CONTROVERSIES OF PHARMACOLOGICAL THERAPY OF VIRAL BRONCHIOLITIS

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FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATE AND GRADUATE UNIVERSITY STUDY OF MEDICINE IN ENGLISH

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GRADUATION THESIS

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Thesis mentor: Srđan Banac, MD, PhD, Full Professor

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1. Assistant Professor Kristina Lah Tomulic, MD, PhD (Committee Head)

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The graduation thesis contains 20 pages, 0 figures, 0 tables, 18 references.

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List of abbreviations and acronyms

All the abbreviations for terms used in the thesis should be listed in alphabetical order. The title of the thesis shouldn't contain abbreviations unless their meaning is well-known.

AAP: American Academy of Pediatrics

CPAP: continuous positive airway pressure

HFNC: heated humidified high-flow nasal cannula

IVIG: intravenous immunoglobulin G

RCT: randomized controlled clinical trial

RSV: respiratory syncytial virus

1. Introduction

1.1.Definition of bronchiolitis

Bronchiolitis is a respiratory tract infection, which most commonly affects children under the age of 2 and is the leading cause of hospitalization in this age group. (1) The diagnosis is made according to the clinical picture of respiratory distress. Usually, the infection begins in the upper respiratory tract and continues to become a lower respiratory tract infection. (2) In research settings, bronchiolitis is described as a first episode of wheezing with physical signs of viral lower respiratory tract infection in children under 2 years of age in the absence of another explanation of wheezing. (3) Although in most cases presenting a mild and self-limited disease, a progression to respiratory failure is possible. The severe forms are more likely to be seen in younger children, however, bronchiolitis can affect adults as well. Acute bronchiolitis is generally known to be caused by viruses, primarily by respiratory syncytial virus. Other viral origins are human rhinovirus, coronavirus, human metapneumovirus, adenovirus, parainfluenza virus, influenza and human bocavirus. Rarely, a bacterial infection leads to bronchiolitis, common pathogens being mycoplasma pneumoniae and Bordetella pertussis. (3) Furthermore, there is a chance of two viruses being present at the same time, which occurs in 30% of hospitalized children. (3) Most commonly, the second virus is human metapneumovirus or rhinovirus. (4) Otherwise, bacterial coinfections may appear. In non-severe cases, signs and symptoms peak on the third to fifth days and persist for 7 to 10 days. Usually, an improvement can be observed within 14 to 21 days. In 10% of mild cases, symptoms can be present for four or more weeks. (2)

About 3% of patients are admitted to the hospital and the mortality rate lies between 0,5% and 7%. The range seen in the mortality rate is accounted for by the differences of care in developed and undeveloped countries (5). Despite the low mortality, infants of ages 6 to 12 weeks or those with low birth weight or an underlying disease are facing a higher mortality rate. (2)

1.2.Epidemiology of bronchiolitis

Within the first year of life, bronchiolitis is the leading cause of hospital admittance with 100 000 admitted infants per year. Being a seasonal infection, which peaks once or twice a year, bronchiolitis is most common from October to April in the Western world.

Air pollutants, tobacco smoke, cold and dry air, as well as crowded housing have been shown to increase the rate of transmission and connected to exacerbations. Male gender can also be named as a risk factor. (1)

1.3.Pathophysiology and symptoms of bronchiolitis

The infection usually begins within the upper respiratory tract and starts with a cough, fever and rhinorrhea. As the virus infects the epithelial cells of the respiratory tract, an inflammation leading to ciliary dysfunction and cell death occurs and the main focus of the infection is shifted to the lower respiratory tract. Due to the inflammation, cytokines are released causing edema of the respiratory tract. In combination with dead cells forming a debris, the lung compliance is lowered. This manifests as air trapping, enhanced mucus production, atelectasis, labored breathing and decreased ventilation. Clinically, the named changes can be seen as respiratory distress, ranging from merely tachypnea to nasal flaring, “severe retractions, grunting and cyanosis” (5). Upon auscultation, crackles, wheezing and rhonchi can be heard and a prolongation of the expiratory phase may present itself. (3) Non-pulmonary symptoms may materialize, such as conjunctivitis, pharyngitis or otitis media. (3)

In some countries, including the USA, wheezing is the clinical fundament for the diagnosis, whereas in other countries, for instance the U.K., wheezing does not have to be present to make the diagnosis. (4) Thus, international comparisons are faced with some difficulties.

