Journal of Clinical Virology 59 (2014) 141–147

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Review

Paediatric human metapneumovirus infection: Epidemiology, prevention and therapy

Nicola Principi, Susanna Esposito*

Pediatric High Intensity Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

ARTICLE INFO

Article history:
Received 19 November 2013
Received in revised form
27 December 2013
Accepted 5 January 2014

Keywords:
Antiviral therapy
Human metapneumovirus
Monoclonal antibodies
Respiratory infection
Respiratory viruses
Vaccines

ABSTRACT

Since its discovery in 2001, human metapneumovirus (hMPV) has been identified as one of the most frequent causes of upper and lower respiratory tract infections. Although a considerable number of hMPV infections are diagnosed in adults and the elderly, the highest incidence of infection is among children as seropositivity for hMPV approaches 100% by 5–10 years of age. Most of the diseases due to hMPV are mild or moderate, tend to resolve spontaneously, and only require outpatient treatment. However, some may be severe enough to require hospitalisation or, albeit rarely, admission to a paediatric intensive care unit because of acute respiratory failure. Mortality is exceptional, but may occur. The most severe diseases generally affect younger patients, prematurely born children, and children who acquire nosocomial hMPV infection and those with a severe chronic underlying disease. Global hMPV infection has a major impact on national health systems, which is why various attempts have recently been made to introduce effective preventive and therapeutic measures; however, although some are already in the phase of development (including vaccines and monoclonal antibodies), there is currently no substantial possibility of prevention and, despite its limitations, ribavirin is still the only possible treatment. Given the risk of severe disease in various groups of high-risk children and the frequency of infection in the otherwise healthy paediatric population, there is an urgent need for further research aimed at developing effective preventive and therapeutic measures against hMPV.

Contents

* Corresponding author at: Pediatric High Intensity Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy. Tel.: +39 02 55032498; fax: +39 02 50320206.
E-mail address: susanna.esposito@unimi.it (S. Esposito).

1386-6532/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jcv.2014.01.003

1. Introduction

Since its discovery in 2001 [1], human metapneumovirus (hMPV) has been identified as one of the most frequent causes of upper (URTI) and lower respiratory tract infection (LRTI), with a disease spectrum that is similar to that of respiratory syncytial virus (RSV) [2]. Although a considerable number of hMPV infections are diagnosed in adults and the elderly, the highest incidence of infection is among children [3,4] as seropositivity for hMPV approaches 100% by 5–10 years of age [3]. Most of the diseases due to hMPV are mild or moderate, tend to resolve spontaneously, and only require outpatient treatment. However, some may be severe enough to require hospitalisation or, albeit rarely, admission to a paediatric intensive care unit (ICU) because of acute respiratory failure [4–17]. Mortality is exceptional and may occur in 5–10% of hMPV-positive children admitted to the ICU [4–17]. This means that global hMPV infection has a major impact on national health systems, which is why various attempts have recently been made to introduce effective preventive and therapeutic measures. The main aim of this paper is to review the attempts made to protect and treat humans against hMPV infection, and to discuss which children may benefit most from the availability of more effective measures.

2. Epidemiology of hMPV infection

A recent evaluation of the total burden of hMPV infection in children living in the USA has found that, every year (mainly during the winter), hMPV leads to a number of hospitalisations and outpatient clinic and emergency department visits that is quite similar to that due to influenza viruses [17]. HMPV was detected in 6% of hospitalised children, 7% of those seen in outpatient clinics, and 7% of those examined in emergency departments, with the highest incidence rates being observed among children in the first months of life. Overall, annual rates of hospitalisation associated with hMPV infection were 1 per 1000 children less than 5 years of age, 3 per 1000 infants less than 6 months of age, and 2 per 1000 children 6–11 months of age. Children hospitalised with hMPV infection, as compared with those hospitalised without hMPV infection, were older and more likely to receive a diagnosis of pneumonia or asthma, to require supplemental oxygen, and to have a longer stay in the intensive care unit. The estimated annual burden of outpatient visits associated with hMPV infection was 55 clinic visits and 13 emergency department visits per 1000 children. The majority of hMPV-positive inpatient and outpatient children had no underlying medical conditions, although premature birth and asthma were more frequent among hospitalised children with hMPV infection than among those without hMPV infection. These data show that hMPV infection is associated with a substantial burden of hospitalisations and outpatient visits among children throughout the first 5 years of life and most children with hMPV infection were previously healthy [17]. The finding that the risk of severe hMPV infection is greater in younger subjects was previously reported by Mullins et al. [18] and Papenburg et al. [19]. However, this does not mean that older children are not at risk of developing severe hMPV infection: Spaeder et al. analysed the demographic and clinical data, and associated morbidity and mortality outcomes, of 111 hMPV-infected children admitted to an ICU because of severe respiratory problems [20], and found that 54% were aged <2 years, but as many as 26% were aged ≥5 years. Similarly, Eggleston et al. found that the mean age of 26 children admitted to an ICU because of hMPV infection was 3.43 years, and that 34.6% were aged ≥5 years [21]. Together with a younger age, prematurity and the nosocomial acquisition of viral infection have almost systematically been found to be risk factors for severe hMPV infection associated with acute respiratory failure [17–21].

