Accepted April 2013

REVIEW

Acute viral lower respiratory tract infections in paediatric intensive care patients

S.T.H. Bontemps, J.B. van Woensel, A.P. Bos

Emma Children's Hospital/Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Correspondence

S.T.H. Bontemps – e-mail: sthbontemps@hotmail.com

Keywords - **Lower respiratory tract infection, children, paediatric intensive care unit, virus**

Abstract

Acute lower respiratory tract infection (LRTI) is common in children and in up to 15% of hospitalized cases subsequent referral to a paediatric intensive care unit is necessary. Respiratory syncytial virus, parainfluenza viruses, rhinoviruses and newly emerging viruses like human metapneumovirus, human bocavirus and coronaviruses are commonly isolated pathogens from these patients. Developmental aspects of respiratory anatomy and mechanics are of great importance in the pathophysiology of LRTI and explain why children with the condition are more susceptible to respiratory insufficiency compared to adults. Studies on histopathological changes in viral LRTI have identified both direct viral induced cellular damage and immunopathology as playing roles in the development of severe respiratory distress. Molecular diagnostic tools, most importantly real time polymerase chain reaction, have shown that mixed viral infections are common. Clinical relevance is, however, uncertain. Host factors like age, co-morbidity and possibly genetic factors are probably more important in modulating disease severity. Treatment is limited to supportive measures. Consensus regarding the optimal mode of invasive ventilatory support is lacking. A shift from invasive ventilatory support to non-invasive ventilation is occurring. Ribavirin, corticosteroids, immunoglobulines and bronchodilators are ineffective in treating viral LRTI. Antibiotics are prescribed commonly, but their effect has not been demonstrated in prospective randomised trials and a bacterial pathogen is only found in half the cases. Surfactant and small interfering RNAs may be promising treatment options in the future. Prospective studies however are needed to demonstrate their effect.

Introduction

Acute lower respiratory tract infection (LRTI) is common in children and is associated with high morbidity and mortality. Pneumonia and bronchiolitis are the most common clinical syndromes of acute LRTI in children, however, specific definitions are lacking. In particular, in infants and young children signs and symptoms of pneumonia and bronchiolitis overlap to a great extent. Therefore, many studies use the term acute lower respiratory tract infection, making no differentiation between pneumonia and bronchiolitis. LRTI in infants and children may be severe and necessitate admission to a paediatric intensive care unit (PICU). This paper will give an up-to-date review on epidemiology, pathophysiology and treatment options of acute life-threatening viral LRTI in children. The aim is to provide health care workers who are less familiar with treating severely ill children with more insight into this condition.

Epidemiology

LRTI accounts for about 20% of all paediatric hospitalizations in the US; of them up to 15% are admitted to a PICU.[1] LRTI is one of the most frequent reasons for mechanical ventilator support in the PICU. In children under the age of 1 year, viral bronchiolitis is the predominant cause (44%), after the first year pneumonia becomes more important (25%).[2] In the first year of life, hospital admission due to LRTI is predominantly caused by viral bronchiolitis. Hospital admittance rates for viral bronchiolitis are approximately 20-30 per 1000 for children younger than 1 year in the US and Europe.[3] Up to 10% of these patients may need PICU admission for supportive treatment and monitoring.[4]

Causative agents

In up to two-thirds children aged 6 months to 15 years, LRTI is caused by a virus.[5] At least 26 different viruses have been described with respiratory syncytial virus (RSV), parainfluenza viruses and rhinoviruses as the most common agents.[5] In children under the age of 1 month, adenovirus (10%) and herpes simplex virus (5.5%) are also important pathogens. In addition, adenoviruses may also lead to severe, life-threatening pneumonia in both older children and adults.[6,7] Especially serotypes 3, 7, and 14 are capable of inducing severe necrotising

pneumonia.[8] Among the more recently discovered viruses, human metapneumovirus (2001), human bocavirus (2005) and coronaviruses are recognised as a frequent cause of LRTI in children.[5,8,9] Finally, influenza A or B viruses mainly cause pneumonia in children under 2 years of age. The importance of viruses as a cause of life-threatening LRTI was emphasised by the emergence of severe acute respiratory syndrome (SARS) in 2002, avian Influenza A (H5N1) in 2003 and pandemic Influenza A (H1N1) in 2009.