1.4.Risk factors for bronchiolitis

Justice and Le defined several risk factors for bronchiolitis in their review paper. (5) Namely, those factors are “low birth weight of premature infants, children under the age of 5 months, airway anomalies, congenital immune deficiency disorders, parenteral smoking, crowded

living environment and chronic lung disease, such as bronchopulmonary dysplasia." (2) Other risk factors include living in higher altitudes, having older siblings and attending daycare. (3)

It is also possible to identify factors, which increase the risk of a severe course of infection. Those conditions include prematurity of less than 32 weeks gestational age, children under the age of 3 months, congenital heart disease, chronic lung illness and immunodeficiency. (5)

1.5.Complications of bronchiolitis

Different complications are known to occur, among which are apnea, respiratory failure, (2), aspiration pneumonia (3), nosocomial infections, barotrauma due to ventilation, arrhythmias if beta-agonists are administered, as well as nutritional deficiencies. (5) If mechanical ventilation is necessary, there is an increased likelihood of pneumothorax and pneumomediastinum afterwards. (3)

Children who suffered from bronchiolitis are more prone to recurrent wheezing in the first 10 years of live. (6) Around 30% of previously healthy children are facing this long-term complication, especially those who required hospitalization and decreased forced expiratory volume can be observed in some children over the same period of time. (2) Those episodes can be triggered by viruses and may be treated like asthma.

Connections between asthma and bronchiolitis have been observed as well. Some studies suggest an increased emergence of asthma following bronchiolitis. However, this could also be due to other predisposing factors for asthma, such as genetics or environmental irritants. On the other hand, RSV is a trigger for asthma attacks in children who have been previously diagnosed with asthma. (6)

1.6.Assessing the severity of bronchiolitis

Noting the progression from mild to severe bronchiolitis is difficult because universal criteria are not defined. However, there are some red flags whose presence signifies a severe infection. Those are "persistently increased respiratory effort as assessed during repeated examinations separated by at least 15 minutes, hypoxemia, apnea and acute respiratory failure". (2) If one of these red flags is present, the infection can be classified as severe. Respectively, the nonappearance of all red flags signifies a mild or moderate infection. (2)

1.7.Diagnostic measures

Although bronchiolitis is diagnosed according to the clinical picture, sometimes further diagnostic measures are used. They are however not routinely necessary. Radiography is applied mostly when the symptoms do not improve as well as expected and differential diagnosis have to be excluded. The changes of bronchiolitis seen on X-ray imaging are nonspecific and consist of patchy atelectasis with volume loss, segmental hyperinflation and periobronchial thickening in acute. (3) Laboratory values may be used to judge complications, bacterial coinfections and comorbidities, as well as hint towards differential diagnosis. Those differentials may be "recurrent viral-triggered wheezing or recurrent wheezing, pneumonia, foreign body aspiration, chronic pulmonary disease, aspiration pneumonia, congenital heart disease, heart failure, and vascular ring." (3) Virology is generally not necessary in case of bronchiolitis, unless the virologic findings change the course of treatment. This applies for instance to palivizumab administration or antibiotic therapy. Furthermore, virology proved to decrease the usage of antibiotics in some studies and can decrease transmission in the hospital setting. (3)

2. Aims and objectives

As previously described, acute bronchiolitis is the leading cause for hospitalization in infants and thus puts an enormous strain on healthcare systems worldwide. (1) The aim of this review paper is to catalog all possible treatment options for this disease, to identify their advantages and disadvantages, as well as to assert whether the individual medications should be routinely prescribed to children. For this purpose, in the following part of this paper different treatment options will be discussed. One of the difficulties of bronchiolitis is posed by the lack of fixed definitions of mild and severe forms of the infection. (2)

Even though a bacterial origin of bronchiolitis is possible, the following passages of this paper are referring to a viral infection, unless clarified otherwise.

3. Literature review

3.1.Preventive measures

The only preventive measure to severe RSV infections, are intramuscular palivizumab injections. This humanized monoclonal antibody to RSF F glycoprotein is injected monthly into infants below the age of one during the season. Palivizumab may lead to fever and rashes, and antibodies can develop. (7) The AAP designed risk factors to facilitate choosing which children to grant the prevention to. The factors defined for children under the age of one are gestational age below 29 weeks, symptomatic congenital heart disease, chronic lung disease of prematurity, neuromuscular disorders causing impairment of proper airway cleaning, airway abnormalities and immunodeficiencies. (5) The prevention can be continued throughout the second year of life if children need interventions to treat chronic lung disease of prematurity, undergo a heart transplantation during RSV season, suffer from cystic fibrosis with severe lung disease or are immunosuppressed. (8)

3.2.Treatment options

To determine appropriate measures of treatment, hydration, the level of respiratory distress and the possibility of hypoxia have to be assessed. However, treatment options are rather limited. (5)

