8. Study intervention

All participating centres will receive a training course on the use of NAVA, to minimize confounding variables related to differences in applying the device.

8.1. Enrollment

All patients that arrive at the PICU under the diagnosis of RSV + bronchiolitis will be considered for the trial. Patients will be enrolled in the study by consecutive non-probabilistic sampling.

Parents or legal tutors of patients who meet our inclusion and exclusion criteria will be asked to enroll in our clinical trial. They will be informed of the objective of the study, the procedure, and the associated risks, through an information sheet. Once they have signed the informed consent, the infants will be enrolled in our research project.

8.2. Randomization

When patients are enrolled in our study, they will be divided into two groups, which will have to be randomized.

There will be a statistician who will create a randomization sequence with statistical software, on an individual basis, with the mission of assigning them into two different groups, with a 1:1 ratio:

- **Control group (A):** Exclusive non-invasive mechanical ventilation with a facial interface.
- **Experimental group (B):** Non-invasive mechanical ventilation with NAVA with a facial interface.

8.3. Blinding

As we have to place a device, the study cannot be blind, since it is necessary to know if we put NAVA or not. So, it will be an open-label trial, which means that both the doctors and the parents/legal tutor know the group they are in.

8.4. Interventions

All patients will receive the same supportive care for bronchiolitis. This will consist of oxygen therapy and continuous enteral nutrition for all.

Regarding pharmacological treatment, there is no medication that has scientific evidence, but if the patient has a lot of secretions, we will add inhaled adrenaline and if it is very bronchospastic, we will add salbutamol.

The non-invasive ventilatory support must be started as soon as possible, with NAVA or not depending on the group to which the patient belongs. We will use facial interface in all patients to avoid bias because there are different types of interfaces that can be used (*See Annex 3*).

We will follow-up on the monitor of the patient, to see if it goes well with this type of ventilation or needs to be intubated. All data will be collected in the Critical Care Centricity Program, which is a computerized system that all paediatric ICUs of participating hospitals have.

We will look at (*See Annex 1: Escala de l'Hospital Sant Joan de Déu*):

- Oxygen saturation (SaO_2)
- Heart rate (HR)
- Respiratory rate (RR)
- We will also do periodic blood gas, every six hours, to control the pH, the PCO2, and the PO2.
- SaFi. We will program to measure it every hour, as it is not an invasive procedure.
- Work of breathing

If the patient at any time meets intubation criteria (*See 5.1.* Indications for intubation) or shows signs of non-invasive ventilation failure (*See 5.2.* Non-invasive ventilation failure criteria*)*, we will proceed to intubate the patient.

9. Data collection

All the information will be recorded in the case report form (*See Annex 8)* during the hospitalization of the patient.

The case report form includes if the patient has been intubated, the length of hospitalization in the ICU, and all the covariables.

Every week each coordinator from the hospitals will collect the information and add it to a database, which will be an excel document shared for all the hospital coordinators and the principal investigator. This resource can be used by the different researchers in each centre; therefore, it facilitates the collection of data from our multicentre clinical trial.

In the first meeting with all hospital coordinators, we will do training for data collection in the case report form and the use of the database, to unify the way of doing it.

