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Mini-review

Human metapneumovirus infections in hematopoietic cell transplant recipients and hematologic malignancy patients: A systematic review

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ABSTRACT

Over the past decade, reported incidence of human metapneumovirus (hMPV) has increased owing to the use of molecular assays for diagnosis of respiratory viral infections in cancer patients. The seasonality of these infections, differences in sampling strategies across institutions, and small sample size of published studies make it difficult to appreciate the true incidence and impact of hMPV infections. In this systematic review, we summarized the published data on hMPV infections in hematopoietic cell transplant recipients and patients with hematologic malignancy, focusing on incidence, hMPV-associated lower respiratory tract infection (LRTI), mortality, prevention, and management with ribavirin and/or intravenous immunoglobulins. Although the incidence of hMPV infections and hMPV-associated LRTI in this patient population is similar to respiratory syncytial virus or parainfluenza virus and despite lack of directed antiviral therapy, the mortality rate remains low unless patients develop LRTI. In the absence of vaccine to prevent hMPV, infection control measures are recommended to reduce its burden in cancer patients.

Introduction

Use of sensitive polymerase chain reaction (PCR) assay has led to increased awareness and identification of human metapneumovirus (hMPV) as a common cause of respiratory viral infection in hematopoietic cell transplant (HCT) recipients and hematologic malignancy (HM) patients.

A recently discovered negative-sense RNA paramyxovirus, hMPV is genetically similar to respiratory syncytial virus (RSV) and it reportedly infects approximately 5%–9% of HCT recipients [1,2]. Progression of upper respiratory tract infection (URTI) to the lower respiratory tract infection (LRTI) occurs in 21%–40% of cases [3], with reported fatality rates of up to 80% in HCT recipients if bronchoalveolar lavage is positive for hMPV [4]. Its presentation is clinically indistinguishable from that of other respiratory viruses, and its growth is unreliable on culture; thus, this viral infection is best diagnosed using PCR-based assays or direct antigen detection. The only drug that has been found to be active against this virus *in vitro* is ribavirin [5,6]; however, there is a dearth of knowledge about this virus and its treatment.

Scattered case reports are available that describe the clinical disease spectrum, management, and overall outcomes of hMPV in cancer patients. Hence, we conducted a systematic review of all published data to summarize the incidence, risk factors, management, long-term outcomes, and associated mortality rates of hMPV infections with a focus on HM patients and HCT recipients. Advances in diagnostic methods, available or new investigational drugs, and vaccines are also discussed. Given the increase in the diagnosis of hMPV infections and the scarcity of available data, this review aims to help clinicians to better understand the implications of this infection in this specific patient population.

Abbreviations: ALL, acute lymphoblastic leukemia; Allo-HCT, allogeneic HCT; AML, acute myeloid leukemia; auto-HCT, autologous HCT; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DFA, direct fluorescent antibody; HCT, hematopoietic cell transplant; HM, hematologic malignancy; hMPV, human metapneumovirus; IF, immunofluorescence; LRTI, lower respiratory tract infection; MDS, myelodysplastic syndrome; MM, multiple myeloma; MMF, mycophenolate mofetil; MMRD, mismatched related donor; MoAb, monoclonal antibody; MRD, matched related donor; MUD, matched unrelated donor; OR, odds ratio; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; RT-PCR, reverse transcriptase polymerase chain reaction; SCID, severe combined immunodeficiency; URTI, upper respiratory tract infection; VLP, virus-like particle.

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Materials and methods

Search strategy and selection criteria

We conducted an electronic literature search using Medline via the Ovid, Embase, Web of Science, and Cochrane library databases in July 2015. The following Medical Subject Heading terms were used: *human metapneumovirus, hematopoietic stem cell transplantation*, *bone marrow transplantation*, *leukemia*, *lymphoma*, *myeloma*, *hematologic malignancy* and *hematologic neoplasms*. The references in all of the selected studies were also reviewed to identify additional articles that did not appear in the initial search. The full texts of the selected articles were reviewed by all the authors. Inclusion and exclusion criteria were defined *a priori*. The following inclusion criteria were used for selecting the articles:

1 HM patients and HCT recipients of any age and had been infected with hMPV,
2 Retrospective or prospective observational studies and randomized controlled trials,
3 No time restriction for the study period,
4 Articles in English.

Exclusion criteria were as follows:

1 Review papers or meta-analyses,
2 Studies with duplicate data or incomplete information.

Case reports and meeting abstracts were included due to limited literature on this topic. We also searched the Clinical Trials registry (U.S. National Institutes of Health, www.clinicaltrials.gov) to identify any registered clinical trials for hMPV infections.

Definitions

Infection episodes and subsequent outcomes were determined by the authors of the original articles using various definitions; however, below are the summarized versions of these definitions used for the current review.

hMPV case: Patients with a positive nasal wash, nasopharyngeal swab, or bronchoalveolar lavage for hMPV by viral diagnostic test were included in this review.
hMPV-LRTI: Was defined as the onset of respiratory symptoms with new or changing pulmonary infiltrates, as seen on chest x-ray or CT scan of chest and/or virus isolated from lower respiratory samples (e.g., endotracheal tube aspirate, sputum, or bronchoalveolar lavage fluid)
hMPV-mortality: Death was attributed to hMPV if a persistent or progressive infection with respiratory failure was identified at the time of death.