3.3.Treatment of mild to moderate symptoms

Should the infection be mild and self-limited, symptoms can be soothed using nasal saline or bulb suctioning in infants, antipyretics and cool-mist humidifiers. The treatment is solemnly supportive and pharmacologic approaches show no benefit. (2) In this case, the child does not require hospital treatment, provided that regular controls by a pediatrician are conducted. The main focus in out-of- hospital treatment lies on sufficient oral hydration, monitoring the body temperature, avoiding smoke exposure and maintaining good hygiene to prevent a spread of infection. (5) Should antipyretics be necessary, the caregivers have to be educated about their proper application. The medications of choice are paracetamol for all children and ibuprofen for those older than 6 months. In children over the age of one, elevating the head can relieve symptoms as well. (6)

The most important point of out-of-hospital treatment is to clarify when hospital treatment should be sought. (5) For that purpose, it is important to beware of "increased rate of breathing worsening chest retractions, nasal flaring, cyanosis, decreased ability to feed, or decreased urine output." (6) Once the child is evidently worsening, emergency care is necessary. (6)

The necessity of hospitalization depends on "the age of the patient, the phase of illness, the presence risk factors, the severity of respiratory distress, the ability to take oral fluids, and social and local circumstances." (4)

If the clinical picture does not improve over a longer period of time, the formerly discussed diagnostic methods may be applied to rule out differential diagnosis. (2)

3.4.Treatment of severe symptoms

Severe forms of bronchiolitis can be suspected when symptoms of acute respiratory distress, hypoxia and dehydration are observed. This can present as grunting, apparent tiring, cessation of breathing or cyanosis. (6) Children depicting the former symptoms are urgently admitted to the hospital and monitored. This occurs in 3% of affected children, most commonly between the ages of 2 to 6 months. (3) Special attention needs to be paid to proper hydration and to ensuring an oxygen saturation of over 90%. The oxygen can be applied via a nasal cannula, mask or an oxygen head box for infants. Otherwise, the discussed supportive therapy to be applied. (5) As in the home setting, precautions to prevent spreading of the virus need to be taken in the hospital as well. (6)

In the event of a progression to respiratory failure, admission to an intensive care unit and commencing mechanical or non-invasive ventilation is advised. The most commonly used non-invasive support is by high-flow nasal cannula. (5) CPAP or high flow oxygen can be applied as well, but endotracheal intubation is preferred in hemodynamically instable children or those with intractable apnea or lack of protective airway reflexes. (2)

Further treatment is based on the individual patient. If oral hydration and calorie intake are difficult, IV or nasogastric applications of fluids and feeding have to be considered.

On average, depending on the source, a child will stay in the hospital for two to four days. After ventilation the time typically spent in the hospital is four to eight days. (6)

3.4.1. Application of heated humidified high-flow nasal cannula

HFNC allows for high inspired gas flows to be combined with increased oxygen concentration. This method is well tolerated due to the humidified air.

With noninvasive ventilation, side effects of endotracheal intubation, such as “laryngeal injury, ventilator-induced lung injury, ventilator-associated pneumonia, narcotic dependence and withdrawal” (2) can be prevented. Observational studies claim that the use of HFNC reduces the need of endotracheal intubation in severe infections. However, clinical trials are yet to prove this observation. HFNC is preferred over CPAP because the length of hospitalization and of the stay in the intensive care unit are shorter and less sedation is needed. Moreover, the risk of adverse effects is lower than with CPAP, which was proven by a meta-analysis. (2)

Complications of this noninvasive ventilation are “abdominal distension, aspiration, barotrauma, and pneumothorax.” (2) The occurrence of the mentioned complications is not more likely than complications of standard oxygen therapy.

There are some contraindications for HFNC application, among which are abnormalities of face or airway, confusion, agitation, vomiting, excessive secretions or bowel obstruction.

Different trials found that the length of hospitalization and oxygen supplementation, as well as the need for intubation and intensive care are not significantly improved by HFNC use. However, a meta-analysis of HFNC use in emergency departments, showed a decrease in treatment failure. (2) Further trials are needed to identify the most effective flow rate, until then the first line application of HFNC does not provide a substantial benefit in treating bronchiolitis. Still, due to the mentioned advantages, it is preferred to endotracheal intubation and should be applied first when ventilation is needed. (2)

3.4.2. Application of contiguous positive airway pressure

CPAP is the second form of noninvasive ventilation but it is used less commonly than HFNC. This disadvantage is present because CPAP causes more severe side effects, such as nasal trauma. Still, CPAP has a positive effect on ventilation, oxygenation and the duration of intensive care. The need of endotracheal intubation is also lowered by CPAP.