Differences between children and adults

Several developmental factors contribute to the relatively high susceptibility of infants for developing respiratory insufficiency over the course of a LRTI.

In the first place, developmental aspects leading to differences in pulmonary anatomy are of interest. Children have fewer alveoli and far less alveolar surface area compared to adults. The number of alveoli grows from 20 million at birth to 300 million at the age of 8 years. Simultaneously, alveolar surface area increases from 2.8 m^2 to 32 m^2. In adulthood alveolar surface comprises 75 m^2. Collateral ventilation channels are not developed in the first years of life, allowing no ventilation distal to an obstructed airway. Interalveolar channels (pores of Krohn) appear at 1 to 2 years of age and bronchiole-alveolar channels (canals of Lambert) at 6 years. Therefore, young children are more at risk of developing atelectasis and consequently ventilation-perfusion mismatch.

Secondly, lung mechanics are different in children. Children have reduced elastic recoil of their alveoli. More importantly the chest wall of an infant is more compliant and the ribs are aligned more horizontally compared to adults. This hampers the generation of negative intra-pleural pressure in cases of imminent respiratory distress. In contrast to the chest wall compliance, lung compliance is reduced in infants, leading to a greater tendency of the lung to collapse in the setting of respiratory disease.

Thirdly, children have significantly narrower airways compared to adults. Considering Poiseuille's law, we can imagine how resistance to airflow can rise dramatically with only a minor decrease in diameter.

Fourthly, because of relatively weak cartilaginous support of the airways, forced expiration and subsequent rise in intra-pleural pressure may easily cause dynamic compression and airway obstruction. Finally, infants are more at risk of serious respiratory infections compared to adults because their immune system is still immature. As the child grows so the lungs mature. Compliance of the lungs increases by 150% during the first year of life and after the age of 6 years lung recoil increases as well. Progressive ossification of the rib cage and growing intercostal muscle tone decrease the compliance of the chest wall. By the age of 10 years the ribs are oriented downward.

Pathology and pathophysiology

Several biological processes occur during viral infection of the lung. Viuff et al. found widespread apoptosis in respiratory epithelial cells in bovine RSV infected calves.[10] In addition, a marked neutrophil infiltration was noted contributing to the obstruction of airways and alveolar filling. These findings suggest the importance of both direct viral induced cellular damage, mainly by apoptosis, as well as immunopathology in the development of severe respiratory distress during viral LRTI.[10-12] Apoptosis and inflammation are probably important mechanisms in the clearance of viral pathogens but when out of balance may also lead to bystander injury and as such contribute to the injurious effects in the lung. It has been shown that severe clinical signs and pathological changes continue even after clearance of the virus.[10] The abundant neutrophil influx as seen during RSV LRTI probably plays a key role in the development of acute respiratory distress syndrome (ARDS) in many children with severe RSV. A characteristic feature of RSV LRTI is the obstruction of small airways and air-trapping by plugs of mucus, fibrin and debris of leucocytes and dead epithelial cells. Because children have small airways, this can already cause hypoventilation. Obstruction is further aggravated by oedema and peribronchiolar cellular infiltrates. Severe progressing disease with subsequent alveolar and interstitial involvement is characterised by infection and cell death of alveolar epithelial cells and alveolar filling. Inflammatory infiltrates and oedema of alveoli and interstitial tissues cause severe difficulties in gas exchange and may present clinically as ARDS.[11,13]