10. Flow chart

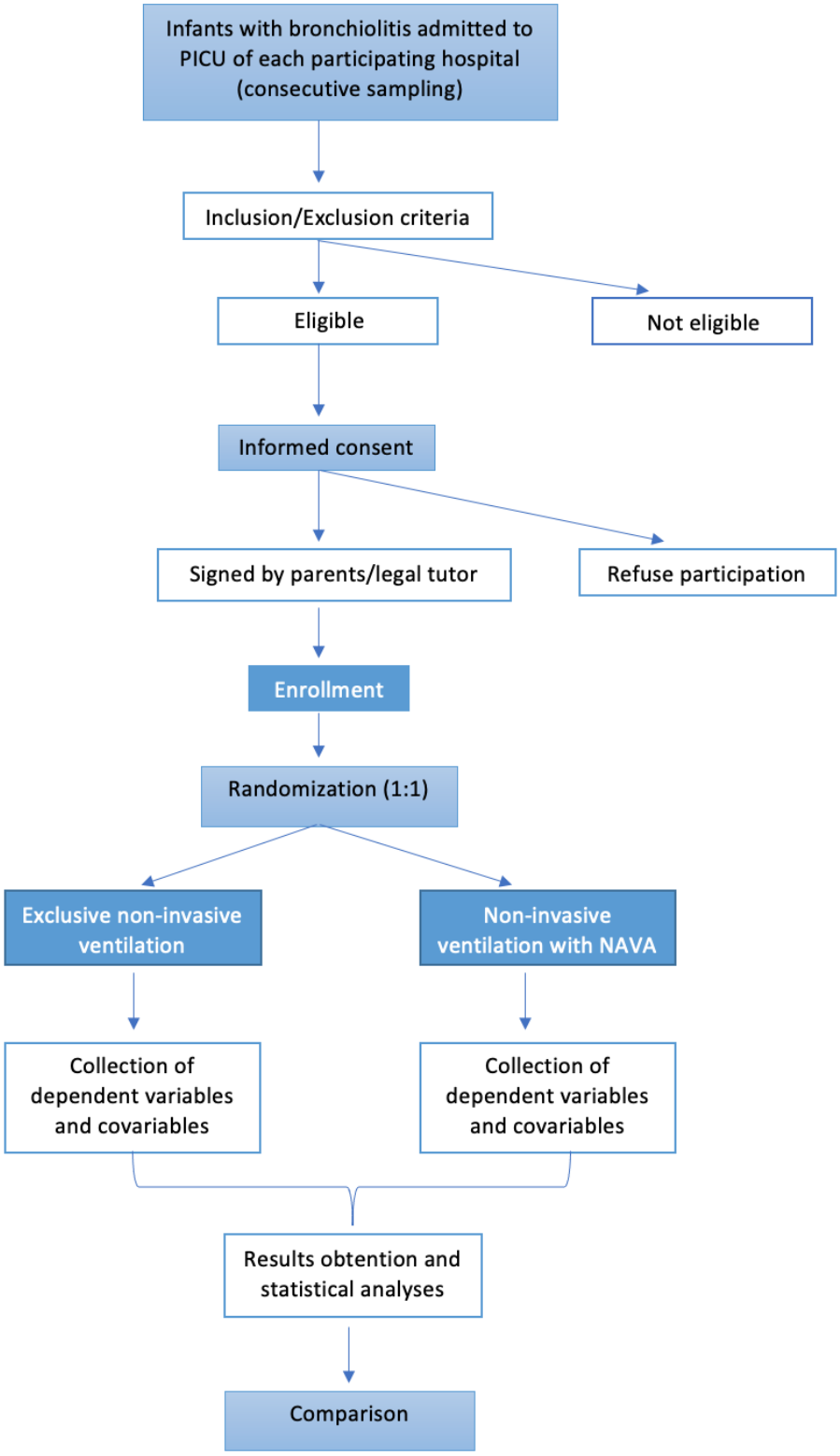

***Figure 8**. Summary of the clinical trial interventions*

11.Safety

Both Non-Invasive Ventilation and Neurally Adjusted Ventilatory Assist (NAVA) are already commonly used in clinical practice in the PICU and the safety of these products has been demonstrated.

The main proven complication of non-invasive ventilation is air leakage (pneumothorax), and this has already been taken into account for this clinical trial.

STATISTICAL ANALYSIS

1. Univariate analysis

A descriptive analysis of all variables will be performed. We will define variables as quantitative or qualitative:

- Quantitative variables and covariables will be described as mean ± standard deviation (SD).
- Qualitative variables and covariables will be described as percentages or proportions.

2. Bivariate analysis

The independent variable and the primary dependent variable are qualitative. To compare proportions between qualitative variables (using NAVA or not and intubation rate) we will use Chi-square test (X^2).

Instead, the secondary dependent variable is quantitative, so for the comparison between these two variables, we will use T-student test.

3. Multivariate analysis

A multivariate analysis will be done to adjust the result of the outcome variable for the potentially confounding effects, that could modify our results. We have to consider that due to the randomization design, the covariables should be equally distributed to both groups.

A logistic regression test will be used to assess the relationship between the use of NAVA or not and the intubation rate, after adjustment for the covariables.

We will use a general linear model to analyse the relationship between the independent variable and the duration of hospitalisation (secondary dependent variable), adjusted to the covariables.

P-value of < 0.05 will be set to indicate statistical significance, defining an interval of confidence of 95%.

The statistical analysis will be performed by a statistician, who will be blinded to the study groups and we will use the Statistical Package for Social Sciences (SPSS) software.

WORK PLAN AND CHRONOGRAM

The research team will be composed by: One principal investigator (**PI**), 6 coordinators of each hospital (**HC**), one statistician (**Sta**) and PICU team of each hospital (**PT**).

The duration of the clinical trial will be 2 years and 4 months and it will follow these stages:

- **First stage**: Protocol design and approbation (5 months; March 2021 – July 2021).
    - **Activity 1:** Literature review and elaboration of the project and protocol for the clinical trial.
    - **Activity 2:** Principal investigator will contact each of the hospitals to ask for their enrolment in our study.
    - **Activity 3:** Centre approval, where each hospital participating approves the trial.
    - **Activity 4:** Recruitment of a coordinator for each centre participating.
    - **Activity 5:** Ethics Committee of Clinical Investigation approval of each centre.