Therefore, CPAP can be applied to avoid mechanical ventilation, still, it cannot replace standard oxygen therapy. (2)

3.4.3. Treatment with hypertonic saline

Nebulized hypertonic saline supposedly lessens symptoms of bronchiolitis such as the airway edema and obstruction by increasing the mucociliary clearance. Several RCTs conducted before the year 2007 suggested this positive effect of hypertonic saline on the symptoms of bronchiolitis. More recent trial however, do not depict an advantage of hypertonic saline over regular saline nebulization. (6) Applying nebulizers with hypertonic saline does not soothe the symptoms in mild or moderate infections. (2)

Some guidelines, such as the 2015 National Institute of Health and Care Excellence bronchiolitis guideline do not recommend the administration of nebulized hypertonic saline and demand more studies to proof the effectiveness. (2) Still, due to the low cost and little side effects of hypertonic saline, its use can sometimes be justified. (6), as the 2014 AAP clinical practice guideline agrees. (2)

3.4.4. Treatment with bronchodilators

Bronchodilators are medications that relax the pulmonary muscles to increase the diameter of the bronchi. They can be divided into short and long acting. The three most common types of bronchodilators are beta-2-agonists, anticholinergics and theophylline. The first two types of drugs exist in long and short-acting forms, while the third is only obtainable in its long-acting from. (9)

In theory, bronchodilators could lessen the strain of breathing by widening the airway. However, the main issue seems to be caused by the “mucus plugs, cellular debris and mucosal edema.” (6) Thus, studies have shown little long-term advantage in regularly using inhaled bronchodilators for bronchiolitis. However, children with severe infection or respiratory failure are commonly excluded from those trials. On account of that, further investigations on the effect of bronchodilators on severe infections should be launched in future trials. (2)

The use of anticholinergics, namely epinephrine, can be justified in some cases in an emergency setting. As an alpha adrenoreceptor stimulator, epinephrine leads to

vasoconstriction in the mucosa of the airway. Consequently, the edema of the respiratory tract can be decreased quickly but only for a limited time.

Conclusively, the positive effects of inhaled bronchodilators in the first episode of bronchiolitis are too marginal to justify the danger of adverse effects and the increased cost of treatment. (2) Routine use is therefore not recommended. Epinephrine may be used individually in emergency situations, especially in out-of-hospital scenarios. (6)

3.4.5. Treatment with systemic corticosteroids

Corticosteroids are anti-inflammatory medications which work with immunosuppression, effecting the protein and carbohydrate metabolism, the central nervous system and blood cells via a genomic and nongenomic route. They influence the glucocorticoid receptors to reduce "proinflammatory cytokines, chemokines, cell adhesion molecules". (10) Furthermore, the nongenomic route operates on the interactions of intracellular and membrane-bound glucocorticoid receptors. Thereby an inhibition of phospholipase A2 is achieved. Corticosteroids can be applied per os, parenterally, topically, rectally or in the form of injections and as an inhalation. (10)

The systemic application of corticosteroids in bronchiolitis has no proven effect on "clinical scores, hospital admission rates, length of stay or readmission rates". (6) If they are to be applied, the most effective route is by intramuscular injection given once, but the effect is likewise very small. The idea of averting wheezing episodes after bronchiolitis by introducing systemic corticosteroids in the acute phase, was also shown to be ineffective. Consequently, the use of systemic corticosteroids cannot be recommended in the first episode of bronchiolitis. (2)

3.4.6. Treatment with inhaled corticosteroids

Inhaled corticosteroids exhibit potent glucocorticoid activity and act on a cellular level. They operate by "reversing capillary permeability and lysosomal stabilization to reduce inflammation." (11) They take a few days to unravel their full effect because the dose increases gradually until the effective dose is reached. The advantages of this route of application are that a smaller dose is required to achieve the same effect as in oral use and

decreased side effects due to less systemic bioavailability. Mainly, inhaled corticosteroids are used in asthma treatment. (11)

In bronchiolitis, inhaled corticosteroids are thought to reduce the inflammation within the airway and to lessen wheezing after the infection. Still, studies could not prove those effects of inhaled corticosteroids, even if they were introduced early in the treatment and if their use was continued during recurrent wheezing episodes. Hence, their routine usage in bronchiolitis treatment cannot be recommended. (6)

3.4.7. Treatment with a combination of inhaled corticosteroids and bronchodilators

In the treatment of asthma, inhaled corticosteroids and long-acting bronchodilators are often combined to decrease inflammation and provide an easier airflow through the dilated airway. (12) Following the positive effect this combination has on asthma patients, prescribing them for bronchiolitis is to be considered. An RCT conducted in 2009 on 800 infants suffering from acute bronchiolitis, was performed, focusing on admission to the hospital in the first seven days of the infection. No significant advantage of the administration of epinephrine with dexamethasone was noted which implies that such treatment cannot be routinely recommended in the first episode of bronchiolitis. (6) Furthermore, more information about the long-term effects of this therapy needs to be collected beforehand. (2)

3.4.8. Treatment with leukotriene receptor antagonists

Leukotriene receptor antagonists are primarily used to treat chronic asthma and exercise-induced bronchospasms. They work by binding to cysteinyl leukotriene receptors of leukotrienes D4 and E4. Leukotrienes act on the respiratory system and cause “airway edema, smooth muscle contraction, and impairment of normal cellular activity.” (13) Those inflammatory effects are prevented once the antagonist binds to the leukotriene receptors on the macrophages and smooth muscle cells. (13) The most commonly used leukotriene receptor antagonist is montelukast.

