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Title: Parainfluenza Virus Infections in Hematopoietic Cell Transplant Recipients and Hematologic Malignancy Patients: A Systematic Review

Dear Dr. Schwab,

Thank you for inviting us to resubmit a revised manuscript. We also want to thank the reviewers for their feedback. The changes made for this revision are described below and the reviewers' comments are addressed point by point. Upon request, we have also uploaded our revised manuscript with and without tracked changes. All the authors have reviewed the final version of the manuscript and agree with this resubmission.

Thank you again for your consideration of our study to be published in your prestigious journal. Please let us know if we can provide further information.

Sincerely,

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Highlights

- First systematic review on PIV infections in HM patients and HCT recipients
- PIV Incidence, risk factors, morbidity, and mortality reviewed from all published studies
- Data on antiviral therapy, ongoing clinical trials and vaccine trials are also examined

Response to Reviewers:

Reviewer 2

In the review, authors have indicated some interesting points and unmet need in clinic at present. However, this review has just focused on a brief and consice style searching and analysis against various hematologic disease and HCT recipients with a simple approach manner. Belows are comments to be considered seriously.

1. HCT as 'hematopoietic cell transplant' or 'hematopoietic stem cell transplant'? Please use the single identifiable term through the whole manuscript.

Response:
We have reviewed the entire manuscript and changed the term '*hematopoietic stem cell transplant'* to '*hematopoietic cell transplant'* throughout the manuscript (Page 1, line 4)

2. In your search strategy for the study, it would be better if you could add multiple myeloma in addition to all at present terms. Because it is very important and frequently developing disease entity of hematologic malignancies related to various fatal immunocompromised infections.

Response:
We ran the search again using the term "multiple myeloma" in addition to the present terms which identified 4 new unique studies. None of these were relevant to this review, hence not included for further analyses. This was reassuring that our original search strategy devised by one of the MD Anderson's expert librarian was comprehensive enough to capture all the relevant articles for hematopoietic cell transplant recipients and patients with hematologic malignancies. We have updated our methods section to reflect the addition of the search by "multiple myeloma" (Page 4, line 6)

3. In line with above notion, please describe what kind of diseases were included in the study. It is quite natural if you define each aspect by discrimination between adults and children/adolescent.

Response:
We reviewed all the studies which reported PIV incidence in patients with hematologic malignancies and have added the following sentence to describe the kind of diseases stratified by children and adult patient population studies. "*Majority of the studies did not provide the breakdown for the type of HM for their study population; however, we observed that the most common HM for children was acute lymphoblastic leukemia (>60%). This information was not available for studies with adult patients*." (Page 7, line 15)

Further, we have also added this as a limitation in the discussion section. "*In addition, the majority of the studies did not report the breakdown for the type of HM for their study population or the details on the type of PIV infection, hence we could not further analyze these variables*" (Page 15, line 15)

4. Please show us about the influences of conditioning regimen intensity, GvHD prophylaxis strategy, and presence or absence of acute/chronic GvHD, esp. in a population of HCT recipients. That's because those parameters are closely related to many critical infections and/or other transplant outcomes in such an immune deteriorated condition. As you already specified in a section 3.2. PIV-LRTI, clinical aspects are very much complicated after allogeneic HCT. Therefore, simple analysis of narrative factors and incidences is not very helpful to precisely understand a real field in clinic.

Response:
We agree with the reviewer about the complex interactions of the underlying risk factors in HCT recipients which increase their susceptibility to severe PIV infections. To illustrate these effects, we have shown the strengths of associations of various risk factors (such as acute and chronic GvHD, reduced intensity conditioning regimen, type of transplant, lymphocytopenia, neutropenia, steroids, and oxygen requirement) and PIV-LRTI or PIV-mortality reported by different articles in figure 1. We have also reported the odds ratio and 95% confidence intervals for these associations in supplemental table 1. Since this review was based on the retrospective studies of heterogeneous population, we could not conduct a meta-regression analyses to identify the independent effects of various host risk factors on the progression to LRTI. We have added the following sentence as a limitation in the discussion section. "*Finally, since this review included a heterogeneous study population, we could not conduct a meta-regression analyses to identify the independent effects of various host risk factors on the progression to LRTI."* (Page 15, line 16)

5. As it is in the review and articles, it should be focused on multiple pathogens at one time, including PIV, RSV, CMV, adeno, HHV etc in these HCT/HM populations. Please show us some more information about those possibilities instead of a single most documented pathogen approach manner.

Response:
The reviews mentioned by the reviewer are brief summaries on the management of various infections in a patient population. They are not detailed systematic reviews which include all the published articles on a particular pathogen as described in this manuscript. We have previously published many systematic reviews on other pathogens such as respiratory syncytial virus in HCT recipients (Shah and Chemaly, Blood, 2012). This is the best suitable approach to have a comprehensive report on a particular infection which could be devastating in immunocompromised patients especially when there is no therapy for it so far.

6. Correct the broken scripts of subtitles in Table 1. Lines should be rearranged in Table 1. No descriptions for each abbreviation used in Table 1.

Response:

Broken scripts of subtitles have been corrected and description for abbreviations added to Table 1. The lines were organized as per the chronological order of the publication year, now they have been rearrange by the age group of the study population (children, adult, any)

Reviewer 4

Major comments:

1. The terms, "PIV infection", "PIV-LRTI", and "PIV-mortality" are not clearly defined in the manuscript.

Response:
We have added the following definitions in the methods section (Page 5)

"PIV infections and subsequent outcomes were ascertained by the authors of the original articles using various definitions; however, below are the summarized versions of these definitions used for the current review.
PIV case: patients with a positive nasal wash, nasopharyngeal swab, or bronchoalveolar lavage for PIV by one of the viral diagnostic tests (viral culture, direct immunofluorescence testing, or PCR) were included in this review.
PIV-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)
PIV-mortality: Death was attributed to PIV if a persistent or progressive infection with respiratory failure was identified at the time of death."

2. The rate of progression from PIV infections to PIV-LRTI was assessed by the authors as described in Table 1. However, not all types of PIV infections are supposed to progress to PIV-LRTI. The authors should make it clear what kind of PIV infections would progress to PIV-LRTI and calculate the progression rate based on this information.

Response:
We agree with the reviewer and reviewed all the studies for this information; however, majority of the studies did not provide the breakdown for the progression to LRTI by the type of PIV infection. Hence, we have added the following sentence as a limitation in the discussion section.
"*In addition, the majority of the studies did not report the breakdown for the type of HM for their study population or the details on the type of PIV infection, hence we could not further analyze these variables*" (Page 15, line 15)

Minor comment:

1. A sentence, such as "Articles in English", should be included in the inclusion criteria selecting the articles in page 4.

Response:

Upon reviewer's recommendation, we have added the term "*Articles in English*" in the inclusion criteria selecting the articles on page 4 and removed the term "*Articles not in English*" from the exclusion criteria on page 5.

The manuscript could be acceptable if all comments would be properly addressed by the authors.

Response:
We hope we have addressed all the comments from the reviewers to their satisfaction. These edits have enhanced its quality and we believe it will be very relevant to the journal's target audience.

Parainfluenza Virus Infections in Hematopoietic Cell Transplant Recipients and Hematologic Malignancy Patients: A Systematic Review

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RUNNING TITLE: PIV infections in cancer patients

WORD COUNT: Abstract: 174 words; Text: ~~3029~~ 3285 words; Tables: 2; Figure: 1; References: 55; supplementary tables: 3; supplementary figures: 1

ABSTRACT

Parainfluenza viral infections are increasingly recognized as common causes of morbidity and mortality in cancer patients, particularly in hematopoietic cell transplant (HCT) recipients and hematologic malignancy (HM) patients because of their immunocompromised status and susceptibility to lower respiratory tract infections. Advances in diagnostic methods, including polymerase chain reaction, have led to increased identification and awareness of these infections. Lack of consensus on clinically significant endpoints, and the small number of patients affected in each cancer institution every year make it difficult to assess the efficacy of new or available antiviral drugs. In this systematic review, we summarized data from all published studies on parainfluenza virus infections in HM patients and HCT recipients, focusing on incidence, risk factors, long-term outcomes, mortality, prevention, and management with available or new investigational agents. Vaccines against these viruses are lacking; thus, infection control measures remain the mainstay for preventing nosocomial spread. A multi-institutional collaborative effort is recommended to standardize and validate clinical endpoints for PIV infections, which will be essential for determining efficacy of future vaccine and antiviral therapies.

KEYWORDS: PIV, stem cell transplant, leukemia, cancer, antiviral therapy, pneumonia

1. INTRODUCTION

Advances in diagnostic methods, including polymerase chain reaction (PCR), have led to increased identification and awareness of paramyxoviruses. Parainfluenza viruses (PIV) are increasingly recognized as common causes of morbidity and mortality in cancer patients, particularly in hematopoietic ~~stem~~ cell transplant (HCT) recipients and hematologic malignancy (HM) patients because of their immunocompromised status. PIV is an enveloped, single-stranded, RNA paramyxovirus; it comprises of four antigens that share serotypes, but most clinical infections are caused by types 1, 2, and 3. A wide range of PIV incidence is reported in HM patients and HCT recipients. PIV type 3 is responsible for up to 90% of infections; it most commonly affects the upper respiratory tract after an incubation period of 1 to 4 days. Clinical manifestations include croup, otitis media, upper respiratory tract infection (URTI), bronchitis, pneumonitis, and less frequently, central nervous system infection. One of the most common complications of PIV URTI is progression to lower respiratory tract infection (LRTI), which occurs in 20% to 39% of HCT recipients and has an associated mortality rate of up to 30%.[1, 2] Whether treating these infections with available (ribavirin) or investigational (DAS 181) antiviral agents affects progression to pneumonitis or mortality remains unknown.

Many conflicting reports exist about the clinical disease spectrum, management, and overall outcomes of PIV infections in HM patients and HCT recipients. Hence, we conducted a systematic review of all published studies to determine the incidence, risk factors, management, long-term outcomes, and mortality rates associated with PIV infections in HM patients and HCT recipients. Advances in diagnostic methods, available or new investigational drugs, and vaccines are also discussed.