  Personnel: PI, CEIC
- **Second stage:** Preparation and training (2 months; August-September 2021).
    - **Activity 6:** First meeting with the coordinators of each hospital in *Hospital Universitari Doctor Josep Trueta*, to explain the protocol, the interventions, to solve all the questions and discuss the organization. From here, representatives of each centre will meet every 2 months during the recruitment time to evaluate if the protocol is being followed properly. Personnel: PI, HC
    - **Activity 7:** Programme formation sessions in each hospital to train doctors and nurses of the ICU to use correctly NAVA, doing all in the same way to avoid bias.

      Personnel: PI
- **Third stage:** Sample recruitment, applying interventions, and data collection (18 months → 2 seasons of bronchiolitis, from October to March; October 2021 – March 2023).

- **Activity 8:** Recruitment of patients, with RSV + bronchiolitis that matches our inclusion criteria, during their admission in the ICU. The recruitment will be done by a consecutive sampling in all the hospitals participating. We will exclude patients that have exclusion criteria. To enroll these patients in the study, parents or legal tutors will be given an information sheet (*See annex 4 and 5*) with all the details of the clinical trial and they will have to sign the consent form (*See annex 6 and 7*).

  Personnel: HC, PI
- **Activity 9:** Patients included will be randomly assigned to the control group (A) or the experimental group (B) and then measures will be applied.

  Personnel: HC, PI, Sta, PT
- **Activity 10:** Data collection using case report form (*See annex 8*), and the hospital coordinators and principal investigator will collect it in a database every week.

  Personnel: HC, PI

- **Fourth stage:** Data analysis and interpretation of the results (1 month; April 2023).
  - **Activity 11:** Statistical analysis will be performed by a subcontracted statistician that will be masked for the different groups.
  - **Activity 12:** Analysis and interpretation of the results.

  Personnel: Sta
- **Fifth stage:** Publication and dissemination of the results (3 months; May-July 2023).
  - **Activity 13:** Redacting an article with the results found. We will do a final meeting with all the coordinators to interpret and discuss the results from the statistical analysis.

    Personnel: PI, HC
  - **Activity 14:** Presentation of the results on Sociedad Española de Cuidados Intensivos Pediatricos (SECIP) and European Society of Paediatric and Neonatal Intensive Care (ESPNIC).

    Personnel: PI
  - **Activity 15:** Publication of the results in scientific journals.

    Personnel: PI

Table 6. *Chronogram*

	Person-nel	2021										2022												2023						
		MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DES	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DES	JAN	FEB	MAR	APR	MAY	JUN	JL
STAGE 1																														
A1: Protocol elaboration	PI																													
A2: Contact with other centres	PI																													
A3: Centre approval	PI																													
A4: Recruitment of coordinators	PI																													
A5: CEIC evaluation	CEIC																													
STAGE 2																														
A6: First meeting	PI, HC																													
A7: Formation sessions	PI																													
STAGE 3																														
A8: Recruitment of patients	PI, HC																													
A9: Randomization and applying interventions	PI, HC, Sta																													
A10: Data collection	PI, HC																													
STAGE 4																														
A11: Data analysis	Sta																													
A12: Result interpretation	Sta																													
STAGE 5																														
A13: Redacting article	PI, HC																													
A14 and A15: Divulgation	PI																													

Periodic meetings

Analyse meeting

BUDGET

Personnel expenses: The coordinators and medical personnel are employees of the selected hospitals; therefore, we will not have to hire any more medical assistance personnel. We will only need to hire a statistician to analyse the results.

- Statistical analysist: 40€/hour x 80h = 3.200 €

Meetings:

- Coordination meetings: 50€/person. 7 persons. 10 meetings = 3.500 €
- Analyse meeting: 50€/person. 7 persons. 1 meeting = 350 €

Trainings:

- NAVA training: 4-hour of use of NAVA training in each hospital (6 hospitals). 80 €/hour x 24 hours = 1.920 €

Material: Since all the hospitals in which we will carry our clinical trial have a PICU department, all the material needed for the study is already available. This material includes NAVA, non-invasive ventilators, facial interfaces, materials for intubation, monitors, etc. Therefore, we will not have to purchase any additional material.
We will print the information sheet and consent form for all participants in our clinical trial.

Liability insurance: If it is considered by the CEIC to be an invasive clinical trial, we will take out insurance to cover any possible complications suffered by patients in our study, attributable to their participation in it. The estimated cost is 25.000 €, but it will be confirmed at the time of the clinical trial kick off.