Since large amounts of leukotrienes can be found in the sputum of children with bronchiolitis during and after the infection, several RCTs tried to prove a positive effect of leukotriene receptor antagonist administration. The “Study of montelukast for the treatment of respiratory

symptoms of post-respiratory syncytial virus bronchiolitis in children" is larger one of those trials and was conducted in 2008 by Bisgaard H, Flores-Nunez A, Goh A, et. al. During this trial, hospitalized infants were treated with montelukast for 24 weeks. A significantly positive effect could not be proven by this or other trials, making a recommendation for routine use in bronchiolitis impossible. (6)

3.4.9. Treatment with immunoglobulins

Immunoglobulins are harvested from human plasma and are applied in patients with autoimmune diseases, inflammations or immunodeficiencies. They are commonly administered intravenously, but are also available as subcutaneous or intramuscular preparations.

Administering IVIGs causes side effects in 20-50% of patients. The first dose is commonly tested in a hospital setting and establishing good hydration, a slow rate of infusion and treating bacterial infections prior to the application, minimizes the occurrence of adverse effects. These side effects can present as allergic and inflammatory reactions, volume overload, thrombosis, acute kidney injury and hyponatremia, hemolysis, neutropenia and eczematous dermatitis. In rare cases anaphylaxis can occur. (14)

Intravenous immunoglobulin reduces the viral load in the lung tissue, and stops the RSV from replicating as well as from further developing of the disease in animals. The IVIG discussed is no longer available, however, but could have been considered in immunocompromised children suffering from an RSV infection. (7)

3.4.10. Treatment with monoclonal antibodies

As previously discussed, monoclonal antibodies, namely palivizumab, are commonly used to prevent bronchiolitis in immunocompromised children. Due to the good outcome in that regard, several trials were conducted to examine the effect in all children no matter the risk factors after the infection had already occurred. No significant advantage was found, implying that the routine use of monoclonal antibodies in treatment of bronchiolitis cannot be recommended once the virus exists in the body. (6) To make a recommendation for immunocompromised children with an acute bronchiolitis caused by RSV, more data is

needed. The adverse effects formerly mentioned have to be considered as well to assess the benefit over the risks of administering palivizumab. (7)

3.4.11. Treatment with antibiotics

Acute bronchiolitis most commonly has a viral causative agent, which cannot be treated with antibiotics. However, there are some children at risk for a coinfection of bacterial origin. In these cases, the bacterial component of the infection should be treated as it would without the coexisting bronchiolitis. The highest risk prevails in those with "nosocomial RSV infections, cyanotic congenital heart disease, or [those requiring] intensive care unit admission". (6) Yet, viral bronchiolitis does not pose a higher risk of severe bacterial infection in previously healthy outpatients. (2) The use of different antibiotics has been investigated, including ampicillin, clarithromycin and azithromycin. Even though, the small study called "clarithromycin in the treatment of RSV bronchiolitis: a double-blind, randomized, placebo-controlled trial" published in 2007 by Tahan F, Ozcan A and Koc N, reported a shortening of hospital stays, most other trials contradicted their findings.

Consequently, antibiotics should not be prescribed in bronchiolitis, unless a bacterial infection is present simultaneously. (6)

3.4.12. Treatment with antivirals

When administering antiviral medication in bronchiolitis, the main drug is ribavirin, a broad-spectrum nucleoside analog. Preparations for oral or nebulized use of ribavirin are available. The usage of antivirals may shorten the time of mechanical ventilation, as well as the hospitalization itself and can hinder the occurrence of wheezing episodes after bronchiolitis. Nevertheless, doubts about the efficacy, safety and cost effectiveness have to be taken into consideration. Ribavirin may cause bronchoconstriction and is therefore contraindicated in children with asthma. Other side effects "include hemolytic anemia, leukopenia, cough, dyspnea, bronchospasm, deterioration in pulmonary function, rash, conjunctival irritation, and neuropsychologic symptoms." (7).

Ascribable to the lack of a sufficient number of RCTs, antivirals are not routinely administered to previously healthy children. (6) In immunocompromised patients however, it may be applied as treatment of RSV bronchiolitis. (7)

3.4.13. Treatment with inhaled furosemide

Furosemide is a loop diuretic which prevents reabsorption of water and sodium, thereby promoting their excretion. Usually used to treat edema or ascites in congestive heart failure or liver cirrhosis respectively (15), in its nebulized form it relieves breathlessness in different conditions. (16) The mechanism of action is yet to be identified, but pulmonary stretch receptors sending sensory signals to the brain via the vagus nerve to increase lung expansion, are likely to participate in the mechanism. (16)

Small trials proved the usage to be safe and possible, however, the clinical improvement was regarded to be too little to make a recommendation. (6) A Study conducted in 2018 on healthy men testing the effect of inhaled furosemide on exercise-induced breathlessness showed no significant advantage over inhaling saline. (16) This finding can likely be transferred to children suffering from bronchiolitis.