2. MATERIALS AND METHODS

2.1 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 ~~May~~ September 2015. The following Medical Subject Heading terms were used: *human parainfluenza virus 1*, *human parainfluenza virus 2*, *human parainfluenza virus 3*, *human parainfluenza virus 4*, *hematopoietic stem cell transplantation*, *bone marrow transplantation*, *leukemia*, *lymphoma*, *multiple myeloma*, 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*.

Inclusion criteria selecting the articles were:

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

Exclusion criteria were:

1. Studies not focusing on PIV infections in HM patients or HCT recipients,
2. Review papers or meta-analyses,
3. Case reports of 10 patients or less

4. Meeting abstracts
5. Studies with duplicate data or incomplete information, and
6. ~~Articles not in English.~~

We also searched the Clinical Trials registry (U.S. National Institutes of Health, www.clinicaltrials.gov) to identify any registered clinical trials for PIV infections.

2.2. Definitions

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

PIV case: patients with a positive nasal wash, nasopharyngeal swab, or bronchoalveolar lavage for PIV by one of the viral diagnostic tests (viral culture, direct immunofluorescence testing, or PCR) were included in this review.

PIV-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)

PIV-mortality: Death was attributed to PIV if a persistent or progressive infection with respiratory failure was identified at the time of death.

2.3. Data abstraction

Two authors (D.P.S. and P.K.S.) independently screened the abstracts using predefined inclusion and exclusion criteria. Three authors (D.P.S., P.K.S. and J.M.A.) 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 PIV infection, progression of PIV-URTI to PIV-LRTI and PIV-associated mortality. Antiviral therapy included ribavirin (aerosolized, intravenous, or oral) alone or in combination with intravenous immunoglobulin (IVIG). 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.

2.~~3~~ 4. 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 progression and death) were descriptively summarized as percentages. We compared treated and untreated patient outcomes using Chi-squared or Fisher exact tests, as appropriate. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs). Forest plot was constructed to demonstrate the significant risk factors associated with acquiring PIV infection, PIV-LRTI and PIV-mortality using adjusted odds ratios from published studies. All statistical analyses were performed using STATA software version 13 (STATA Corp., College Station, TX, USA).

3. RESULTS

We reviewed ~~437~~ 441 abstracts on PIV infections in HM patients or HCT recipients. Of these, ~~270~~ 274 were not specific to PIV infection or the pre-defined population or focus of the study. Of the remaining 167 abstracts, 101 were excluded from further review (49 were review studies on respiratory viruses, 12 were outbreak investigations, 24 were case reports with ≤ 10 patients, and 16 had overlapping data with an included study, had incomplete information, or were meeting abstracts); thus, we included 66 full-text articles. Twenty one studies measured the incidence of respiratory viruses in HM patients or HCT recipients and 11 studies provided primary data for LRTI risk factors and management and mortality, including antiviral therapy effects; thus, data were abstracted for PIV incidence, PIV-LRTI, and associated mortality. Furthermore, we reviewed studies that evaluated new diagnostic methods (9) and investigational new drugs (4); long-term outcomes such as airflow obstruction (6); prophylaxis (2); and pathophysiologic and immunogenetic factors (14). (A detailed flowchart of the abstract screening process is shown in Supplemental Figure S1). The agreement between the two authors during the selection of abstracts and the selection of full-texts, as measured by Cohen's Kappa, was 0.903 [95% CI: 0.862 – 0.945] and 0.926 [0.867 – 0.984], respectively which is regarded as substantial to excellent.

3.1 Incidence of PIV Infections

A total of 32 studies were reviewed, including 2 studies [1, 3] that were divided into two parts to stratify information on HM patients and HCT recipients. Majority of the studies did not provide the breakdown for the type of HM for their study population; however, we observed that the most common HM for children was acute lymphoblastic leukemia (>60%). This information was not available for studies with adult patients.The incidence of PIV infections is displayed in Table 1. We identified 1196 PIV infections in 31,730

patients, giving an incidence of 4%, with a wide range of 0.2% to 30%. The reported incidence of PIV infections in HCT recipients (4% [838 of 21,062]) was significantly higher than that in HM patients (2% [246 of 9,685]) (OR: 1.6; 95% CI: 1.4, 1.8; P value<0.0001). Furthermore, a significantly higher PIV infection rate was reported in allogeneic HCT recipients (5% [482 of 10,147]) than in autologous HCT recipients (3% [206 of 7365]) (OR: 1.73; 95% CI: 1.46, 2.05; P value<0.0001).

The significant risk factors for acquiring PIV infections in HCT recipients and HM patients are displayed in Figure 1. Adults who underwent HCT from a matched unrelated donor or mismatched related donor had a significantly higher risk of PIV infection than did those who underwent matched related or autologous HCT.[4, 5] Similarly, children who underwent allogeneic HCT or total body irradiation were more likely to acquire symptomatic infections, when adjusted for other variables.[6] In children with HM, age less than 2 years (OR: 2.69, 95% CI: 1.5-4.8) and having ALL rather than other malignancies (OR: 4.13, 95% CI: 2.37-7.21) were significant risk factors for PIV infections.[7]

3.2 PIV-LRTI

The incidence of PIV-LRTI in HM patients and HCT recipients, as reported in 28 studies, is shown in Table 1. We identified 428 PIV-LRTI cases among 1163 PIV infections, giving an incidence of 37% for all studies combined (range, 0% to 74%). Stratified by underlying condition, PIV-LRTI was observed in 95 of 246 HM patients (39%) and 299 of 837 HCT recipients (36%) with PIV infections. PIV-LRTI incidence information was not available for different types of HCT.

The risk factors for PIV-LRTI are shown in Figure 1. In brief, allo-HCT,[5, 8] especially infection within 100 days after HCT,[6] lymphocytopenia,[6, 7] neutropenia at the onset of infection,[1, 6, 7] use of corticosteroids during PIV-URTI,[6, 9] and respiratory co-infections[1, 10] were significant predictors of LRTI progression.

3.3 PIV-associated mortality

Twenty six studies reported PIV-associated mortality in HM patients and HCT recipients (Table 1). This rate varied greatly, ranging from 0% to 31%, with a total of 117 PIV-deaths in 1138 PIV infected patients (10%). It was not significantly different in HCT recipients (12% [96 of 826]) than in HM patients (7% [16 of 230]); OR: 1.75; 95% CI: 1.0, 3.3; P value = 0.05). However, significantly higher mortality rate was observed in patients with PIV-LRTI (27% [117 of 428]; OR: 3.3, 95% CI: 2.4, 4.4, P value<0.0001), irrespective of the underlying condition.

PIV-LRTI has been found to be a major risk factor for PIV-associated mortality in both HM patients and HCT recipients, irrespective of age.[5, 6, 10] Other risk factors are displayed in Figure 1 and include lymphocytopenia,[6, 10] younger age,[5] allo-HCT or mismatched related allo-HCT,[5, 8] refractory or relapsed underlying malignancy,[1] APACHE II score > 15,[1] respiratory co-infections,[5] and steroid use at infection onset.[1, 5, 6] (Supplemental Table S1)

3.4 Other outcomes

Late-onset non-infectious pulmonary complications after respiratory infections included diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, bronchiolitis obliterans (BO), and bronchiolitis obliterans with organizing pneumonia. Many studies have implicated respiratory viruses in the development of BO in HCT recipients. One study demonstrated that PIV infection independently

increases the risk of airflow decline, which was immediately detectable after infection in HCT recipients.[11] On the other hand, another study found no association between respiratory viral infection and BO development in HCT recipients.[12] Hence, studies in HCT recipients or HM patients are needed to systematically estimate the incidence of BO after respiratory infections, identify associated risk factors, and test preventive strategies when applicable.

3.5 Diagnosis

Clinically, PIV infections cannot be differentiated from other respiratory viruses in immunocompromised patients; therefore, diagnosis is dependent on laboratory confirmation. Several laboratory methods, such as rapid antigen testing, enzyme immunoassays, real-time PCR, and viral cultures, have been used to diagnose PIV infections.[13-15] A recent study reported that the PCR technique was two and four times as sensitive as culture and fluorescence antigen detection assays, respectively, at detecting respiratory viruses, especially PIV.[16] High-resolution CT of the chest has been reported to aid in diagnosing respiratory viral infections in HCT recipients; however, caution should be exercised in interpreting the results because of the considerable overlap between the imaging appearances of bacterial and viral pneumonia.[17, 18] Similar to most viral pneumonias, PIV-LRTI can range from mild scattered to scattered centrilobular nodules (predominantly in the upper lobes) to patchy ground-glass opacities on high-resolution CT.[19] A lung biopsy may reveal giant-cell pneumonia, intra-cytoplasmic viral inclusions, and interstitial pneumonia, consistent with PIV-LRTI;[8, 20] however, lung biopsies are seldom performed to establish the diagnosis.

3.6 Antiviral therapy

Ten retrospective studies reported the use of antiviral therapy for PIV infections, including 8 in HCT recipients and 2 in HM patients. Most of these studies found that ribavirin was not significantly effective at preventing PIV-LRTI or PIV-associated mortality; however, therapy was mainly administered to patients with LRTI. In fact, the PIV-associated mortality rate was slightly higher in patients treated with ribavirin-based therapy at the LRTI stage (34% [37 of 108]) than in those who were not treated (25% [49 of 193]), which could be explained by a selection bias for treating sicker patients (Table 2). Information on the use of ribavirin at the URTI stage was only available from 6 studies in HCT recipients and HM patients. LRTI progression was not significantly different in HCT recipients who were treated with ribavirin-based therapy at the URTI stage (35% [8 of 23]) and those who were not treated (46% [118 of 256]) (OR: 0.62; 95% CI: 0.22, 1.64; P value=0.296). Similarly, no significant difference in PIV-associated mortality was observed for HCT recipients who were treated at the URTI stage and those who were not treated (0% [0 of 23] versus 11% [28 of 256]; P value=0.094). Among HM patients, only 1 study reported the use of antiviral therapy at the URTI stage; thus, a pooled analysis was not possible. This study did not report any significant reduction in PIV-LRTI or PIV-associated mortality with antiviral therapy at the URTI stage.[1]

3.7 Investigational drugs

Because no commercially available antiviral agent exists for PIV, novel drugs such as DAS181 (a recombinant sialidase fusion protein)[21] and BCX2798 (a hemagglutinin-neuraminidase inhibitor)[22] are being evaluated (Supplemental Table S2). DAS181 enzymatically removes sialic acid moieties to temporarily disable PIV receptors in the airway epithelium.[23] DAS181 has shown efficacy against PIV *in vitro*, in a cotton rat infection model, and in three immunocompromised patients with respiratory infections,

including two HCT recipients.[21, 23, 24] Other compounds, such as BCX2798 and BCX2855, have been found to have antiviral activity against PIV-3, significantly reducing pulmonary viral titers and mortality in rats when given intranasally within 24 hours of infection;[22] however, no human studies are available. Given the significant mortality rate associated with PIV-LRTI in immunocompromised patients, there is an unmet need for managing these infections. Data on the efficacy and cost-benefit of these compounds in this vulnerable population are needed.