Clinical patterns

Both pneumonia and bronchiolitis can cause severe respiratory distress. Bronchiolitis occurs mainly in young children under the age of 1 year and is associated with widespread crackles, wheezing and hyperinflation.[3] Pneumonia may also occur in older children and may be associated with consolidation, infiltration or pleural effusion.[14] Initial signs of LRTI usually include cough, fever and poor feeding. Because of the compliant chest wall and reduced lung compliance, the work involved in breathing is higher in children compared with adults. Clinically this presents as marked tachypnoea, intercostal retractions, nasal flaring and the use of respiratory accessory muscles. Obstructed narrow airways may cause hyperinflation, wheezing and a prolonged expiratory phase. Some infants will stop breathing from fatigue when facing excessive respiratory demands. RSV is also able to cause significant apnoea not induced by fatigue in which altered sensitivity of laryngeal chemoreceptors may be involved.[15] Despite the increased work of breathing, hypoxemia and hypoventilation may develop. Atelectasis is common and may worsen hypoxemia.

Diagnostics

The aetiology of childhood LRTI is often difficult to establish. Clinical signs and symptoms of viral and bacterial

LRTI highly overlap and the isolation of a causative agent is hampered by the difficulty of collecting lung secretions from the lower respiratory tract. However, sputum induction through the inhalation of hypertonic saline can provide a solution to this problem.[16] Bronchoalveolar lavage (BAL) is an invasive technique that involves endotracheal intubation or bronchoscopy. Therefore, it is more common to obtain material from the upper respiratory tract by nasopharyngeal washes or swabs. It is still controversial whether or not viruses isolated from the upper respiratory tract truly reflect the causative agents involved in lower respiratory disease. In particular, rhinoviruses are notorious within this context. They are found in up to 35% of asymptomatic children and remain detectable for five weeks after infection.[17,18]

Molecular Diagnostic Tools

Traditionally used methods for detecting respiratory viruses include viral culture, immunofluorescense assays and measuring antibodies in paired serum samples. Viral culture is unfit for guiding initial management strategy since it takes days to weeks before the results are known. More importantly, detecting viruses through cultures is not possible for all viruses.[19] Immunofluorescense assays improve patient outcome by shortening hospitalization and reducing antibiotic use.[20] Furthermore, an important financial benefit has been noted.[20,21] Real time polymerase chain reaction (PCR) has proved to surpass other methods for diagnosing viral LRTI. Besides its ability to present results readily, it is possible to detect a much broader range of viral pathogens with this technique.[1,19,22-24] Multiplex PCR assays are very sensitive and specific. Potential benefits lie in the prevention of nosocomial infections, reduction of diagnostic procedures and possibly antibiotic use.[21]

The antibiotic controversy

Differentiating between viral, bacterial or mixed infections on clinical grounds is not usually possible and bacterial co-infection is not uncommon in viral LRTI.[25-28] Furthermore, some patients are suspected of concomitant sepsis. For these reasons the majority (55-95%) of children admitted to the PICU with viral LRTI are still treated with antibiotics. This poses considerable overtreatment because a bacterial pathogen is only isolated in 18-57% of cases.[26-28] A number of studies, performed in an emergency department or paediatric ward, found a reduction in the prescription of antibiotics if the results of fast viral testing by PCR were available. Only one study has been performed in a PICU setting, showing that PCR had no impact on antibiotic use in children ventilated for LRTI.[29] Physicians seem more reluctant to withhold antibiotics when treating severely ill patients with LRTI. Clinical deterioration may be the result of bacterial superinfection and results of bacterial cultures are usually not available on admission. It has been shown that mechanically ventilated patients with RSV LRTI with a positive culture of blood or endotracheal aspirate require prolonged ventilator support, suggesting that in some infants bacterial superinfection contributes to the development of respiratory failure.[27,30] Unrecognised bacterial co-infection may aggravate the clinical course, especially in patients with underlying diseases. In contrast, it is unlikely that all patients needing PICU admission will benefit from antibiotics. Prospective randomized trials are needed to show whether patients with viral LRTI admitted to the PICU benefit from treatment with antibiotics. Performing a BAL on admission may help in guiding antibiotic treatment, as previously shown by Bonten et al. in adult ICU patients.[31]