In conclusion, inhaling furosemide in bronchiolitis cannot be routinely recommended.

3.4.14. Treatment with surfactant

Since secondary surfactant insufficiency can be observed in children who suffer from severe cases of bronchiolitis, applying exogenous surfactant could be considered. (6) Normally, exogenous surfactant is applied in pediatrics to treat respiratory distress syndrome in newborns, where it improves the survival rate greatly. (17)

A meta-analysis conducted in 2006 on 79 patients investigated the influence of exogenous surfactant on mechanically ventilated children suffering from bronchiolitis. Although the time spent in an intensive care unit was decreased by 3.3 days, no other significant improvement was seen. (6) Therefore, not enough evidence could be collected to recommend a routine use of surfactant in mechanically ventilated children with bronchiolitis.

3.4.15. Treatment with heliox

Heliox is a mixture of oxygen and helium, in which helium substitutes nitrogen in the airway. Due to the lower density of helium, the resistance in the lung, as well as the pleural pressure swings and dynamic hyperinflation are decreased and the airflow becomes less turbulent (18). Thereby the static compliance of the lung is increased which eases ventilation (18) and reduces the work of breathing. (6) A meta-analysis from 2010 performed on 84 children with bronchiolitis needing intensive care treatment, evidenced a decrease in respiratory distress. Its effect persisted only for the first hour of treatment and no further advantage of using heliox was seen. This finding is consistent with the fast action of heliox. (18) Another meta-analysis including 560 children, performed in 2022 showed no reduction of CPAP, intubation and duration of hospitalization. (2) Under those circumstances, no recommendation for routine use of heliox in treating bronchiolitis can be made.

3.4.16. Treatment with chest physiotherapy

Chest physiotherapy is commonly applied in children with cystic fibrosis to ease the clearance of respiratory secretions and thereby influence the gas exchange in the lung. (6) Since excessive secretions and mucus plugs can also be found in bronchiolitis, chest physiotherapy was tested in three RCTs and their data analyzed in 2008. Percussion and vibration were the treatment of choice, as well as putting the children in draining positions. However, the systemic review performed afterwards, did not find enough advantages to previously healthy children to recommend routine use of chest physiotherapy in bronchiolitis. (6) Children whose comorbidities impede proper clearing of respiratory secretions, may benefit from chest physiotherapy and should receive it. Among those diseases are neuromuscular disorders and cystic fibrosis. (2)

4. Discussion

Of the treatment options discussed in this review, only few qualify to be used routinely. The treatment of mild to moderate forms of acute viral bronchiolitis in children is merely

supportive. Since only 3% of patients require hospitalization, this outpatient care proves to have a good effect and to successfully prevent progression to severe disease in 97% of patients. (3)

In the developed world, the mortality rate of acute viral bronchiolitis in children is below 0,1%. (2) Consequently, it can be argued that adequate treatment options are available. Most of this success is accounted for by modern ventilation techniques though. Many children experience an improvement with noninvasive ventilation using CPAP or HFNC (2) but if respiratory distress is present despite the application of those methods, endotracheal intubation is performed. Accordingly, the care for children in need of ventilatory assistance is sufficient. In spite of that, options for symptoms needing treatment between supportive care and ventilation are very limited. In the hospital, monitoring of the vital signs, hydration status and respiration can be done more closely than in an outpatient setting, but there are hardly any medications or procedures available to decrease virus replication and progression of the symptoms. (2)

One of the issues of identifying more treatment options is that too little data is available to validate the effects of certain treatment methods. When comparing recommendations published in 2011 to those released in 2022, very little progress can be observed. This implies that in 11 years, the number of trials performed in this field did not suffice to prove the effectiveness of certain medications.

The cause of this may be that performing and interpreting trials is aggravated by the lack of a worldwide agreement on necessary clinical features of bronchiolitis (4) and the lack of an acknowledged categorization of moderate and severe disease. (2) Another problem is that the occurring pathologies often do not respond to treatment which serves the same symptoms in other diseases. An example for this phenomenon is the validated existence of leukotrienes in the sputum of children with bronchiolitis and the missing effect of montelukast on that in acute viral bronchiolitis. (6) Furthermore, new clinical trials ought to include all patient groups with acute viral bronchiolitis to gain broad insight into the possible applications.