Given the significant morbidity and mortality of PIV infections, there has been substantial interest in developing an effective vaccine over the past few years. Many clinical trials (phase I or II studies) are being conducted to test vaccine efficacy against PIV in healthy infants or children (Supplemental Table S3). Interestingly, mucosal immunization has been suggested as a promising alternative vaccination strategy because of recent advances in delivery systems and improved knowledge about site-specific mucosal immune mechanisms.[25] However, the protective potential of active immunizations in immunocompromised patients is usually suboptimal.

In the absence of an effective therapy or vaccine, infection control measures such as contact isolation, hand hygiene, and masks and gloves, along with universal precautions, are the mainstay for preventing the spread of PIV in HCT recipients and HM patients. Viral shedding after infection, especially in asymptomatic patients, may be a key factor in propagating this virus in the immunocompromised population. The results of a recent study suggested that a long duration of viral shedding and “ping-pong” transmission between patients and healthcare personnel or caregivers may be responsible for periodic community-wide and nosocomial outbreaks.[26] Furthermore, asymptomatic or subclinical PIV infections have been well documented in HCT recipients

and HM patients. Thus, subclinical infection, along with prolonged duration of viral shedding, may explain the failure of infection control practices in containing the transmission of this virus, unlike respiratory syncytial virus and influenza.[27]

4. DISCUSSION

In this systematic review, we attempted to assemble all published data on PIV infections in HM patients and HCT recipients to generate meaningful conclusions about their incidence, LRTI and mortality rates, long-term outcomes, management (including antiviral therapy and new investigational drugs), and prevention measures, including vaccines.

We identified high rates of PIV infection in HM patients and HCT recipients. The incidence varied widely, which could be attributed to factors such as patient sampling methods, patient age, transplant and underlying malignancy type, season and study period, publication bias, and diagnostic method used (i.e., RT-PCR vs. direct fluorescence antigen assay vs. culture). Over the past few decades, the number of reported PIV infections increased because of increased awareness and increased availability of fast, inexpensive, reliable diagnostic methods.

Further, we observed high morbidity and mortality rates after these infections with 37% rate of progression to LRTI and 10% virus-associated mortality rates following PIV infections. High mortality rate following progression to LRTI (27%) was observed. Additionally, we observed no differences in LRTI or mortality rates between HM patients and HCT recipients following PIV infections. This finding was not shared by other studies of both populations, in which PIV-LRTI was more common in HM patients than in HCT recipients.[1]

Similar risk factors for PIV-LRTI were consistently identified in many studies, which may help clinicians identify high-risk patients. Lymphocytopenia,[6, 7] neutropenia,[1, 6, 7] and corticosteroid usage[6, 9] were significantly associated with PIV-LRTI; however, we could not abstract primary data for these risk factors to conduct a pooled analysis. Other variables such as age,[7] type of

transplant (allo-HCT vs. auto-HCT)[8], and time from HCT[6] were inconsistently reported as risk factors for PIV-LRTI; however some studies found no such association.[1, 20, 28]

Ribavirin has had promising results against PIV in animal models and children with severe combined immunodeficiency.[29, 30] Large case series have demonstrated that it has no effect on viral shedding, symptom duration, hospital stay duration, PIV-LRTI progression, or mortality in HCT recipients,[1, 2, 20] with the caveat that in most published studies, it was used in patients that had already experienced progression to LRTI. We hypothesized that the time of initiation of ribavirin-based therapy might affect outcomes but based on our pooled analysis of ribavirin used at the URTI stage, it did not affect the LRTI progression or mortality rate significantly. Randomized trials are needed to evaluate ribavirin's effects at the URTI stage to prevent LRTI progression and mortality in this patient population. Although active against PIV *in vitro*,[31] ribavirin's role in treating PIV infections in HCT recipients and HM patients is still not known. In the absence of an effective drug or vaccine, infection control measures remain the mainstay in preventing these infections and any subsequent morbidity and mortality in immunocompromised patients.

There are many limitations of this systematic review. One limitation is that we only reviewed studies published in English; thus, we missed many publications from other countries, especially developing nations. In addition, our reliance on secondary data may be subject to interpretation errors; we tried to minimize this by having three different investigators (D.P.S., P.K.S. and J.M.A.) validate the data; and outcomes were reconfirmed by R.F.C. Most of the studies were retrospective and non-randomized in nature; hence, the results of this systematic review should be interpreted with caution. In addition, the majority of the studies did not report the breakdown for the type of HM for their study population or the details on the type of PIV infection, hence we could not further

analyze these variables. Finally, since this review included a heterogeneous study population, we could not conduct a meta-regression analyses to identify the independent effects of various host risk factors on the progression to LRTI. We attempted to decrease the publication bias by including almost all published studies with minimal exclusion criteria. Another limitation of these studies was the lack of standardized definition for PIV-LRTI. As reported in a recent study in HCT recipients, 90-day survival probabilities were significantly different between possible, probable, and proven LRTI based on univariable regression analysis.[32] We propose a multi-institutional collaborative effort to standardize and validate clinical endpoints for PIV infections, which will be essential for determining efficacy of future vaccine and antiviral therapies.

In summary, to our knowledge, this is the first comprehensive review on PIV infections in HM patients and HCT recipients examining the incidence, risk factors, morbidity, mortality, diagnosis, and management limitations, and the importance of prevention in decreasing nosocomial spread.

ACKNOWLEDGEMENTS

We are grateful to our librarian, Ms. Yimin Geng, The University of Texas MD Anderson Research Medical Library for her assistance with electronic search for this review. We also thank Ms. Ann Sutton, Department of Scientific Publications, The University of Texas MD Anderson Cancer Center, for her editorial support.

AUTHOR CONTRIBUTIONS

D.P.S. and R.F.C. designed the study, D.P.S., P.K.S. screened the abstracts; D.P.S., P.K.S. and J.M.A. extracted data from full text articles, D.P.S and R.F.C. wrote the manuscript and all authors reviewed the full text articles and provided critical feedback and final approval for the manuscript.

FUNDING SUPPORT

This research was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant CA016672.

DECLARATION OF CONFLICTS OF INTEREST

R.F.C received research grant from Ansun pharmaceuticals. All other authors have no conflicts of interest to declare.

Table 1: Incidence of PIV infections, lower respiratory tract infection, and PIV-associated mortality in HCT recipients and HM patients, n (%)

Author	Years of infection	Location	Study population	Age	Surveillance	Diagnosis	PIV incidence	PIV-LRTI	PIV-associated mortality	LRTI related deaths
HCT recipients										
Wasserman, 1988[33]	Jan 1979 - Jul 1986	Philadelphia, PA	96	Children	S	Culture	5 (5)	1 (20)	0	0
Lujan-Zilbermann, 2001[34]	Jan 1994 - Dec 1997	Memphis, TN	274	Children	S	Culture, DFA	17 (6)	7 (41)	1 (6)	1 (14)
Srinivasan, 2011[6]	Jan 1995 - Dec 2009	Memphis, TN	738	Children	S	Culture, DFA, PCR	46 (6)	18 (39)	6 (13)	6 (33)
Fazekas-A, 2012[3]	Nov 2007 - Feb 2009	Vienna, Austria	31	Children	AS	RT-PCR	1 (3)	NA	NA	NA
Lee, 2012[35]	Jan 2007- Aug 2009	Seoul, Korea	176	Children	S	Culture, PCR	1 (0.5)	0	0	0
Choi, 2013[36]	Jan 2007 - Mar 2010	Seoul, Korea	358	Children	S	PCR	22 (6)	8 (36)	1 (5)	1 (13)
Srinivasan-A, 2013[37]	Oct 2010 - Sep 2011	Memphis, TN	42	Children	S	PCR	6 (14)	3 (50)	1 (17)	1 (33)
Lewis, 1996[8]	Jan 1991 - Sep 1994	Houston, TX	1173	Adult	S	Culture, IIF	61 (5)	27 (44)	10 (16)	10 (37)
Whimbey, 1996[38]	Nov 1992 - May 1993; Nov 1993 - May1994	Houston, TX	217	Adult	S	Culture	6 (3)	1 (17)	0	0
Williamson, 1999[39]	Jun 1990 - Jun 1997	Bristol, UK	60	Adult	S	DFA	9 (15)	4 (44)	0	0