Mixed infections

Most children suffering from viral respiratory disease only have mild symptoms. Determining why a small subgroup of children will develop a severe, life-threatening syndrome poses an intriguing scientific question. PCR has shown that viral co-infections in paediatric LRTI occur in up to 35% of cases.[17,22,32,33] The clinical relevance of the detection of multiple viruses, however, is uncertain and there is much controversy on this point.[19,32-35] A cumulative pathogenic effect may result in more severe disease during co-infections. Viral load in children with RSV and hMPV infections has indeed been associated with disease severity.[36,37,38] Alternatively, there are reports that rhinovirus mediates triggering of interferon stimulated genes inducing an antiviral state, thereby protecting the child from a severe course of disease after infection with a second virus.[17] Clearly, a major role of multiple infections in the determination of disease severity has not been demonstrated.

Host factors

Host factors are likely to be of greater importance in determining disease severity. Well known risk groups for severe disease include young infants under the age of 3 months, premature infants and those with an underlying illness such as chronic lung disease, congenital heart disease, neurological disease or immunodeficiency.[3,11] In addition, genetic factors may be of importance. Polymorphisms in genes encoding for TLR4, chemokine receptors and interleukins and surfactant proteins, all of which may modulate the inflammatory response, have been associated with disease severity in RSV LRTI.[39,40]

Treatment

Antiviral drugs

Ribavirin has broad antiviral activity against both DNA and RNA viruses. There has been much debate on the effectiveness of Ribavirin in infections caused by adenovirus, human metapneumovirus, parainfluenza virus and RSV.[7,41-44] Apparent clinical success is limited to case reports and small series and

as far as we know there have been no prospective randomized controlled trials.[45] Ribavirin is therefore not recommended. Varicella-Zoster or Herpes Simplex LRTI may be treated with Aciclovir. Influenza A and B infections can be treated with neuraminidase inhibitors such as Oseltamivir and Zanamivir. If started within 48 hours after the onset of symptoms, they reduce median time to resolution of symptoms by 0.5-2.5 days.[46] According to WHO guidelines, Oseltamivir is also the drug of choice in the treatment of pandemic influenza A (H1N1) and avian influenza (H5N1).[47,48]

Antibiotics

The British Thoracic Society (BTS) advises considering treating every child with severe LRTI with antibiotics since bacterial and viral LRTI cannot be reliably distinguished from each other.[49] Randomised controlled trials evaluating the effect of antibiotics in mild to moderate RSV LRTI, have shown that antibiotics are not beneficial.[50] However, no such data for children admitted to a PICU are available. Consequently, a reduction in antibiotic use is unlikely until prospective trials have shown whether these patients will benefit from antibiotics. Performing a BAL on admission may be helpful in guiding antibiotic treatment.

Corticosteroids and Intravenous immunoglobulines

Besides cytopathic effects on respiratory epithelial cells, the host cellular immune response contributes to the pathogenesis of RSV LRTI. Therefore, patients may benefit from treatment with immunosuppressive drugs such as corticosteroids or intravenous immunoglobulin. There is abundant evidence, however, that corticosteroids are not effective in the treatment of RSV. In 2010 a Cochrane review found no clinical relevant effect of systemic or inhaled glucocorticoids in the treatment of acute viral bronchiolitis.[51] Furthermore, no beneficial effect of dexamethasone was found in children mechanically ventilated for severe RSV LRTI.[52,53] Although not based on solid scientific data, corticosteroids are not recommended for treatment of coronaviruses (including SARS), seasonal influenza, pandemic H1N1 and avian influenza H5N1.[7,47,48] Intravenous immunoglobulin with a high neutralizing activity against RSV has showed to be ineffective and should not be used.[54]

Surfactant

Damage to pneumocytes and alveolar filling result in reduced synthesis and inactivation of surfactant. Depletion of surfactant may be aggravated by damage to the alveolo-capillary membrane and by mechanical ventilation. Exogenous surfactant therefore, is a potentially promising intervention. A meta-analysis on the treatment of bronchiolitis indeed found a significant reduction in the duration of mechanical ventilation and the length of stay in the PICU.[55] Data on the effects of exogenous surfactant on children with severe viral LRTI are limited. Exogenous surfactant can not, therefore, be recommended as routine treatment but may be used in severe cases.