Publication and dissemination expenses

- Article publication: 2500 €
- National congress: 1000 €
- International congress: 2000 €

Table 7. *Summary of budget*

	Description	Quantity	Cost	Total Cost
Personnel costs	Statistician	80 hours	40 €/hour	3.200 €
Meeting expenses	Coordination meetings	10 meetings (7 persons)	50 €/person/ meeting	3.500 €
	Analyse meeting	1 meeting (7 persons)	50 €/person/ meeting	350 €
Trainings	NAVA training	24 hours	80 €/hour	1.920 €
Material	Information sheet	522 x 4 pages	0,03 €/page	62,64 €
	Consent form	522 x 1 page	0,03 €/page	15,66 €
Liability insurance	Liability insurance		25.000 €	25.000 €
Publication and dissemination	Article publication		2.500 €	2.500 €
	National congress		1.000 €	1.000 €
	International congress		2.000 €	2.000 €
TOTAL				**39.548,30 €**

FEASIBILITY

This clinical trial is multicentred and will be carried out in the six Catalan hospitals that have PICU service; Hospital Universitari Doctor Josep Trueta, Hospital Sant Joan de Déu, Hospital Universitari Vall d'Hebron, Hospital Universitari Parc Taulí, Hospital de la Santa Creu i Sant Pau, and Hospital Joan XXIII, which have a high number of admissions for bronchiolitis each season, in order to recruit enough sample.

Apart from a statistical specialist, we will not need to hire additional personnel, since the different activities will be carried out by the paediatricians of each hospital PICU, who are perfectly trained to carry out this study, and they will not charge an additional remuneration.

The main investigator will be a paediatrician specialized in intensive care from Hospital Universitari Doctor Josep Trueta, who is prepared to coordinate and carry out this study. He will not charge an extra salary either.

Not much extra material is necessary to carry out this clinical trial, since both the respirators for non-invasive ventilation and NAVA, as well as the instruments we need for follow-up, are used in the clinical practice of these hospitals. Therefore, we will not require the purchase of additional material. We will only need to print the explanatory documents and the informed consent, and we will do it in the same hospital, with a price of 0,03 € per page. So, with regard to material, our clinical trial has a low price.

Finally, note that the different tasks are well described in our work plan, with well-defined and feasible periods of time.

ETHICAL AND LEGAL CONSIDERATIONS

This clinical trial is designed according to World Medical Association *Declaration of* ***Helsinki*** *for Ethical Principles for Medical Research Involving Human Subjects* (last revision October 2013 by World Health Association).

We will present the study protocol to the *Comitè Ètic d'Investigació Clínica* (CEIC) of each centre involved in the research project, to evaluate and approve the clinical trial. If they had any suggestions, we would modify the protocol as needed.

As participation in a clinical trial is voluntary, all parents or legal guardians of patients who enroll in our clinical trial have to be fully informed with an information sheet (*See Annex 4 and 5)* written in a comprehensive language and sign an informed consent (*See Annex 6 and 7)*, before being included in our clinical trial, as stated on ***Ley 41/2002*** *Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.*

This study includes medical devices (such as ventilators and NAVA) and also uses invasive techniques; therefore, it will be developed according to the following laws:

- ***Ley 14/2007*** *de 3 de Julio, de investigación biomédica con procedimientos invasivos.*
- ***Real decreto 1090/2015****, investigaciones clínicas con productos sanitarios.*

All the data that we collect from each patient to be analysed will be anonymous, preserving the confidentiality of the patient according to:

- ***Ley Orgánica 3/2018****, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*.
- ***Reglamento UE 2016/679 del Parlamento Europeo y del Consejo,*** *de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos.*

All the investigators will have to declare no conflict of interest.

LIMITATIONS OF THE STUDY

This clinical trial is multicentred, which has both advantages and disadvantages. First of all, we are including 6 different centres, so there may be differences between hospitals in terms of the placement of ventilation devices or intubation criteria. We solved this problem by protocol standardization and doing training sessions for all hospitals to use the same techniques and have the same criteria. We will need a lot of organization. Even so, there may still be differences between centres.

Although we include covariables in the study that we are going to take into account, it is difficult to control all the factors that may interfere with the results, since we are faced with an acute pathology that can behave differently in each patient.

This research project is an open-label clinical trial, both professionals and parents/legal tutors know if NAVA is being used or not; therefore, the results may be biased. So, the statistical expert who makes the analysis will be blinded.

In terms of external validity, it is a clinical trial conducted on a sample of the population but may not be representative of the entire population suffering from bronchiolitis. We have solved this by carrying out a multicentred study in Catalonia, to cover more of the population. Further studies must be performed to represent the worldwide population.

IMPACT ON THE NATIONAL HEALTH SYSTEM

Bronchiolitis is a very common pathology in the world, causing a lot of morbidity and mortality. In the case of patients under one year of age, who are assisted with non-invasive ventilation, a high percentage of asynchronies has been demonstrated. This causes a constant patient-ventilator fight, and it's harder for them to improve their clinic and prognostic.

This clinical trial will have a great clinical importance if we reduce intubations and length of hospitalization. Furthermore, we will decrease the economic resources used in bronchiolitis, which are currently high. We will also reduce the parental concern, due to the fact that having your child in the hospital for many days and intubated causes a lot of suffering.

If the results are significant and our hypotheses are validated, the NAVA device could begin to be used routinely in patients under 12 months with acute RSV + bronchiolitis admitted to the PICU. This could be a big change in clinical practice since we would reduce intubations and days of hospitalization, and release ICUs from patients in bronchiolitis season.