Chakrabarti, 2002[2]	Jun 1997 - Aug 2001	Birmingham, UK	83	Adult	S	Culture, DFA	16 (19)	13 (81)	2 (13)	2 (15)
Roghmann, 2003[40]	Jan 2001-Apr 2001	Baltimore, MD	62	Adult	AS	Culture, PCR	5 (8)	0	0	-
Hassan, 2003[41]	May 1996 - May 2001	Manchester, UK	626	Adult	S	Culture, Rapid Ag test	4 (1)	2 (50)	1 (25)	1 (50)
Martino, 2005[42]	Sep 1999 - Oct 2003	Barcelona, Spain	386	Adult	S	IIF, culture	8 (2)	3 (38)	0	0
Dignan, 2006[43]	Jul 2004- Jun 2005	Surrey, UK	145	Adult	AS	Culture, DIF	24 (14)	12 (8)	1 (4)	1 (8)
Schiffer, 2009[44]	Dec1997-Mar2005	Seattle, WA	2,901	Adult	S	Culture, DFA	122 (4)	27 (1)	13 (11)	13 (46)
Chemaly-A, 2012[1]	Oct 2002 - Nov 2007	Houston, TX	3473	Adult	S	DFA, Culture	120 (3)	46 (38)	8 (7)	8 (17)
Ljungman, 1989[45]	Jan 1987-Apr 1987	Seattle, WA	78	Any	AS	Culture, IIF	8 (10)	2 (25)	0 (0)	0
Wendt, 1992[20]	Mar 1974 - Apr 1990	Minneapolis, MN	1253	Any	S	Culture	27 (2)	19 (70)	6 (22)	6 (32)
Elizaga, 2001[28]	Jan 1990 - Sep 1996	London, UK	456	Any	S	Culture, IIF	26 (6)	14 (54)	8 (31)	8 (57)
Nichols, 2001[9]	Jul 1990 - Jun 1999	Seattle, WA	3577	Any	S	Culture, DFA	253 (7)	56 (22)	19 (8)	19 (34)
Ljungman, 2001[46]	Oct 1997 - Sep 1998	37 EBMT centers, Europe	1973	Any	S	Culture, IIF, ELISA	4 (0.2)	1 (25)	0	0
Crippa, 2002[47]	Apr 1995 - Nov 1998	Seattle, WA	305	Any	S	Culture, DFA,	13 (4)	6 (46)	NA	NA
Machado, 2003[48]	Apr 2001 - Apr 2002	Sao Paulo, Brazil	179	Any	S	DFA	12 (7)	0	0	-
Raboni, 2003[49]	Mar 1993 - Aug 1999	Parana, Brazil	722	Any	S	IIF	7 (1)	2 (29)	2 (29)	2 (100)
Peck, 2007[27]	Dec 2000 - Jun	Seattle,	122	Any	AS	Culture,	17	2 (12)	1 (6)	1 (50)

	2004	WA				DFA, PCR	(14)			
Ustun, 2012[5]	Jan 1974 - Dec 2010	Minneapolis, MN	5178	Any	S	Culture	173 (3)	75 (43)	32 (18)	32 (43)
HM patients										
Craft, 1979[50]	1979-1981	UK	64	Children	S	FAT, culture	4 (6)	2 (50)	1 (25)	1 (50)
Mottonen, 1995[51]	Nov 1987 - Dec 1989	Oulu, Finland	62	Children	AS	Culture, EIA, serum antibody (CF)	12 (19)	0	NA	NA
Srinivasan, 2011[7]	Jan 2000 - Dec 2009	Memphis, TN	820	Children	S	Culture, DFA, PCR	83 (10)	17 (20)	0	0
Fazekas-B, 2012[3]	Nov 2007 - Feb 2009	Vienna, Austria	103	Children	AS	PCR	4 (4)	NA	NA	NA
Srinivasan-B, 2013[37]	Oct2010-Sep2011	Memphis, TN	121	Children	S	PCR	16 (13)	1 (6)	0 (0)	0 (0)
Marcolini, 2003[10]	Jul 1994 - Dec 1997	Houston, TX	770	Adult	S	Culture	47 (6)	26 (55)	7 (15)	7 (27)
Chemaly-B, 2012[1]	Oct 2002 - Nov 2007	Houston, TX	7745	Adult	S	DFA, Culture	80 (1)	49 (61)	8 (10)	8 (16)
HCT recipients and HM patients										
Martino, 2003[52]	Oct 1999 - May 2001	Barcelona, Spain	130	Adult	S	DFA, culture	8 (6)	1 (13)	1 (13)	1 (100)
Park, 2013[53]	Jan 2009-Feb 2012	Seoul, Korea	737	Adult	S	PCR, DFA	64 (9)	NA	7 (11)	NA
Chemaly, 2006[54]	Jul 2000 - Jun 2002	Houston, TX	306	Adult	S	Culture, Rapid Ag test	92 (30)	34 (37)	4 (4)	4 (12)

Couch, 1997[55]	1992-1995	Houston, TX	668	Any	S	culture	28 (4)	NA	NA	NA

S indicates symptomatic; AS, asymptomatic; PCR, polymerase chain reaction; DFA, direct fluorescent antibody; IIF, indirect immunofluorescence; FAT, fluorescent antibody technique; EIA, enzyme immunoassay; PIV, parainfluenza virus; LRTI, lower respiratory tract infection; NA, not available.

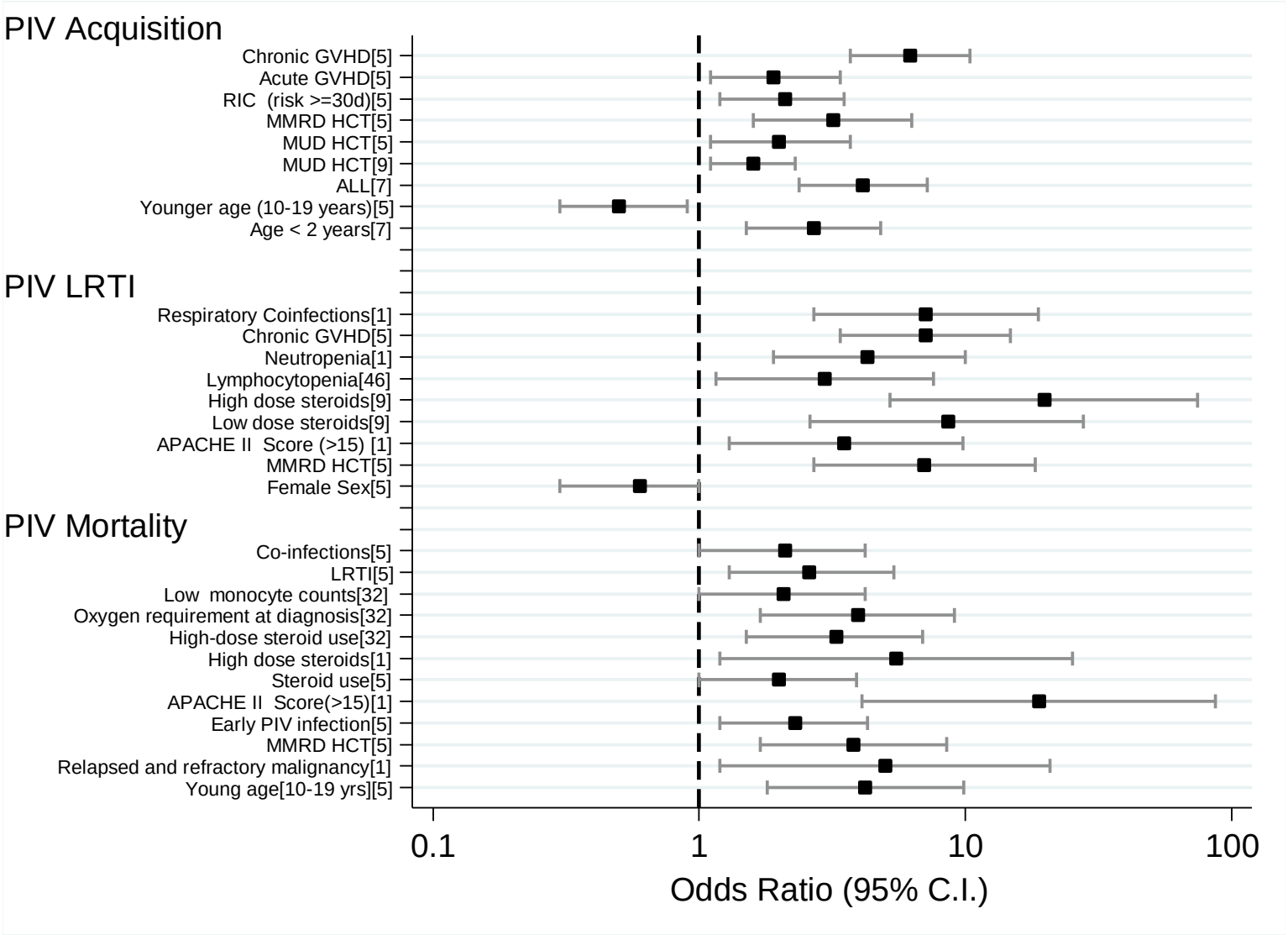
Table 2: Effect of antiviral therapy on PIV-LRTI and PIV mortality in HCT recipients and HM patients, no. (%)

Author, Year	PIV cases	Total treated	Antiviral therapy	Treated, URTI stage			Not treated, URTI stage			Treated, LRTI stage		Not treated, LRTI stage	
				No.	Progression to LRTI	Deaths	No.	Progression to LRTI	Deaths	No.	Deaths	No.	Deaths
HCT recipients													
Chemaly-A, 2012[1]	120	10 (8)	AR ± IVIG	5	3 (60)	0	115	43 (37)	8 (7)	5	1 (20)	38	7 (18)
Chemaly, 2006[54]	92	23 (25)	AR	7	4 (57)	0	85	30 (35)	4 (5)	16	2 (13)	18	2 (11)
Wendt, 1992[20]	27	9 (33)	AR	2	0	0	25	19 (76)	6 (24)	7	2 (29)	12	4 (33)
Chakrabarti, 2002[2]	16	14 (88)	AR or IR	1	0	0	15	13 (87)	2 (13)	13	2 (15)	0	0
Elizaga, 2001[28]	24	18 (75)	AR	8	1 (13)	0	16	13 (81)	8 (50)	10	6 (60)	4	2 (50)
Ustun, 2012[5]	173	51 (29)	AR ± IVIG	10	-	-	163	-	-	41	19 (46)	34	13 (38)
Lujan-Zilberman, 2001[34]	17	3 (18)	AR	0	-	-	17	-	-	3	1 (33)	4	0
Lewis, 1996[8]	61	5 (8)	AR	0	-	-	61	-	-	5	2 (40)	22	8 (36)
Dignan, 2006[43]	23	8 (35)	AR or IR	2	-	0	15	-	1 (6)	6	1 (17)	6	2 (33)
Total	553	141 (25)		35	8 (23)	0	512	118 (23)	28 (5)	106	36 (34)	138	38 (28)
HM patients													
Chemaly-B, 2012[1]	80	9 (11)	AR ± IVIG	6	6 (100)	1 (17)	74	43 (58)	7 (9)	3	1 (33)	40	7 (18)

Marcolini, 2003[10]	47	5 (11)	AR	0	-	-	47	-	-	5	1 (20)	21	6 (29)
Total for all studies combined	680	155 (23)		41	14 (34)	1 (2)	633	161 (25)	35 (6)	114	8 (7)	199	51 (26)

AR, aerosolized ribavirin; IR, intravenous ribavirin; and IVIG, intravenous immunoglobulin.