In regard to prevention, palivizumab is a good measure to avoid severe infections. (5) This monoclonal antibody does not prevent the infection from occurring altogether. Also, ascribable to its high cost, this prevention is not available to all children under the age of two but only to certain risk groups. Since the risk of acquiring bronchiolitis is connected with kindergarten attendance and in general contact with other children, the main focus of

prevention should lie on hygiene and teaching proper hygienic measures to children and parents. (5)

5. Conclusion

Treating mild to moderate forms of acute viral bronchiolitis in children is accomplished with supportive care in an outpatient setting. Here, the main focus lies on hydration, antipyretics and regular controls by a pediatrician. (5) Regarding severe courses of infection, as formerly discussed, little can be done to prevent a progression to mechanical ventilation, besides more invasive supportive care. CPAP or HFNC are solid alternatives that are less invasive, have less long-term side effects and are more tolerable for the children. (2) Nebulized hypertonic saline does not depict much advantage over regular nebulized saline, but ascribable to its low price and neglectable side effects it can still be applied, even though no recommendation has been made. (6) Bronchodilators and inhaled or systemic corticosteroids, applied in a combination or individually have no significant effect on severe symptoms and should thus not be administered. While increased amounts of leukotrienes can be observed in the lung tissue during a viral bronchiolitis, leukotriene receptor antagonists have too little effect on the outcome to justify their routine use. (6) IVIGs did show some effect on mice, but are no longer available and were not tested on humans. They are also connected to significant side effects. (7) While the monoclonal antibody palivizumab is a good choice for prevention of severe RSV infection in risk groups, it has no effect when it is administered once the infection prevails. Antibiotics should be prescribed when a bacterial coinfection is present, but have no effect on the viral infection. Regarding the use of the antiviral medication ribavirin, too little clinical expertise exists to recommend routine administration. It can however be considered in immunocompromised children with severe infections. (6) Administering inhaled furosemide does not improve the clinical picture of acute viral bronchiolitis. (16) The same can be noted for treatment with exogenous surfactant. Although heliox reduces the work of breathing and eases ventilation, this effect does not positively affect the outcome in the investigated infection. (2) Lastly, chest physiotherapy helps children with neuromuscular diseases or cystic fibrosis to ease the clearance of respiratory secretions, but does not have a significant on influence other children. (6)

Consequently, clinicians are facing great struggles in finding effective treatment methods for severe acute viral bronchiolitis. Some of the discussed treatment options are promising,

however due to lack of clinical evidence they cannot be routinely applied. Therefore, more focus should be put on clinical trials whose outcome to give treatment a new perspective.

6. Summary

Acute bronchiolitis is a seasonal respiratory tract infection which is the leading cause of hospitalization of children under the age of two, posing the largest risk to those prematurely born, with congenital cardiopulmonary diseases or immunocompromised. (5) This risk group should receive palivizumab during RSV season to a prevent severe course of disease. (5) Although the symptoms can occasionally origin from a bacterial infection, most commonly their cause is viral, most frequently RSV. (3) The diagnosis is made based on the clinical picture, which consists of first upper and later on lower respiratory tract infection symptoms. 30% of previously healthy children experience recurrent episodes of wheezing throughout the first decade of life. (2) The clinical course of the infection can be mild-moderate or severe. (5) In the former case, supportive outpatient care with fluids, antipyretic medications and nebulized saline is sufficient, as long as the symptoms do not worsen or red flags occur. (6) The later course of infection commonly requires hospitalization to administer equal supportive treatment, oxygen supplementation and close monitoring of the vital signs, fluid balance and respiration. (5) In cases of severe respiratory distress, mechanical ventilation, CPAP or HFNC may be necessary. (2) Many medications have been discussed and considered to treat the first episode of viral bronchiolitis in previously healthy children, but none can be recommended for routine use. In children at risk for severe disease, ribavirin can be considered (7) and chest physiotherapy should be performed if comorbidities impeding clearance of respiratory secretions are present. (2) Antibiotics may be prescribed only if a bacterial coinfection is present. (6)

Key words:

Bronchiolitis, hospitalization, infants, supportive treatment, trials, viral

7. Literature cited

(1) Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. The Lancet [Internet]. 2017 Jan;389(10065):211–24. [accessed March 18, 2023] Available from: https://www.sciencedirect.com/science/article/pii/S0140673616309515

(2) Piedra PA, Stark AR. Bronchiolitis in infants and children: Treatment, outcome, and prevention. In: UpToDate. UpToDate Waltham, MA; 2023. [accessed March 18, 2023] available from: https://www.uptodate.com/contents/bronchiolitis-in-infants-and-children-treatment-outcome-and-prevention?sectionName=Heliox&topicRef=541&anchor=H364307199&source=see_link#H364307199