Table 1
Risk factors for severe paediatric human metapneumovirus infection.

Characteristic	Risk factor
Age	<2 years
Gestational age	<37 weeks
Acquisition of infection	Nosocomial
Underlying disease	Presence of chronic pulmonary disease (including asthma), congenital heart disease, neuromuscular disorders, trisomy 21, or congenital or acquired immunodeficiency

However, the factor most clearly associated with more severe hMPV infection is the presence of an underlying severe chronic disease. Edwards et al. found that 40% of the children hospitalised because of hMPV-related respiratory problems had underlying high-risk conditions, including asthma and chronic lung disease, whereas only 22% of the outpatients with hMPV infection had a chronic clinical problem [17]. Spaeder et al. found that 59% of the paediatric patients admitted to an ICU with laboratory-confirmed hMPV infection showed severe respiratory involvement, with chronic lung and neuromuscular diseases being among the most frequent [20]. In their study, there were 111 patients with laboratory-confirmed hMPV admitted to an ICU: the median hospital length of stay was 7 days (interquartile range 4–18 days) and median ICU length of stay was 4 days (interquartile range 1–10 days). Ten patients (9%) did not survive to discharge. Adjusting for female gender, chronic medical conditions, hospital acquisition of infection and severity of illness score, logistic regression analysis demonstrated that female gender, hospital acquisition of infection, and chronic medical conditions each independently increased the odds of mortality (odds ratios 14.8, 10.7, and 12.7, respectively). Hahn et al. found that 68% of 238 children hospitalised because of hIMPV infection had at least one underlying medical condition, with chronic pulmonary disease, congenital heart disease, neuromuscular disorders and trisomy 21 being the most frequently associated with hMPV-related acute respiratory failure [22]. Immunocompromising clinical problems such as cancer or hematopoietic stem cell transplantation (HSCT) are documented risk factors in adults [23,24] and, although there are few published data concerning children with these conditions, some case reports of fatal or very severe pneumonia in immunocompromised paediatric patients suggest that a significant reduction in the efficiency of the immune system may also be a risk factor for the development of severe hMPV infection during the first years of life [24–26].

A higher viral load can condition the severity of hMPV infection as Bosis et al. found significantly higher hMPV loads in hospitalised children and those with LRTIs than in outpatients with URTIs [27].

Genetic analysis of hMPV isolates has revealed two major groups (A and B) and four minor sub-groups (A1, A2, B1 and B2), mainly based on the sequence variability of the attachment (G) and fusion (F) surface glycoproteins [28]. The existence of two further subgroups, A2a and A2b, has also been suggested [29,30]. Multiple lineages can circulate each year and predominant circulating hMPV lineages vary by year [30]. In several studies, hMPV-F appeared highly conserved, whereas hMPV-G exhibited greater diversity [30,31]. According to some authors, the highly conserved F protein constitutes an antigenic determinant that mediates cross-lineage neutralisation and protection [32], while other studies have reported a difference in reactivity between the two genotypes [33].

In conclusion, the available epidemiological data indicate that hMPV infection is common at all paediatric ages, but is more likely to be severe in younger patients, prematurely born children, children acquiring nosocomial hMPV infection, and those with severe chronic underlying diseases (Table 1). These are therefore the subjects that may receive the greatest benefit from effective preventive and therapeutic measures although, given the