Bronchodilators

There is no scientific basis for routine use of β2-agonists in viral LRTI. A recent trial could not demonstrate any significant benefit of bronchodilator treatment with β2-agonists or racemic epinephrine in mechanically ventilated patients with RSV-bronchiolitis.[56] In addition, a 2010 cochrane review found no benefit of bronchodilators in the treatment of acute viral bronchiolitis.[57] β2-agonists may be administered on a trial and error basis if lower airway obstruction is clinically apparent, but should be discontinued if no clinical improvement is demonstrated. There is no evidence of effectiveness for epinephrine in the treatment of acute viral bronchiolitis in children under 2 years of age.[58] A combination of epinephrine and dexamethasone was also shown to be ineffective.[58]

Ventilatory support

Ventilatory support may be lifesaving in severe viral LRTI. However, consensus regarding the optimal mode of ventilatory support and ventilation technique in conventional mechanical ventilation is lacking.[11] Data on high frequency oxygenation (HFO) for viral LRTI are limited. Moreover, there are concerns about the risk of air-trapping due to the passive expiration phase. Although a small series described successful use with active expiration, routine use is not recommended.[59] Non-invasive ventilation (NIV) is suggested as a safe and effective method for infants with bronchiolitis.[60] Yet, evidence to define indications and methods of NIV in children is lacking.[61] Retrospective data show that NIV reduces the rate of ventilator associated pneumonia and is associated with a decreased need for invasive respiratory support.[62,63] NIV was successful in 83% of cases overall and 94% if no risk factor was present and resulted in a reduction in length of stay in the PICU. In cases of failure of conventional ventilatory support methods, extracorporeal membrane oxygenation may be used as a rescue therapy.

Future therapy

A promising novel antiviral treatment strategy currently under development is that of small interfering RNAs (siRNA). The majority of RNA within cells is the so called non-coding RNA. It exerts specific and profound functional control on the regulation of protein production and controls the expression of all genes through processes collectively known as RNA interference. Controlling this naturally occurring regulation of protein production has huge therapeutic potential. It regulates gene expression through the silencing of specific messenger RNAs. Methods are under development that allow the degradation of targeted mRNAs with specifically designed

siRNAs. These have been shown to exert potent antiviral effects against RSV, parainfluenza virus, influenza, coronaviruses, measles and hMPV in vitro and in vivo.[64] Clearly, prospective trials are needed to demonstrate clinical benefits before routine use can be recommended.

Conclusion

Acute viral LRTI is a major reason for mechanical ventilatory support in the PICU. Children more than adults are at risk of respiratory insufficiency due to differences in respiratory anatomy and mechanics. Viral agents may cause severe lung damage leading to severe respiratory distress, development of ARDS and a need for mechanical ventilation. This is due to both direct virus induced cellular damage and inflammation of the lower respiratory tract. Mixed infections are common, but clinical significance in determining disease severity is still unclear. Host factors are more likely important modulators of disease severity. A reduction of antibiotic overtreatment is challenging, because bacterial co-infection does not add specific symptoms to the signs already present in viral LRTI, but may aggravate the clinical course. Therapeutic options are mainly supportive. A shift from invasive ventilatory support to NIV has been noted. Future research is needed to expand current limited causative treatment options and determine the role of antibiotics in treating severe, viral LRTI in children.