Figure 1: Risk factors significantly associated with PIV infection, PIV-LRTI and PIV-mortality in HCT recipients and HM patients



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Supplementary Tables

Table S1: Risk factors significantly associated with PIV infection, PIV-LRTI and PIV-mortality in HCT recipients and HM patients

Author, Year	Risk Factors	Odds Ratios (95% CI)	P value
Risk factors for associated with acquisition of PIV-infection			
Ustun[b], 2012[5]	Reduced intensity conditioning regimen (risk ≥30d)	2.1 (1.2- 3.5)	0.01
	MUD HCT	2.0 (1.1 – 3.7)	0.03
	MMRD HCT	3.2 (1.6 – 6.3)	< 0.01
	Younger age (10-19 years)	0.5 (0.3 – 0.9)	0.03
	Acute GVHD	1.9 (1.1 – 3.4)	0.03
	Chronic GVHD	6.2 (3.7 – 10.4)	< 0.01
Srinivasan[b], 2011[6]	Allogeneic HCT	N A	< 0.001
	TBI–based conditioning regimen	N A	< 0.001
Nichols[b], 2001[9]	HCT from unrelated donor compared to autologous HCT	1.6 (1.1 – 2.3)	0.01
Srinivasan[c], 2011[7]	Age < 2 years	2.69 (1.5 – 4.8)	0.002
	ALL	4.13 (2.37 – 7.2)	< 0.001

Risk Factors associated with PIV-LRTI			
Ustun[b], 2012[5]	MMRD HCT	7.0 (2.7 – 18.3)	< 0.01
	Female sex	0.6 (0.3 – 1.0)	0.04
	Chronic GVHD	7.1 (3.4 – 14.8)	< 0.01
Chemaly[a], 2012[1]	Neutropenia (ANC<500 cells/µL)	4.3 (1.9 – 10..0)	< 0.001
	APACHE II score >15	3.5 (1.3 – 9.8)	0.016
	Respiratory co-infections	7.1 (2.7 – 18.8)	< 0.001
Srinivasan[b], 2011[6]	First 100 days post-HCT	N/A	0.006
	Lymphocytopenia (ALC<100 cells/mL)	N/A	<0.001
	Neutropenia (ANC<500 cells/µL)	N/A	<0.001
	Steroid use	N/A	0.035
Nichols[b], 2001[9]	Steroids at the time of URTI diagnosis		
	1 to less than 2mg/kg/day	8.6 (2.6 – 27.8)	0.0003
	At least 2mg/kg/day	19.8 (5.2 – 74.6)	<0.001
Elizaga[b], 2001[28]	No difference between allogeneic HCT versus autologous HCT	N/A	-
Srinivasan[c], 2011[7]	Younger age (27 months vs. 56 months)	N/A	0.005
	Lymphocytopenia (ALC <100 cells/µL)	N/A	0.008

	Fever with severe neutropenia (ANC <500 cells/µL)	N/A	0.02
Schiffer[b] 2009[44]	Lymphocytopenia (ALC<300 cells/mL)	3 (1.2-7.6)	0.02
Risk factors associated with PIV-mortality			
Seo[b],2014[32]	Oxygen requirement at diagnosis	3.96 (1.7–9.1)	.001
	Low monocyte counts (<100 cells/µL)	2.07 (1.0–4.2)	.041
	High-dose steroid use (>2 mg/kg/day)	3.27 (1.5–6.9)	.008
Ustun[b], 2012[5]	LRTI	2.6 (1.3 – 5.4)	< 0.01
	Early PIV infection (<30 days post-HCT)	2.3 (1.2 – 4.3)	< 0.01
	Young age (10 - 19 years)	4.2 (1.8 – 9.9)	< 0.01
	MMRD	3.8 (1.7 – 8.5)	< 0.01
	Co-infections	2.1 (1.0 – 4.2)	0.04
	Steroid use	2.0 (1.0 -3.9)	0.05
Chemaly[a], 2012[1]	Relapsed and refractory malignancy	5.0 (1.2 – 20.8)	0.028
	APACHE II score >15	18.9 (4.1 – 86.9)	< 0.001
	High-dose steroids	5.5 (1.2 – 25.3)	0.028
Srinivasan[b], 2011[6]	African-American ethnicity	N/A	0.013
	LRTI	N/A	0.002

	Steroid use	N/A	< 0.001
	Mechanical ventilation	N/A	< 0.001
	Lymphocytopenia (ALC <100 cells/µL)	N/A	0.01

a HM patients and HCT recipients combined
b HCT recipients only
c HM patients only

NA, not available; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; MUD, matched unrelated donor; MMRD, mismatched related donor; GVHD, graft versus host disease; TBI, total body irradiation; HCT, hematopoietic cell transplant; LRTI, lower respiratory tract infection

Table S2: Randomized, double-blind interventional clinical trials on safety and efficacy of drugs for the treatment of PIV infections (www.clinicaltrials.gov, US National Institutes of Health)

NCT number	Objective	Phase	Intervention model	Intervention	Enrollment	Start date	Status
NCT00876161	Single-dose escalation study in healthy adults	1	Single	DAS181 dry powder inhalant	45	Apr 2009	Completed
NCT00527865	Single-dose escalation study of DAS181 in adults	1	Single	DAS181	36	Oct 2007	Completed
NCT01441024	DAS181 in patients with parainfluenza (adults)	2	Parallel	DAS181	50	Jul 2011	Recruiting
NCT01651494	Influenza antiviral DAS181-F04 in healthy adults	1	Parallel	DAS181	9		Recruiting
NCT01173224	Influenza antiviral DAS181-F03	1	Parallel	DAS181	27	Nov 2010	Recruiting
NCT01644877	DAS181 in immunocompromised patients with PIV infection	2	Parallel	DAS181 dry powder, formulation F02	0	Dec 2012	Withdrawn
NCT00938353	Efficacy of nebulized beclomethasone dipropionate for moderate croup in children	3	Parallel	BDP suspension for nebulization 800 mcg	6	Apr 2010	Terminated

Table S3: Randomized, double-blind interventional clinical trials on safety and efficacy of vaccines for prevention of PIV infections (www.clinicaltrials.gov, US National Institutes of Health)

NCT number	Objective	Phase	Intervention	Intervention model	Enrollment	Start date	Status
NCT00345670	Safety of MEDI-534 vaccine against RSV and PIV-3 in healthy children	1	MEDI-534	Single	120	Jun 2006	Completed
NCT00686075	Safety, tolerability, immunogenicity, and vaccine-like viral shedding of MEDI-534 against RSV and PIV3 in healthy children	1,2	MEDI-534	Parallel	720	Jul 2008	Active, not recruiting
NCT00493285[a]	Safety and tolerability of MEDI-534 in children (6 to < 24 months)	1	MEDI-534	Parallel	49	Jul 2007	Completed
NCT00508651[a]	Safety, immunogenicity, and shedding of MEDI-560 in infants (1 to < 12 months)	1,2	MEDI-560	Parallel	30	Oct 2007	Terminated
NCT01139437	Safety of a live, attenuated PIV-2 vaccine for adults, children, and infants	1	Standard-dose PIV2 vaccine vs. low-dose PIV2 vaccine vs. placebo	Parallel	90	Jun 2010	Recruiting
NCT00641017	Safety of and immune response to recombinant live-attenuated PIV-1 vaccine	1	rPIV1 84/del170/942A, Lot PIV1 #104A vaccine	Parallel	110	Mar 2008	Recruiting
NCT00366782	Safety of and immune response to a cow/human parainfluenza virus vaccine (rb/PIV-3) in healthy infants, children, and adults	1	rB/PIV3	Parallel	51	Mar 2007	Completed
NCT01254175	Safety and immunogenicity of a PIV-3 vaccine in infants and children	1	rPIV3cp45 vaccine	Parallel	28		Active, not recruiting