(3) Piedra PA, Stark AR. Bronchiolitis in infants and children: Clinical features and diagnosis. In: UpToDate. UpToDate Waltham, MA; 2023. [accessed March 19, 2023] available from: https://www.uptodate.com/contents/bronchiolitis-in-infants-and-children-clinical-features-and-diagnosis?sectionName=Complications&topicRef=6020&anchor=H536690534&source=see_link#H536690534

(4) Eber E. Treatment of Acute Viral Bronchiolitis. The Open Microbiology Journal [Internet]. 2011 Dec 30 5(1):159–64. [accessed March 20,2023]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3258671/

(5) Justice NA, Le JK. Bronchiolitis. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. [accessed March 23, 2023] Available from: https://www.ncbi.nlm.nih.gov/books/NBK441959/

(6) Piedra PA, Stark AR. Patient education: Bronchiolitis and RSV in infants and children (Beyond the Basics). In: UpToDate. UpToDate Waltham, MA; 2023. [accessed March 23, 2023] Available from: https://www.uptodate.com/contents/bronchiolitis-and-rsv-in-infants-and-children-beyond-the-basics#H8

(7) Barr FE, Graham BS. Respiratory syncytial virus infection: Treatment. In: UpToDate. UpToDate Waltham, MA; 2023. [accessed March 24, 2023] Available from: https://www.uptodate.com/contents/respiratory-syncytial-virus-infection-treatment?sectionName=Ribavirin&topicRef=6020&anchor=H3129033651&source=see_link#H3129033651

(8) Acheson EE, Acton J, Afolabi T. Palivizumab: Pediatric drug information. In: UpToDate. UpToDate Waltham, MA; 2023. [accessed March 24, 2023] Available

from: https://www.uptodate.com/contents/palivizumab-pediatric-drug-information?topicRef=9849&source=see_link#F205792

(9) NHS. Overview - Bronchodilators [Internet]. NHS. 2019. [accessed March 25, 2023] Available from: https://www.nhs.uk/conditions/bronchodilators/

(10) Hodgens A, Sharman T. Corticosteroids. [Updated 2022 Jul 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. [accessed March 25, 2023] Available from: https://www.ncbi.nlm.nih.gov/books/NBK554612/

(11) Liang TZ, Chao JH. Inhaled Corticosteroids. [Updated 2022 May 15]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan- [accessed March 26, 2023] Available from: https://www.ncbi.nlm.nih.gov/books/NBK470556/

(12) THE CHANGING ROLE OF INHALED CORTICOSTEROIDS IN ASTHMA MANAGEMENT WHAT ARE INHALED CORTICOSTEROIDS? [Internet]. National Heart, Lung, and Blood Institute; 2020 Dec. [accessed March 26, 2023] Available from: https://www.nhlbi.nih.gov/sites/default/files/publications/Inhaled-Corticosteroids.pdf

(13) Wermuth HR, Badri T, Takov V. Montelukast. [Updated 2022 Apr 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. [accessed March 27, 2023] Available from: https://www.ncbi.nlm.nih.gov/books/NBK459301/

(14) Perez EE, Shehata N. Intravenous immune globuline: Adverse effects. In: UpToDate. UpToDate Waltham, MA; 2023. [assessed March 27, 2023] Available from: https://www.uptodate.com/contents/intravenous-immune-globulin-adverse-effects?topicRef=4431&source=see_link#H32

(15) DrugBank. Furosemide [Internet]. go.drugbank.com. 2023. [accessed March 28, 2023] Available from: https://go.drugbank.com/drugs/DB00695

(16) Waskiw-Ford M, Wu A, Mainra A, Marchand N, Alhuzaim A, Bourbeau J, et al. Effect of Inhaled Nebulized Furosemide (40 and 120 mg) on Breathlessness during Exercise in the Presence of External Thoracic Restriction in Healthy Men. Frontiers in Physiology [Internet]. 2018 Feb 12;9. [accessed March 29, 2ß23] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5816054/

(17) Freddi NA, Filho JOP, Fiori HH. Exogenous surfactant therapy in pediatrics. Jornal de Pediatria. 2003 Nov 15;79(8):205–12. [accessed March 29, 2023]

(18) Hallowell R, Hyes MM. Physiology and clinical use of heliox. In: UpToDate. UpToDate Waltham, MA; 2023. [accessed April 1, 2023] Available from: https://www.uptodate.com/contents/physiology-and-clinical-use-of-heliox#H23

8. Curriculum Vitae

Luisa Maria Spannbauer was born in Aschaffenburg in Germany on the 16th of February 1998. From 2004 to 2008, she attended the “Pestalozzi Grundschule” elementary school and continued to the “Friedrich Dessauer-Gymnasium” high school in 2008. She finished highschool in 2016 and enrolled into the Medical Faculty of Rijeka in 2017. Ever since then, she has been living in Rijeka and will graduate from the university in July 2023. Thereafter she would like to begin her residency in the field of neurology.