Given the above, we believe that this clinical trial could have a great impact not only on the daily clinical practice and clinical improvement of patients, but also on the immediate economic impact on our National Health System.

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ANNEXES

1. Annex 1: Escala de l'Hospital Sant Joan de Déu to assess the severity

From (27).

	0	1	2	3
Sibilancias	No	Inspiratorios	Inspiratorios, espiratorios	
Tiraje	No	Subcostal, intercostal inferior	Previo + supraclavicular y aleteo nasal	Intercostal superior y supraesternal
Entrada de aire	Normal	Regular, simétrica	Asimétrica	Muy disminuida
Saturación O_2 **Sin O_2** **Con O_2**	 ≥95% Sin O_2	 91-94% >94 F_{IO2} < 40%	 <91% ≤94 F_{IO2} >40%	
FR < 3 meses **3-12 meses** **12-24 meses**	< 40 rpm < 30 rpm < 30 rpm	40-59 rpm 30-49 rpm 30-39 rpm	60-70 rpm 50-60 rpm 40-50 rpm	> 70 rpm > 60 rpm > 50 rpm
FC < 1 año **1-2 años**	< 130 lpm < 110 lpm	130-149 lpm 110-120 lpm	150-170 lpm 120-140 lpm	> 170 lpm > 140 lpm

Afectación Leve: < 5 puntos. **Afectación moderada**: 6-10 puntos. **Afectación grave:** 11-16 puntos.

FC: frecuencia cardiaca; FR: frecuencia respiratoria; rpm: respiraciones por minuto;

2. Annex 2: NAVA

3. Annex 3: Facial interface

4. Annex 4: Explanatory document for the participant (Catalan)

FULL D'INFORMACIÓ AL FAMILIAR RESPONSABLE O REPRESENTANT LEGAL

NOM DE L'ESTUDI: Comparació de la taxa d'intubació en pacients amb bronquiolitis, amb NAVA i ventilació no invasiva versus en pacients amb ventilació no invasiva exclusiva.
Centre assistencial:

Investigador/a principal:

INTRODUCCIÓ

Benvolgut/da,

Ens dirigim a vostè, com a pare/mare/tutor legal de l'infant, per informar-lo sobre un estudi d'investigació en el qual se'l convida a participar, portat a terme pels serveis d'UCI pediàtrica de diversos hospitals de referència a Catalunya.

La nostra intenció és que vostè rebi la informació correcta i suficient perquè pugui avaluar i jutjar si vol que l'infant participi o no en aquest estudi. Llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir.

PARTICIPACIÓ VOLUNTÀRIA

Ha de saber que la seva participació en aquest estudi és voluntària i que pot decidir que l'infant no participi o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que això alteri la relació amb el seu metge ni es produeixin perjudicis en el tractament de l'infant.

Abans que l'infant participi en aquest estudi, vostè com a pare/mare/tutor legal, haurà de firmar un consentiment informat on corrobora que ha llegit el document explicatiu i està d'acord amb el projecte. Si en algun moment volgués que l'infant deixés de participar, ho podrà fer mitjançant la revocació del consentiment informat.

DESCRIPCIÓ I OBJECTIUS DE L'ESTUDI

En primer lloc, aquest projecte ha estat prèviament aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC) de cada hospital participant, d'acord amb la legislació vigent, ***Ley 14/2007*** *del 3 de Julio, de investigación biomédica con procedimientos invasivos* i ***Real decreto 1090/2015****, investigaciones clínicas con productos sanitarios.*

En aquest assaig clínic s'han inclòs els 6 centres de Catalunya que disposen d'UCI pediàtrica. Esperem incloure aproximadament 522 infants per sota els 12 mesos d'edat amb bronquiolitis aguda causada per VRS (Virus respiratori sincicial), ingressats a la UCIP i amb necessitats de ventilació no invasiva.

El grup d'investigació estarà format per pediatres especialitzats en cures intensives.

La bronquiolitis aguda és una patologia molt freqüent al nostre medi, sobretot causada pel VRS. Cada any origina molts ingressos a les UCI pediàtriques (UCIP) catalanes. Tot i això, no té cap tractament específic; aquest es basa en teràpia de suport.

Una d'aquestes mesures de suport és la ventilació no invasiva i els sistemes que disposem actualment no estan totalment adaptats per a lactants de menys de 12 mesos, ja que aquests mobilitzen mínims volums d'aire i el sistema no és capaç de detectar-los, causant un problema de dessincronització entre el pacient i el ventilador.
Això pot fer que el pacient empitjori clínicament, causant en alguns dels casos una estança més llarga a la UCIP i pot arribar a requerir intubació per part dels professionals.