References

1. Aramburo A, van Schaik S, Louie J, Boston E. Role of real-time reverse transcription polymerase chain reaction for detection of respiratory viruses in critically ill children with respiratory disease: Is it time for a change in algorithm? Pediatr Crit Care Med 2011;12:e160-5
2. Randolph AG, Meert KL, O'Neil ME et al. The feasibility of conducting clinical trials in infants and children with acute respiratory failure. Am J Respir Crit Care 2003;167:1334-40
3. Smyth RL, Openshaw PJM. Bronchiolitis. Lancet 2006;368:312-22
4. Behrendt CE, Decker MD, Burch DJ, Watson PH. International variation in the management of infants hospitalized with respiratory syncytial virus. Eur J Pediatr 1998;57:215-20
5. Honkinen M, Lahti E, Osterback R, Ruuskanen O, Waris M. Viruses and bacteria in sputum samples of children with community-acquired pneumonia. Clin Microbiol Infect 2012;18:300-7
6. Abzug MJ, Beam AC, Gyorkos EA, Levin MJ. Viral pneumonia in the first month of life. Pediatr Infect Dis J 1990;9:881-5
7. Abzug MJ, Levin MJ. Neonatal adenovirus infection: four patients and review of the literature. Pediatrics 1991;87:890-896
8. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet 2011;377:1264-75
9. Jartti T, Hedman K, Jartti L, Ruuskanen O, Allander T, Soderlund-Venermo M. Human bocavirus-the first 5 years. Rev Med Virol. 2012;22:46-64
10. Viuff B, Tjornehoj K, Larsen LE et al. Replication and clearance of respiratory syncytial virus: apoptosis is an important pathway of virus clearance after experimental infection with bovine respiratory syncytial virus. Am J Pathol 2002;161:2195-207
11. Hennus MP, Bem RA, Bos AP, van Vught AJ. Life-threatening respiratory syncytial virus disease in children. Curr Resp Med Rev 2011;7:187-95
12. Welliver TP, Reed JL, Welliver RC Sr. Respiratory syncytial virus and influenza virus infections: observations from tissues of fatal infant cases. Pediatr Infect Dis J 2008;27:s92-6
13. Johnson JE, Gonzales RA, Olson SJ, Wright PF, Graham BS. The histopathology of fatal untreated human respiratory syncytial virus infection. Mod Pathol 2007;20:108-19
14. Langley JM, Bradley JS. Defining pneumonia in critically ill infants and children. Pediatr Crit Care Med 2005;6:S9-13
15. Lindgren C, Jing L, Graham B, Grogaard J, Sundell H. Respiratory syncytial virus infection reinforces reflex apnea in young lambs.Pediatr Res 1992;31:381-5
16. Lahti E, Peltola V, Waris M et al. Induced sputum in the diagnosis of childhood community-acquired pneumonia. Thorax 2009;64:252-7
17. Brand KH, de Groot R, Galama JMD et al. Infection with multiple viruses is not associated with increased disease severity in children with bronchiolitis. Pediatr Pulmonol 2012;47:393-400
18. Jartti T, Lehtinen P, Vuorinen T, Koskenvuo M, Ruuskanen O. Persistence of rhinovirus and enterovirus RNA after acute respiratory illness in children. J Med Virol 2004;72:695-699
19. Lam WY, Yeung AC, Tang JW, Ip M. Rapid multiplex nested PCR for detection of respiratory viruses. J Clin Microbiol 2007;45:3631-40
20. Van de Pol AC, Wolfs TFW, Jansen NJG, van Loon AM, Rossen JWA. Diagnostic value of real-time polymerase chain reaction to detect viruses in young children admitted to the paediatric intensive care unit with lower respiratory tract infection. Crit Care 2006;10:R61-7
21. Barenfanger J, Drake C, Leon N, Mueller T, Troutt T. Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study. J Clin Microbiol 2000;38:2824-8