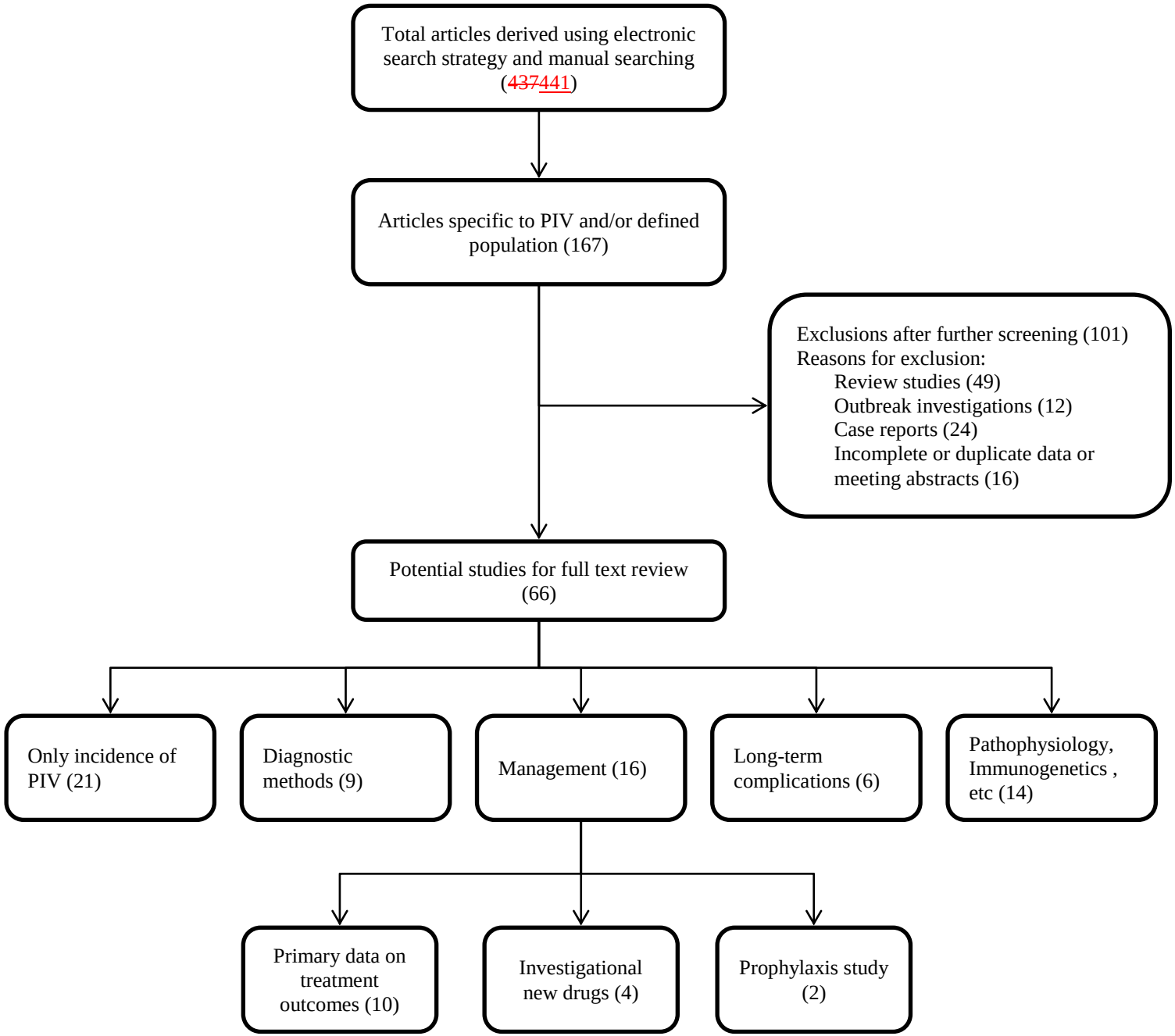
NCT00308412	Safety of and immune response to a PIV vaccine (rPIV3cp45) in healthy infants	1	rPIV3cp45	Parallel	45	Jun 2006	Completed
NCT01021397	Safety of and immune response to recombinant live attenuated PIV-3 vaccine in healthy infants and children	1	rPIV3cp45	Parallel	30	Nov 2009	Completed
NCT00186927[b, c]	Safety of live intranasal Sendai virus vaccine in children and toddlers	1	Sendai virus vaccine	Parallel	30	Mar 2005	Active, not recruiting

a study has results

b open label

c non-randomized

Supplementary Figure S1: Flow diagram of study selection of PIV infections in HM patients and HCT recipients



ABSTRACT

Parainfluenza viral infections are increasingly recognized as common causes of morbidity and mortality in cancer patients, particularly in hematopoietic cell transplant (HCT) recipients and hematologic malignancy (HM) patients because of their immunocompromised status and susceptibility to lower respiratory tract infections. Advances in diagnostic methods, including polymerase chain reaction, have led to increased identification and awareness of these infections. Lack of consensus on clinically significant endpoints, and the small number of patients affected in each cancer institution every year make it difficult to assess the efficacy of new or available antiviral drugs. In this systematic review, we summarized data from all published studies on parainfluenza virus infections in HM patients and HCT recipients, focusing on incidence, risk factors, long-term outcomes, mortality, prevention, and management with available or new investigational agents. Vaccines against these viruses are lacking; thus, infection control measures remain the mainstay for preventing nosocomial spread. A multi-institutional collaborative effort is recommended to standardize and validate clinical endpoints for PIV infections, which will be essential for determining efficacy of future vaccine and antiviral therapies.

DECLARATION OF CONFLICTS OF INTEREST

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Parainfluenza Virus Infections in Hematopoietic Cell Transplant Recipients and Hematologic Malignancy Patients: A Systematic Review

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ABSTRACT

Parainfluenza viral infections are increasingly recognized as common causes of morbidity and mortality in cancer patients, particularly in hematopoietic cell transplant (HCT) recipients and hematologic malignancy (HM) patients because of their immunocompromised status and susceptibility to lower respiratory tract infections. Advances in diagnostic methods, including polymerase chain reaction, have led to increased identification and awareness of these infections. Lack of consensus on clinically significant endpoints, and the small number of patients affected in each cancer institution every year make it difficult to assess the efficacy of new or available antiviral drugs. In this systematic review, we summarized data from all published studies on parainfluenza virus infections in HM patients and HCT recipients, focusing on incidence, risk factors, long-term outcomes, mortality, prevention, and management with available or new investigational agents. Vaccines against these viruses are lacking; thus, infection control measures remain the mainstay for preventing nosocomial spread. A multi-institutional collaborative effort is recommended to standardize and validate clinical endpoints for PIV infections, which will be essential for determining efficacy of future vaccine and antiviral therapies.

KEYWORDS: PIV, stem cell transplant, leukemia, cancer, antiviral therapy, pneumonia

1. INTRODUCTION

Advances in diagnostic methods, including polymerase chain reaction (PCR), have led to increased identification and awareness of paramyxoviruses. Parainfluenza viruses (PIV) are increasingly recognized as common causes of morbidity and mortality in cancer patients, particularly in hematopoietic cell transplant (HCT) recipients and hematologic malignancy (HM) patients because of their immunocompromised status. PIV is an enveloped, single-stranded, RNA paramyxovirus; it comprises of four antigens that share serotypes, but most clinical infections are caused by types 1, 2, and 3. A wide range of PIV incidence is reported in HM patients and HCT recipients. PIV type 3 is responsible for up to 90% of infections; it most commonly affects the upper respiratory tract after an incubation period of 1 to 4 days. Clinical manifestations include croup, otitis media, upper respiratory tract infection (URTI), bronchitis, pneumonitis, and less frequently, central nervous system infection. One of the most common complications of PIV URTI is progression to lower respiratory tract infection (LRTI), which occurs in 20% to 39% of HCT recipients and has an associated mortality rate of up to 30%.[1, 2] Whether treating these infections with available (ribavirin) or investigational (DAS 181) antiviral agents affects progression to pneumonitis or mortality remains unknown.

Many conflicting reports exist about the clinical disease spectrum, management, and overall outcomes of PIV infections in HM patients and HCT recipients. Hence, we conducted a systematic review of all published studies to determine the incidence, risk factors, management, long-term outcomes, and mortality rates associated with PIV infections in HM patients and HCT recipients. Advances in diagnostic methods, available or new investigational drugs, and vaccines are also discussed.

2. MATERIALS AND METHODS

2.1 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 September 2015. The following Medical Subject Heading terms were used: *human parainfluenza virus 1*, *human parainfluenza virus 2*, *human parainfluenza virus 3*, *human parainfluenza virus 4*, *hematopoietic stem cell transplantation*, *bone marrow transplantation*, *leukemia*, *lymphoma*, *multiple myeloma*, 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*.

Inclusion criteria selecting the articles were:

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

Exclusion criteria were:

1. Studies not focusing on PIV infections in HM patients or HCT recipients,
2. Review papers or meta-analyses,
3. Case reports of 10 patients or less

4. Meeting abstracts
5. Studies with duplicate data or incomplete information, and

We also searched the Clinical Trials registry (U.S. National Institutes of Health, www.clinicaltrials.gov) to identify any registered clinical trials for PIV infections.

2.2. Definitions

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

PIV case: patients with a positive nasal wash, nasopharyngeal swab, or bronchoalveolar lavage for PIV by one of the viral diagnostic tests (viral culture, direct immunofluorescence testing, or PCR) were included in this review.

PIV-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)

PIV-mortality: Death was attributed to PIV if a persistent or progressive infection with respiratory failure was identified at the time of death.

2.3. Data abstraction

Two authors (D.P.S. and P.K.S.) independently screened the abstracts using predefined inclusion and exclusion criteria. Three authors (D.P.S., P.K.S. and J.M.A.) 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 PIV infection, progression of PIV-URTI to PIV-LRTI and PIV-associated mortality. Antiviral therapy included ribavirin (aerosolized, intravenous, or oral) alone or in combination with intravenous immunoglobulin (IVIG). 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.

2.4. 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 progression and death) were descriptively summarized as percentages. We compared treated and untreated patient outcomes using Chi-squared or Fisher exact tests, as appropriate. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs). Forest plot was constructed to demonstrate the significant risk factors associated with acquiring PIV infection, PIV-LRTI and PIV-mortality using adjusted odds ratios from published studies. All statistical analyses were performed using STATA software version 13 (STATA Corp., College Station, TX, USA).

3. RESULTS

We reviewed 441 abstracts on PIV infections in HM patients or HCT recipients. Of these, 274 were not specific to PIV infection or the pre-defined population or focus of the study. Of the remaining 167 abstracts, 101 were excluded from further review (49 were review studies on respiratory viruses, 12 were outbreak investigations, 24 were case reports with ≤ 10 patients, and 16 had overlapping data with an included study, had incomplete information, or were meeting abstracts); thus, we included 66 full-text articles. Twenty one studies measured the incidence of respiratory viruses in HM patients or HCT recipients and 11 studies provided primary data for LRTI risk factors and management and mortality, including antiviral therapy effects; thus, data were abstracted for PIV incidence, PIV-LRTI, and associated mortality. Furthermore, we reviewed studies that evaluated new diagnostic methods (9) and investigational new drugs (4); long-term outcomes such as airflow obstruction (6); prophylaxis (2); and pathophysiologic and immunogenetic factors (14). (A detailed flowchart of the abstract screening process is shown in Supplemental Figure S1). The agreement between the two authors during the selection of abstracts and the selection of full-texts, as measured by Cohen's Kappa, was 0.903 [95% CI: 0.862 – 0.945] and 0.926 [0.867 – 0.984], respectively which is regarded as substantial to excellent.