En els últims anys, s'ha desenvolupat un nou dispositiu, el NAVA (Neurally adjusted ventilatory assist), el qual té uns elèctrodes que es col·loquen, a través d'una sonda nasogàstrica, a l'alçada del diafragma de l'infant. Aquests detecten l'activitat elèctrica del diafragma, fent que el ventilador proporcioni el suport necessari i en sincronia amb els esforços respiratoris del pacient.

L'objectiu del nostre estudi és estudiar la taxa d'intubacions que es realitzen en els pacients que porten un sistema de ventilació no invasiva exclusiva sense el NAVA versus els pacients que porten un sistema de ventilació no invasiva amb el dispositiu NAVA. A més a més, s'analitzaran els dies d'hospitalització a la UCIP de cadascun d'aquests pacients.

Per a estudiar el nostre objectiu, s'ha dissenyat un assaig clínic on es proporcionarà, de forma aleatòria, els dos tipus de suport respiratori; ventilació no invasiva exclusiva (sistema estàndard) o ventilació no invasiva amb NAVA. Al ser un procés aleatoritzat, tots els pacients tenen les mateixes possibilitats de pertànyer a un grup o a l'altre.

RISCS DE L'ESTUDI

Tant la ventilació no invasiva com el dispositiu NAVA ja s'utilitzen a les UCIP de Catalunya, per tant aquest estudi clínic no té riscs sobreafegits per emprar aquests dispositius.

Un risc potencial és en relació amb la confidencialitat de les dades clíniques de l'infant, que evitarem tractant-les d'acord amb la *Llei de Protecció de Dades*.

POSSIBLES BENEFICIS DE L'ESTUDI

Aquest estudi pretén ser una referència per implementar de manera estàndard la col·locació del dispositiu NAVA en els pacients de menys de 12 mesos amb bronquiolitis VRS+ que requereixin ventilació no invasiva.

Si vostè ho desitgés, se li facilitaria un resum dels resultats de l'estudi.

INTERRUPCIÓ DE L'ESTUDI

Si durant la realització de l'assaig clínic s'observés una gran diferència entre els dos grups, l'estudi s'aturaria.

CONFIDENCIALITAT

Si acceptés la participació de l'infant com a pare, mare o tutor legal, vostè permetria a l'investigador registrar algunes dades de la seva història clínica, les quals seran confidencials. La privacitat del pacient està protegida i recollida a la ***Llei orgànica 3/2018****, del 5 de desembre, de Protecció de Dades Personals i garantia dels drets digitals.*

La informació recollida no inclourà cap classe de dades que permetin identificar al nen/a, com; nom, número d'història clínica, ni cap informació personal, només les necessàries per a l'estudi. Aquesta informació anirà vinculada a un codi, i aquest vincle només el coneixerà el seu metge responsable.

Aquesta informació no serà accessible per ningú que no sigui el seu metge responsable, i no serà difosa de cap forma, preservant l'anonimat.

En la publicació dels resultats es conservarà sempre l'anonimat dels pacients. A més a més, amb la finalitat de revisar els resultats de l'estudi, les autoritats sanitàries i organismes regulars podran accedir a totes les dades. Totes les persones i entitats estan subjectes i obligades a mantenir en secret la identitat del pacient.

COMPENSACIÓ ECONÒMICA

Com s'ha exposat anteriorment, la participació en aquest estudi és voluntària. Per tant, si vostè decideix que l'infant participi, no rebrà cap compensació econòmica. La participació en l'estudi no li suposarà cap despesa.

CONTACTE

En cas de qualsevol dubte o pregunta durant la realització d'aquest estudi, podrà posar-se en contacte amb el responsable i coordinador d'estudi:

Metge/essa responsable: Dr/Dra _____
Telèfon: _____

5. Annex 5: Explanatory document for the participant (Spanish)

DOCUMENTO DE INFORMACIÓN AL FAMILIAR RESPONSABLE O REPRESENTANTE LEGAL

NOMBRE DEL ESTUDIO: Comparación de la tasa de intubación en pacientes con bronquiolitis con NAVA y ventilación no invasiva versus en pacientes con ventilación no invasiva exclusiva. **Centro asistencial:** **Investigador/a principal:**

INTRODUCCIÓN

Bienvenido/a,

Nos dirigimos a usted, como padre/madre/tutor legal del paciente, para informarlo sobre un estudio de investigación en el cual se le invita a participar, llevado a cabo por los servicios de UCI pediátrica de varios hospitales de referencia en Cataluña.

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere que el niño/a participe o no en este estudio. Lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir.

PARTICIPACIÓN VOLUNTARIA

Tiene que saber que su participación en este estudio es voluntaria y puede decidir que el niño/a no participe o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que esto altere la relación con su médico ni se produzca perjuicios en el tratamiento del niño/a.

Antes de que el niño/a participe en este estudio, usted como padre/madre/tutor legal, tendrá que firmar un consentimiento informado donde corrobora que ha leído el documento explicativo y está de acuerdo con el proyecto. Si en algún momento quisiera que el niño/a dejara de participar, lo podrá hacer mediante la revocación del consentimiento informado.