Data abstraction

Two authors (D.P.S. and P.K.S.) independently screened the abstracts using the predefined inclusion and exclusion criteria. Four authors (D.P.S., P.K.S., J.M.A., and F.E.C.) used standardized coding rules to abstract important variables from the final list of articles independently and discrepancies were resolved by discussion. Primary variables of interest for this study were incidence of hMPV infection, progression of hMPV-URTI to hMPV-LRTI and hMPV-associated mortality. Antiviral therapy included ribavirin (aerosolized, intravenous, or oral) alone or in combination with intravenous immunoglobulins (IVIGs). The effect of antiviral therapy was measured by comparing incidence rates of these outcomes in treated and untreated patients. Outcome data from selected full-text articles were validated by R.F.C. For studies reporting outcomes in HM patients and HCT recipients, the data abstraction was split into two parts to capture the characteristics and outcomes of each group, respectively.

Statistical analysis

Agreement between the two independent authors in the first and second phase of the full-text selection process was checked by calculating Cohen's Kappa. Outcomes (i.e., LRTI and death) were descriptively summarized as percentages. We compared treated and untreated patient outcomes using Chi-squared or Fisher's exact tests, as appropriate. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs). All statistical analyses were performed using STATA software version 13 (STATA Corp., College Station, TX, USA). A p value of 0.05 was considered significant.

Results

Of the 111 abstracts retrieved for hMPV review (105 by electronic search and 6 by manual search), 93 were specific to hMPV infection in the defined population, hence screened further. Of these, 31 were review studies of respiratory viruses and 12 had overlapping data with an included study or had incomplete information; these were excluded from further review, leaving 50 full-text articles and abstracts (hMPV incidence [17], case reports and data on outcomes [19], diagnostic methods [11], and other studies [3]). Study screening flowchart is shown in Fig. 1. The agreement between the two authors during the selection of abstracts and the selection of full-texts, as measured by Cohen's Kappa, was 0.942 [95% CI: 0.829–0.999] and 0.98 [0.94–0.984], respectively, which is regarded as substantial to excellent.

Clinical presentation and diagnosis

The clinical presentation of hMPV infection is similar to that of other respiratory infections, such as RSV and PIV, ranging from mild URTI to LRTI to progressive respiratory failure and death. Some of the common presenting symptoms of hMPV are fever, cough, nasal congestion, rhinorrhea, headache, sore throat, and dyspnea, along with other prodromal symptoms [4,7–16]. Diagnosing hMPV infections is particularly dependent on the availability of RT-PCR because the viral culture yield is extremely low as a result of the delayed cytopathic effect of hMPV and masking by other concurrent viral infections [12]. Some earlier studies that used direct fluorescence antigen assay or culture reported an almost doubled

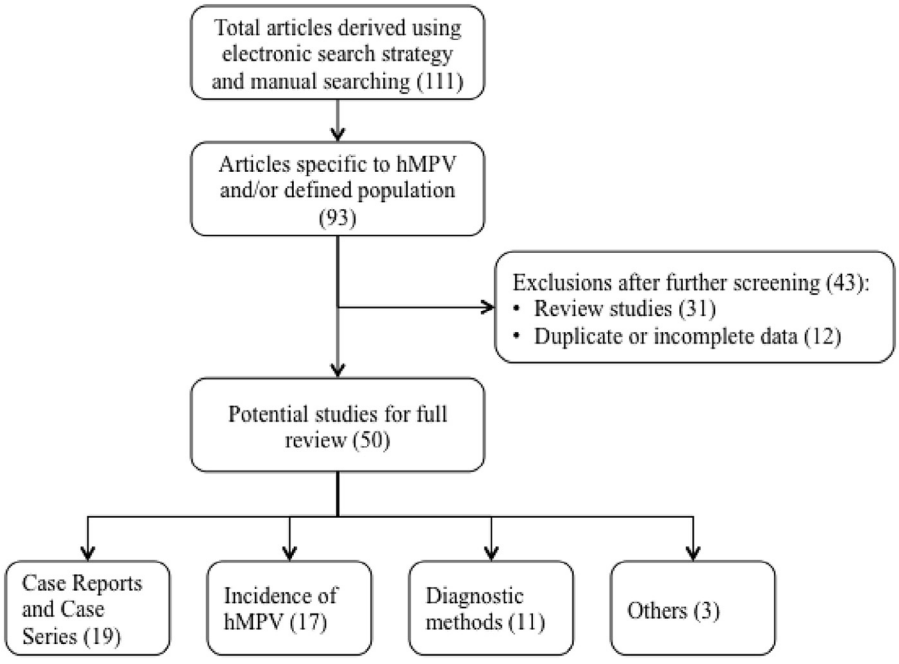

Fig. 1. Flow diagram of study selection of hMPV infections in HM patients and HCT recipients.