3.1 Incidence of PIV Infections

A total of 32 studies were reviewed, including 2 studies [1, 3] that were divided into two parts to stratify information on HM patients and HCT recipients. Majority of the studies did not provide the breakdown for the type of HM for their study population; however, we observed that the most common HM for children was acute lymphoblastic leukemia (>60%). This information was not available for studies with adult patients.The incidence of PIV infections is displayed in Table 1. We identified 1196 PIV infections in 31,730

patients, giving an incidence of 4%, with a wide range of 0.2% to 30%. The reported incidence of PIV infections in HCT recipients (4% [838 of 21,062]) was significantly higher than that in HM patients (2% [246 of 9,685]) (OR: 1.6; 95% CI: 1.4, 1.8; P value<0.0001). Furthermore, a significantly higher PIV infection rate was reported in allogeneic HCT recipients (5% [482 of 10,147]) than in autologous HCT recipients (3% [206 of 7365]) (OR: 1.73; 95% CI: 1.46, 2.05; P value<0.0001).

The significant risk factors for acquiring PIV infections in HCT recipients and HM patients are displayed in Figure 1. Adults who underwent HCT from a matched unrelated donor or mismatched related donor had a significantly higher risk of PIV infection than did those who underwent matched related or autologous HCT.[4, 5] Similarly, children who underwent allogeneic HCT or total body irradiation were more likely to acquire symptomatic infections, when adjusted for other variables.[6] In children with HM, age less than 2 years (OR: 2.69, 95% CI: 1.5-4.8) and having ALL rather than other malignancies (OR: 4.13, 95% CI: 2.37-7.21) were significant risk factors for PIV infections.[7]

3.2 PIV-LRTI

The incidence of PIV-LRTI in HM patients and HCT recipients, as reported in 28 studies, is shown in Table 1. We identified 428 PIV-LRTI cases among 1163 PIV infections, giving an incidence of 37% for all studies combined (range, 0% to 74%). Stratified by underlying condition, PIV-LRTI was observed in 95 of 246 HM patients (39%) and 299 of 837 HCT recipients (36%) with PIV infections. PIV-LRTI incidence information was not available for different types of HCT.

The risk factors for PIV-LRTI are shown in Figure 1. In brief, allo-HCT,[5, 8] especially infection within 100 days after HCT,[6] lymphocytopenia,[6, 7] neutropenia at the onset of infection,[1, 6, 7] use of corticosteroids during PIV-URTI,[6, 9] and respiratory co-infections[1, 10] were significant predictors of LRTI progression.

3.3 PIV-associated mortality

Twenty six studies reported PIV-associated mortality in HM patients and HCT recipients (Table 1). This rate varied greatly, ranging from 0% to 31%, with a total of 117 PIV-deaths in 1138 PIV infected patients (10%). It was not significantly different in HCT recipients (12% [96 of 826]) than in HM patients (7% [16 of 230]); OR: 1.75; 95% CI: 1.0, 3.3; P value = 0.05). However, significantly higher mortality rate was observed in patients with PIV-LRTI (27% [117 of 428]; OR: 3.3, 95% CI: 2.4, 4.4, P value<0.0001), irrespective of the underlying condition.

PIV-LRTI has been found to be a major risk factor for PIV-associated mortality in both HM patients and HCT recipients, irrespective of age.[5, 6, 10] Other risk factors are displayed in Figure 1 and include lymphocytopenia,[6, 10] younger age,[5] allo-HCT or mismatched related allo-HCT,[5, 8] refractory or relapsed underlying malignancy,[1] APACHE II score > 15,[1] respiratory co-infections,[5] and steroid use at infection onset.[1, 5, 6] (Supplemental Table S1)

3.4 Other outcomes

Late-onset non-infectious pulmonary complications after respiratory infections included diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, bronchiolitis obliterans (BO), and bronchiolitis obliterans with organizing pneumonia. Many studies have implicated respiratory viruses in the development of BO in HCT recipients. One study demonstrated that PIV infection independently

increases the risk of airflow decline, which was immediately detectable after infection in HCT recipients.[11] On the other hand, another study found no association between respiratory viral infection and BO development in HCT recipients.[12] Hence, studies in HCT recipients or HM patients are needed to systematically estimate the incidence of BO after respiratory infections, identify associated risk factors, and test preventive strategies when applicable.

3.5 Diagnosis

Clinically, PIV infections cannot be differentiated from other respiratory viruses in immunocompromised patients; therefore, diagnosis is dependent on laboratory confirmation. Several laboratory methods, such as rapid antigen testing, enzyme immunoassays, real-time PCR, and viral cultures, have been used to diagnose PIV infections.[13-15] A recent study reported that the PCR technique was two and four times as sensitive as culture and fluorescence antigen detection assays, respectively, at detecting respiratory viruses, especially PIV.[16] High-resolution CT of the chest has been reported to aid in diagnosing respiratory viral infections in HCT recipients; however, caution should be exercised in interpreting the results because of the considerable overlap between the imaging appearances of bacterial and viral pneumonia.[17, 18] Similar to most viral pneumonias, PIV-LRTI can range from mild scattered to scattered centrilobular nodules (predominantly in the upper lobes) to patchy ground-glass opacities on high-resolution CT.[19] A lung biopsy may reveal giant-cell pneumonia, intra-cytoplasmic viral inclusions, and interstitial pneumonia, consistent with PIV-LRTI;[8, 20] however, lung biopsies are seldom performed to establish the diagnosis.

3.6 Antiviral therapy

Ten retrospective studies reported the use of antiviral therapy for PIV infections, including 8 in HCT recipients and 2 in HM patients. Most of these studies found that ribavirin was not significantly effective at preventing PIV-LRTI or PIV-associated mortality; however, therapy was mainly administered to patients with LRTI. In fact, the PIV-associated mortality rate was slightly higher in patients treated with ribavirin-based therapy at the LRTI stage (34% [37 of 108]) than in those who were not treated (25% [49 of 193]), which could be explained by a selection bias for treating sicker patients (Table 2). Information on the use of ribavirin at the URTI stage was only available from 6 studies in HCT recipients and HM patients. LRTI progression was not significantly different in HCT recipients who were treated with ribavirin-based therapy at the URTI stage (35% [8 of 23]) and those who were not treated (46% [118 of 256]) (OR: 0.62; 95% CI: 0.22, 1.64; P value=0.296). Similarly, no significant difference in PIV-associated mortality was observed for HCT recipients who were treated at the URTI stage and those who were not treated (0% [0 of 23] versus 11% [28 of 256]; P value=0.094). Among HM patients, only 1 study reported the use of antiviral therapy at the URTI stage; thus, a pooled analysis was not possible. This study did not report any significant reduction in PIV-LRTI or PIV-associated mortality with antiviral therapy at the URTI stage.[1]

3.7 Investigational drugs

Because no commercially available antiviral agent exists for PIV, novel drugs such as DAS181 (a recombinant sialidase fusion protein)[21] and BCX2798 (a hemagglutinin-neuraminidase inhibitor)[22] are being evaluated (Supplemental Table S2). DAS181 enzymatically removes sialic acid moieties to temporarily disable PIV receptors in the airway epithelium.[23] DAS181 has shown efficacy against PIV *in vitro*, in a cotton rat infection model, and in three immunocompromised patients with respiratory infections,

including two HCT recipients.[21, 23, 24] Other compounds, such as BCX2798 and BCX2855, have been found to have antiviral activity against PIV-3, significantly reducing pulmonary viral titers and mortality in rats when given intranasally within 24 hours of infection;[22] however, no human studies are available. Given the significant mortality rate associated with PIV-LRTI in immunocompromised patients, there is an unmet need for managing these infections. Data on the efficacy and cost-benefit of these compounds in this vulnerable population are needed.

Given the significant morbidity and mortality of PIV infections, there has been substantial interest in developing an effective vaccine over the past few years. Many clinical trials (phase I or II studies) are being conducted to test vaccine efficacy against PIV in healthy infants or children (Supplemental Table S3). Interestingly, mucosal immunization has been suggested as a promising alternative vaccination strategy because of recent advances in delivery systems and improved knowledge about site-specific mucosal immune mechanisms.[25] However, the protective potential of active immunizations in immunocompromised patients is usually suboptimal.

In the absence of an effective therapy or vaccine, infection control measures such as contact isolation, hand hygiene, and masks and gloves, along with universal precautions, are the mainstay for preventing the spread of PIV in HCT recipients and HM patients. Viral shedding after infection, especially in asymptomatic patients, may be a key factor in propagating this virus in the immunocompromised population. The results of a recent study suggested that a long duration of viral shedding and “ping-pong” transmission between patients and healthcare personnel or caregivers may be responsible for periodic community-wide and nosocomial outbreaks.[26] Furthermore, asymptomatic or subclinical PIV infections have been well documented in HCT recipients

and HM patients. Thus, subclinical infection, along with prolonged duration of viral shedding, may explain the failure of infection control practices in containing the transmission of this virus, unlike respiratory syncytial virus and influenza.[27]

4. DISCUSSION

In this systematic review, we attempted to assemble all published data on PIV infections in HM patients and HCT recipients to generate meaningful conclusions about their incidence, LRTI and mortality rates, long-term outcomes, management (including antiviral therapy and new investigational drugs), and prevention measures, including vaccines.

We identified high rates of PIV infection in HM patients and HCT recipients. The incidence varied widely, which could be attributed to factors such as patient sampling methods, patient age, transplant and underlying malignancy type, season and study period, publication bias, and diagnostic method used (i.e., RT-PCR vs. direct fluorescence antigen assay vs. culture). Over the past few decades, the number of reported PIV infections increased because of increased awareness and increased availability of fast, inexpensive, reliable diagnostic methods.

Further, we observed high morbidity and mortality rates after these infections with 37% rate of progression to LRTI and 10% virus-associated mortality rates following PIV infections. High mortality rate following progression to LRTI (27%) was observed. Additionally, we observed no differences in LRTI or mortality rates between HM patients and HCT recipients following PIV infections. This finding was not shared by other studies of both populations, in which PIV-LRTI was more common in HM patients than in HCT recipients.[1]

Similar risk factors for PIV-LRTI were consistently identified in many studies, which may help clinicians identify high-risk patients. Lymphocytopenia,[6, 7] neutropenia,[1, 6, 7] and corticosteroid usage[6, 9] were significantly associated with PIV-LRTI; however, we could not abstract primary data for these risk factors to conduct a pooled analysis. Other variables such as age,[7] type of

transplant (allo-HCT vs. auto-HCT)[8], and time from HCT[6] were inconsistently reported as risk factors for PIV-LRTI; however some studies found no such association.[1, 20, 28]

Ribavirin has had promising results against PIV in animal models and children with severe combined immunodeficiency.[29, 30] Large case series have demonstrated that it has no effect on viral shedding, symptom duration, hospital stay duration, PIV-LRTI progression, or mortality in HCT recipients,[1, 2, 20] with the caveat that in most published studies, it was used in patients that had already experienced progression to LRTI. We hypothesized that the time of initiation of ribavirin-based therapy might affect outcomes but based on our pooled analysis of ribavirin used at the URTI stage, it did not affect the LRTI progression or mortality rate significantly. Randomized trials are needed to evaluate ribavirin's effects at the URTI stage to prevent LRTI progression and mortality in this patient population. Although active against PIV *in vitro*,[31] ribavirin's role in treating PIV infections in HCT recipients and HM patients is still not known. In the absence of an effective drug or vaccine, infection control measures remain the mainstay in preventing these infections and any subsequent morbidity and mortality in immunocompromised patients.