DESCRIPCIÓN Y OBJETIVOS DEL ESTUDIO

Antes de todo, este proyecto ha estado previamente aprobado por el Comité de Ética e Investigación Clínica (CEIC) de cada hospital participante, de acuerdo con la legislación

vigente, ***Ley 14/2007*** *del 3 de Julio, de investigación biomédica cono procedimientos invasivos y* ***Real decreto 1090/2015****, investigaciones clínicas cono productos sanitarios.*

En este ensayo clínico se han incluido los 6 centros de Cataluña que disponen de UCI pediátrica. Esperamos incluir aproximadamente 522 lactantes por debajo los 12 meses con bronquiolitis aguda causada por VRS (Virus respiratorio sincitial), ingresados a la UCIP y con necesidades de ventilación no invasiva.

El grupo de investigación estará formado por pediatras especializados en cuidados intensivos.

La bronquiolitis aguda es una patología muy frecuente en nuestro medio, sobre todo causada por el VRS. Cada año origina muchos ingresos en las UCI pediátricas (UCIP) catalanas. Aun así, no tiene ningún tratamiento específico; este se basa en terapia de apoyo.

Una de estas medidas de apoyo es la ventilación no invasiva y los sistemas de los que disponemos actualmente no están totalmente adaptados para lactantes de menos de 12 meses, puesto que estos movilizan cantidades muy pequeñas de aire y el sistema no es capaz de detectarlo, causando un problema de asincronía entre el paciente y el ventilador.

Esto puede hacer que el paciente empeore clínicamente, causando en algunos de los casos una estancia más larga en la UCIP y puede llegar a requerir intubación por parte de los profesionales.

En los últimos años, se ha desarrollado un nuevo dispositivo, el NAVA (Neurally adjusted ventilatory assist), el cual tiene unos electrodos que se colocan a través de una sonda nasogástrica a la altura del diafragma del niño. Estos detectan la actividad eléctrica del diafragma, haciendo que el ventilador proporcione el apoyo necesario y en sincronía con los esfuerzos respiratorios del paciente.

El objetivo de la presente investigación es estudiar la tasa de intubaciones que se realizan en los pacientes que llevan un sistema de ventilación no invasiva exclusiva sin el NAVA versus los pacientes que llevan un sistema de ventilación no invasiva con el dispositivo NAVA. Además, se estudiarán los días de hospitalización a la UCIP en cada uno de estos pacientes.

Para estudiar nuestro objetivo, se ha diseñado un ensayo clínico donde se proporcionará de forma aleatoria los dos tipos de apoyo respiratorio; ventilación no invasiva exclusiva

(sistema estándar), o ventilación no invasiva con NAVA. Al ser un proceso aleatorizado todos los pacientes tienen las mismas posibilidades de pertenecer a un grupo o al otro.

RIESGOS DEL ESTUDIO

Tanto la ventilación no invasiva como el dispositivo NAVA ya se utilizan en las UCIP de Cataluña, por lo tanto, este estudio clínico no tiene riesgos sobreañadidos por emplear estos dispositivos.

Un riesgo potencial es en relación con la confidencialidad de los datos clínicos del niño/a, que evitaremos tratándolos de acuerdo con la *Ley de Protección de Datos.*

POSIBLES BENEFICIOS DEL ESTUDIO

Este estudio pretende ser una referencia para implementar de manera estándar la colocación del dispositivo NAVA en los pacientes menores de 12 meses con bronquiolitis VRS+ que requieran ventilación no invasiva.

Si usted lo deseara, se le facilitaría un resumen de los resultados del estudio.

INTERRUPCIÓN DEL ESTUDIO

Si durante la realización del ensayo clínico se observara una gran diferencia entre los dos grupos, el estudio se interrumpiría.

CONFIDENCIALIDAD

Si acepta la participación como padre, madre o tutor legal, usted permitiría al investigador registrar algunos datos de su historia clínica, las cuales serán confidenciales. La privacidad del paciente está protegida y recogida en la ***Ley Orgánica 3/2018****, del 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales.*

La información recogida no incluirá ninguna clase de información que permita identificar al niño/a, como nombre, número de historia clínica, ni ninguna información personal, solo la información necesaria para el estudio. Esta información irá vinculada a un código, y este vínculo solo lo conocerá su médico responsable.

Esta información no será accesible por nadie que no sea su médico responsable, y no será difundida de ninguna forma, preservando el anonimato.

En la publicación de los resultados se conserva siempre el anonimato de los pacientes. Además, con el fin de revisar los resultados del estudio, las autoridades sanitarias y organismos regulares podrán acceder a todos los datos. Todas las personas y entidades están sujetas y obligadas a mantener en secreto la identidad del paciente.