22. Freymuth F, Vabret A, Cuvillon-Nimal D, Simon S, Dina J, Legrand L, Gouarin S et al. Comparison of multiplex PCR assays and conventional techniques for the diagnostic of respiratory virus infections in children admitted to hospital with an acute respiratory illness. J Med Virol 2006;78:1498-504
23. Kuypers J, Wright N, Ferrenberg J, Huang ML, Cent A, Corey L, Morrow R. Comparison of real-time PCR assays with fluorescent-antibody assays for diagnosis of respiratory virus infections in children. J Clin Microbiol 2006;44:2382-8
24. Weinberg GA, Erdman DD, Edwards KM, Hall CB, Walker FJ, Griffin MR, Schwartz B et al. Superiority of reverse-transcription polymerase chain reaction to conventional viral culture in the diagnosis of acute respiratory tract infections in children. J Infect Dis 2004;189;706-10
25. Duttweiler L, Nadal D, Frey B. Pulmonary and systemic bacterial co-infections in severe RSV-bronchiolitis. Arch Dis Child 2004;89:1155-7
26. H van Woensel JBM, von Rosenstiel IA, Kimpen JLL, Spanjaard L, van Aalderen WCM. Antibiotic use in pediatric intensive care patients with lower respiratory tract infection due to respiratory syncytial virus. Intensive Care Med 2001;27:1436
27. Thorburn K, Harigopal S, Reddy V, Taylor N, van Saene HKF. High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. Thorax 2006;61:611-5
28. Hon KL, Hung E, Tang J et al. Premorbid factors and outcome associated with repiratory virus infections in a pediatric intensive care unit. Pediatr Pulmonol 2008;43:275-80
29. van de Pol AC, Wolfs TF, Tacke CE et al. Impact of PCR for respiratory viruses on antibiotic use: Theory and practice. Pediatr Pulmonol 2010;46:428-34
30. Kneyber MC, Blusse v O-A, Uiterwaal CS, Kimpen JL, van Vught AJ. Concurrent bacterial infection and prolonged mechanical ventilation in infants with respiratory syncytial virus lower respiratory tract disease. Intensive Care Med 2005;31:680-5
31. Bonten MJM, Bergmans CJJ, Stobberingh EE et al. Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use. Am J Respir Crit Care Med 1997;156:1820-4
32. Calvo C, Garcia-Garcia ML, Blanco C et al. Multiple simultaneous viral infections in infants with acute respiratory tract infections in Spain. J Clin Virol 2008;42:268-72
33. Cilla G, Onate E, Perez-Yarza EG, Montes M, Vicente D, Perez-Trallero E. Viruses in community-acquired pneumonia in children less than 3 years old: High rate of viral co-infection. J Med Virol 2008;80:1843-9
34. Richard N, Komurian-Pradel F, Javouhey E et al. The impact of dual viral infection in infants admitted to a pediatric intensive care unit associated with severe bronchiolitis. Pediatr Infect Dis J 2008;27:123-7
35. Marguet C, Lubrano M, Gueudin M et al. In very young infants severity of acute bronchiolitis depends on carried viruses. PLoS One2009;4:e4596
36. Bosis S, Esposito S, Osterhaus AD et al. Association between high nasopharyngeal viral load and disease severity in children with human metapneumovirus infection. J Clin Virol 2008;42:286-90
37. DeVincenzo JP, El Saleeby CM, Bush AJ. Respiratory syncytial virus load predicts disease severity in previously healthy infants. J Infect Dis 2005191;1861-8
38. Houben ML, Counjaerts FE, Rossen JW et al. Disease severity and viral load are are correlated in infants with primary respiratory syncytial virus infection in the community. J Med Virol 2010;82:1266-71