COMPENSACIÓN ECONÓMICA

Como se ha expuesto anteriormente, la participación en este estudio es voluntaria. Por lo tanto, si usted decide que el niño/a participe, no recibirá ninguna compensación económica. La participación en el estudio no le supondrá ningún gasto.

CONTACTO

En caso de cualquier duda o pregunta durante la realización de este ensayo clínico, podrá ponerse en contacto con el responsable y coordinador de la investigación:

Médico/a responsable: Dr/Dra _____
Teléfono: _____

6. Annex 6: Consent form (Catalan)

CONSENTIMENT INFORMAT DEL FAMILIAR RESPONSABLE/REPRESENTANT LEGAL

NOM DE L'ESTUDI: Comparació de la taxa d'intubació, en pacients amb bronquiolitis, amb NAVA i ventilació no invasiva versus en pacients amb ventilació no invasiva exclusiva.
Centre assistencial: _____
Investigador/a principal: _____

Jo, _____, amb document d'identificació personal (DNI/NIE) _____, com a pare/mare/tutor legal de _____ afirmo que:

- He rebut una còpia del full d'informació per al pacient.
- He rebut i entès tota la informació que apareix en el document d'informació per al pacient.
- He pogut plantejar qualsevol dubte que m'ha sorgit al responsable de l'estudi, i me l'ha resolt adequadament.
- Estic conforme amb la quantitat d'informació que se m'ha proporcionat.
- Entenc que la participació de l'infant és voluntària i no remunerada.
- Comprenc que puc decidir retirar al pacient de l'estudi en qualsevol moment sense que això repercuteixi al tractament del meu fill/a i sense que se'm demani una explicació al respecte.
- Entenc els potencials riscos i beneficis derivats de participar en aquest estudi.
- Accepto que els investigadors utilitzin les dades de l'infant i accedeixin a la història clínica, sempre respectant l'anonimat i confidencialitat.

I doncs, dono la meva conformitat perquè _____ participi en el present assaig clínic.

Firma del pare/mare/tutor legal: **Firma de l'investigador:**

Nom: _____ Nom: _____
Data: _____ Data: _____

7. Annex 7: Consent form (Spanish)

CONSENTIMIENTO INFORMADO DEL FAMILIAR RESPONSABLE/REPRESENTANTE LEGAL

NOMBRE DEL ESTUDIO: Comparación de la tasa de intubación, en pacientes con bronquiolitis, con NAVA y ventilación no invasiva versus en pacientes con ventilación no invasiva exclusiva.
Centro asistencial: _____
Investigador/a principal: _____

Yo, _____, con documento de identificación personal (DNI/NIE) _____, cómo padre/madre/tutor legal de _____ afirmo que:

- He recibido una copia del documento de información para el paciente.
- He recibido y entendido tota la información que aparece en el documento de información para el paciente.
- He podido preguntar cualquier duda que he tenido al responsable del estudio, y me la ha resuelto adecuadamente.
- Estoy conforme con la cantidad de información que se me ha proporcionado.
- Entiendo que la participación del niño/a es voluntaria y no remunerada.
- Comprendo que puedo decidir retirar al paciente del estudio en cualquier momento sin que esto repercuta a su tratamiento y sin que se me pida una explicación al respeto.
- Entiendo los potenciales riesgos y beneficios derivados de participar en este estudio.
- Acepto que los investigadores usen los datos del niño/a y accedan a la historia clínica, siempre respetando la anonimidad y la confidencialidad.

Presto mi conformidad a que _____ participe en el presente ensayo clínico.

Firma del padre/madre/tutor legal: **Firma del investigador:**

Nombre: _____ Nombre: _____
Fecha: _____ Fecha: _____

8. Annex 8: Case Report Form

CASE REPORT FORM			
Projecte: Comparison of the intubation rate in bronchiolitis patients with NAVA and non-invasive ventilation versus patients with exclusive non-invasive ventilation			
Hospital: ☐ **Hospital Universitari Doctor Josep Trueta** ☐ **Hospital Sant Joan de Déu** ☐ **Hospital Universitari Vall d'Hebron** ☐ **Hospital Universitari Parc Taulí** ☐ **Hospital de la Santa Creu i Sant Pau** ☐ **Hospital Joan XXIII**		**Data recollida de dades:** __/__/____ **Persona que recull les dades**: _____ **Número d'identificació del pacient**: _____	
Data de naixement	__/__/____	**Pes**	(quilograms)
Ètnia	☐ Caucàsic ☐ Africà ☐ Llatinoamericà ☐ Asiàtic ☐ Altre	**Sexe**	☐ Masculí ☐ Femení
Història de prematuritat	☐ Si ☐ No	**Infecció bacteriana durant l'ingrés**	☐ Si ☐ No
Necessitat d'intubació	☐ Si ☐ No	**Dia d'intubació:**	__/__/____
Data d'admissió	__/__/____	**Data d'alta**	__/__/____
Durada de l'ingrés	(dies)		