39. Amanatidou V, Apostolakis S, Spandidos DA. Genetic diversity of the host and severe respiratory syncytial virus-induced lower respiratory tract infection. Pediatr Infect Dis 2009;28:135-40

40. Miyairi I, De Vincenzo JP. Human genetic factors and respiratory syncytial disease severity. Clin Microbiol Rev 2008;21:686-703

41. Gavin PJ, Katz BZ. Intravenous Ribavirin treatment for severe adenovirus disease in immunocompromised children. Pediatrics 2002;110:e9

42. Bonney D, Razali H, Turner A, Will A. Succesful treatment of human metapneumovirus pneumonia using combination therapy with intravenous ribavirin and immune globulin. Br J Haematol 2009;145:667-9

43. Elizaga J, Olavarria E, Apperley JF, Goldman JM, Ward KN. Parainfluenza virus 3 infection after stem cell transplant: relevance to outcome of rapid diagnosis and ribavirin treatment. Clin Infect Dis 2001;32:413-8

44. Balfour HH. Antiviral drugs. N Engl J Med 1999:340;1255-67

45. Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. Cochrane Database Syst Rev 2007;CD000181

46. Shun-shin M, Thompson M, Heneghan C, Perara R, Harnden A, Mant D. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. BMJ 2009;339:3172-80

47. Writing committee of the second World Health Organisation consultation on clinical aspects of human infection with avian Influenza A (H5N1) virus. Update on avian Influenza A (H5N1) virus infection in humans. N Engl J Med 2008;358:261-73

48. Sasbon JS, Centeno MA, Garcia MD, Boada MB, Lattini MB, Motto EA, Zuazaga MA. Influenza A(H1N1) infection in children admitted to a pediatric intensive care unit: differences with other respiratory viruses. Pediatr Crit Care Med 2011;12:e136-40

49. British Thoracic Society of Standards of Care Committee. British Thoracic Society guidelines for the management of community acquired pneumonia in childhood. Thorax 2002;57:i1-24

50. Kneyber MC, van Woensel JB, Uijtendaal E, Uijterwaal CS, Kimpen JS. Azithromycin does not improve disease course in hospitalized infants with respiratory syncytial virus(RSV) lower respiratory tract disease: a randomised equivalence trial. Pediatr Pulmonol 2008;43:142-9

51. Fernandes RM, Bialy LM, Vandermeer B et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev 2010;CD004878

52. van Woensel JB, Vyas H. Dexamethasone in children mechanically ventilated for lower respiratory infection caused by respiratory syncytial virus: a randomized controlled trial. Crit Care Med 2011;39:1779-83

53. van Woensel JB, van Aalderen WM, de Weerd W, Jansen NJ, van Gestel JP, Markhorst DG, van Vught AJ et al. Dexamethasone for treatment of patients mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus. Thorax 2003;58:383-7

54. Fuller H, Del Mar C. Immunoglobulin treatment for respiratory syncytial virus infection. Cochrane Database Syst Rev 2006;CD004883

55. Jat KR, Chawla D. Surfactant therapy for bronchiolitis in critically ill infants. Cochrane Database Syst Rev 2012;CD009194

56. Levin DL, Garg A, Hall LJ, Slogic S, Jarvis JD, Leiter JC. A prospective randomized controlled blinded study of three bronchodilators in infants with respiratory syncytial virus bronchiolitis on mechanical ventilation. Pediatr Crit Care Med 2008;9:598-604

57. Gadomski AM, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Rev 2010;CD001266

58. Hartling L, Bialy LM, Vandermeer B et al. Epinephrine for bronchiolitis. Cochrane Database Syst Rev 2011;CD003123

59. Berner ME, Hanquinet S, Rimensberger PC. High frequency oscillatory ventilation for respiratory failure due to RSV bronchiolitis. Intensive Care Med 2008;34:1698-702

60. Mayordomo-Colunga j, Medina A, Rey C et al. Predictive factors of non invasive ventilation failure in critically ill children: a prospective epidemiological study. Intensive care Med 2009;35:527-36

61. Javouhey E, Barats a, Richard N, Stamm D, Floret D. Non-invasive ventilation as primary ventilatory support for infants with severe bronchiolitis. Intensive Care Med 2008;34:1608-14

62. Javouhey E, Barats A, Richard N, Stamm D, Floret D. Non-invasive ventilation as primary ventilatory support for infants with severe bronchiolitis. Intensive Care Med 2008;34:1608-14

63. Ganu SS, Gautam A, Wilkins B, Egan J. Increase in use of non-invasive ventilation for infants with severe bronchiolitis is associated with decline in intubation rates over a decade. Intensive Care Med 2012;38:1177-83

64. Devincenzo JP. The promise, pitfalls and progress of RNA-interference-based antiviral therapy for respiratory viruses. Antiviral Therapy 2012;17:213-25.