There are many limitations of this systematic review. One limitation is that we only reviewed studies published in English; thus, we missed many publications from other countries, especially developing nations. In addition, our reliance on secondary data may be subject to interpretation errors; we tried to minimize this by having three different investigators (D.P.S., P.K.S. and J.M.A.) validate the data; and outcomes were reconfirmed by R.F.C. Most of the studies were retrospective and non-randomized in nature; hence, the results of this systematic review should be interpreted with caution. In addition, the majority of the studies did not report the breakdown for the type of HM for their study population or the details on the type of PIV infection, hence we could not further

analyze these variables. Finally, since this review included a heterogeneous study population, we could not conduct a meta-regression analyses to identify the independent effects of various host risk factors on the progression to LRTI. We attempted to decrease the publication bias by including almost all published studies with minimal exclusion criteria. Another limitation of these studies was the lack of standardized definition for PIV-LRTI. As reported in a recent study in HCT recipients, 90-day survival probabilities were significantly different between possible, probable, and proven LRTI based on univariable regression analysis.[32] We propose a multi-institutional collaborative effort to standardize and validate clinical endpoints for PIV infections, which will be essential for determining efficacy of future vaccine and antiviral therapies.

In summary, to our knowledge, this is the first comprehensive review on PIV infections in HM patients and HCT recipients examining the incidence, risk factors, morbidity, mortality, diagnosis, and management limitations, and the importance of prevention in decreasing nosocomial spread.

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AUTHOR CONTRIBUTIONS

D.P.S. and R.F.C. designed the study, D.P.S., P.K.S. screened the abstracts; D.P.S., P.K.S. and J.M.A. extracted data from full text articles, D.P.S and R.F.C. wrote the manuscript and all authors reviewed the full text articles and provided critical feedback and final approval for the manuscript.

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DECLARATION OF CONFLICTS OF INTEREST

R.F.C received research grant from Ansun pharmaceuticals. All other authors have no conflicts of interest to declare.

Table 1: Incidence of PIV infections, lower respiratory tract infection, and PIV-associated mortality in HCT recipients and HM patients, n (%)

Author	Years of infection	Location	Study population	Age	Surveillance	Diagnosis	PIV incidence	PIV-LRTI	PIV-associated mortality	LRTI related deaths
HCT recipients										
Wasserman, 1988[33]	Jan 1979 - Jul 1986	Philadelphia, PA	96	Children	S	Culture	5 (5)	1 (20)	0	0
Lujan-Zilbermann, 2001[34]	Jan 1994 - Dec 1997	Memphis, TN	274	Children	S	Culture, DFA	17 (6)	7 (41)	1 (6)	1 (14)
Srinivasan, 2011[6]	Jan 1995 - Dec 2009	Memphis, TN	738	Children	S	Culture, DFA, PCR	46 (6)	18 (39)	6 (13)	6 (33)
Fazekas-A, 2012[3]	Nov 2007 - Feb 2009	Vienna, Austria	31	Children	AS	RT-PCR	1 (3)	NA	NA	NA
Lee, 2012[35]	Jan 2007- Aug 2009	Seoul, Korea	176	Children	S	Culture, PCR	1 (0.5)	0	0	0
Choi, 2013[36]	Jan 2007 - Mar 2010	Seoul, Korea	358	Children	S	PCR	22 (6)	8 (36)	1 (5)	1 (13)
Srinivasan-A, 2013[37]	Oct 2010 - Sep 2011	Memphis, TN	42	Children	S	PCR	6 (14)	3 (50)	1 (17)	1 (33)
Lewis, 1996[8]	Jan 1991 - Sep 1994	Houston, TX	1173	Adult	S	Culture, IIF	61 (5)	27 (44)	10 (16)	10 (37)
Whimbey, 1996[38]	Nov 1992 - May 1993; Nov 1993 - May1994	Houston, TX	217	Adult	S	Culture	6 (3)	1 (17)	0	0
Williamson, 1999[39]	Jun 1990 - Jun 1997	Bristol, UK	60	Adult	S	DFA	9 (15)	4 (44)	0	0

Chakrabarti, 2002[2]	Jun 1997 - Aug 2001	Birmingham, UK	83	Adult	S	Culture, DFA	16 (19)	13 (81)	2 (13)	2 (15)
Roghmann, 2003[40]	Jan 2001-Apr 2001	Baltimore, MD	62	Adult	AS	Culture, PCR	5 (8)	0	0	-
Hassan, 2003[41]	May 1996 - May 2001	Manchester, UK	626	Adult	S	Culture, Rapid Ag test	4 (1)	2 (50)	1 (25)	1 (50)
Martino, 2005[42]	Sep 1999 - Oct 2003	Barcelona, Spain	386	Adult	S	IIF, culture	8 (2)	3 (38)	0	0
Dignan, 2006[43]	Jul 2004- Jun 2005	Surrey, UK	145	Adult	AS	Culture, DIF	24 (14)	12 (8)	1 (4)	1 (8)
Schiffer, 2009[44]	Dec1997-Mar2005	Seattle, WA	2,901	Adult	S	Culture, DFA	122 (4)	27 (1)	13 (11)	13 (46)
Chemaly-A, 2012[1]	Oct 2002 - Nov 2007	Houston, TX	3473	Adult	S	DFA, Culture	120 (3)	46 (38)	8 (7)	8 (17)
Ljungman, 1989[45]	Jan 1987-Apr 1987	Seattle, WA	78	Any	AS	Culture, IIF	8 (10)	2 (25)	0 (0)	0
Wendt, 1992[20]	Mar 1974 - Apr 1990	Minneapolis, MN	1253	Any	S	Culture	27 (2)	19 (70)	6 (22)	6 (32)
Elizaga, 2001[28]	Jan 1990 - Sep 1996	London, UK	456	Any	S	Culture, IIF	26 (6)	14 (54)	8 (31)	8 (57)
Nichols, 2001[9]	Jul 1990 - Jun 1999	Seattle, WA	3577	Any	S	Culture, DFA	253 (7)	56 (22)	19 (8)	19 (34)
Ljungman, 2001[46]	Oct 1997 - Sep 1998	37 EBMT centers, Europe	1973	Any	S	Culture, IIF, ELISA	4 (0.2)	1 (25)	0	0
Crippa, 2002[47]	Apr 1995 - Nov 1998	Seattle, WA	305	Any	S	Culture, DFA,	13 (4)	6 (46)	NA	NA
Machado, 2003[48]	Apr 2001 - Apr 2002	Sao Paulo, Brazil	179	Any	S	DFA	12 (7)	0	0	-
Raboni, 2003[49]	Mar 1993 - Aug 1999	Parana, Brazil	722	Any	S	IIF	7 (1)	2 (29)	2 (29)	2 (100)
Peck, 2007[27]	Dec 2000 - Jun	Seattle,	122	Any	AS	Culture,	17	2 (12)	1 (6)	1 (50)

	2004	WA				DFA, PCR	(14)			
Ustun, 2012[5]	Jan 1974 - Dec 2010	Minneapolis, MN	5178	Any	S	Culture	173 (3)	75 (43)	32 (18)	32 (43)
HM patients										
Craft, 1979[50]	1979-1981	UK	64	Children	S	FAT, culture	4 (6)	2 (50)	1 (25)	1 (50)
Mottonen, 1995[51]	Nov 1987 - Dec 1989	Oulu, Finland	62	Children	AS	Culture, EIA, serum antibody (CF)	12 (19)	0	NA	NA
Srinivasan, 2011[7]	Jan 2000 - Dec 2009	Memphis, TN	820	Children	S	Culture, DFA, PCR	83 (10)	17 (20)	0	0
Fazekas-B, 2012[3]	Nov 2007 - Feb 2009	Vienna, Austria	103	Children	AS	PCR	4 (4)	NA	NA	NA
Srinivasan-B, 2013[37]	Oct2010-Sep2011	Memphis, TN	121	Children	S	PCR	16 (13)	1 (6)	0 (0)	0 (0)
Marcolini, 2003[10]	Jul 1994 - Dec 1997	Houston, TX	770	Adult	S	Culture	47 (6)	26 (55)	7 (15)	7 (27)
Chemaly-B, 2012[1]	Oct 2002 - Nov 2007	Houston, TX	7745	Adult	S	DFA, Culture	80 (1)	49 (61)	8 (10)	8 (16)
HCT recipients and HM patients										
Martino, 2003[52]	Oct 1999 - May 2001	Barcelona, Spain	130	Adult	S	DFA, culture	8 (6)	1 (13)	1 (13)	1 (100)
Park, 2013[53]	Jan 2009-Feb 2012	Seoul, Korea	737	Adult	S	PCR, DFA	64 (9)	NA	7 (11)	NA
Chemaly, 2006[54]	Jul 2000 - Jun 2002	Houston, TX	306	Adult	S	Culture, Rapid Ag test	92 (30)	34 (37)	4 (4)	4 (12)

Couch, 1997[55]	1992-1995	Houston, TX	668	Any	S	culture	28 (4)	NA	NA	NA

S indicates symptomatic; AS, asymptomatic; PCR, polymerase chain reaction; DFA, direct fluorescent antibody; IIF, indirect immunofluorescence; FAT, fluorescent antibody technique; EIA, enzyme immunoassay; PIV, parainfluenza virus; LRTI, lower respiratory tract infection; NA, not available.

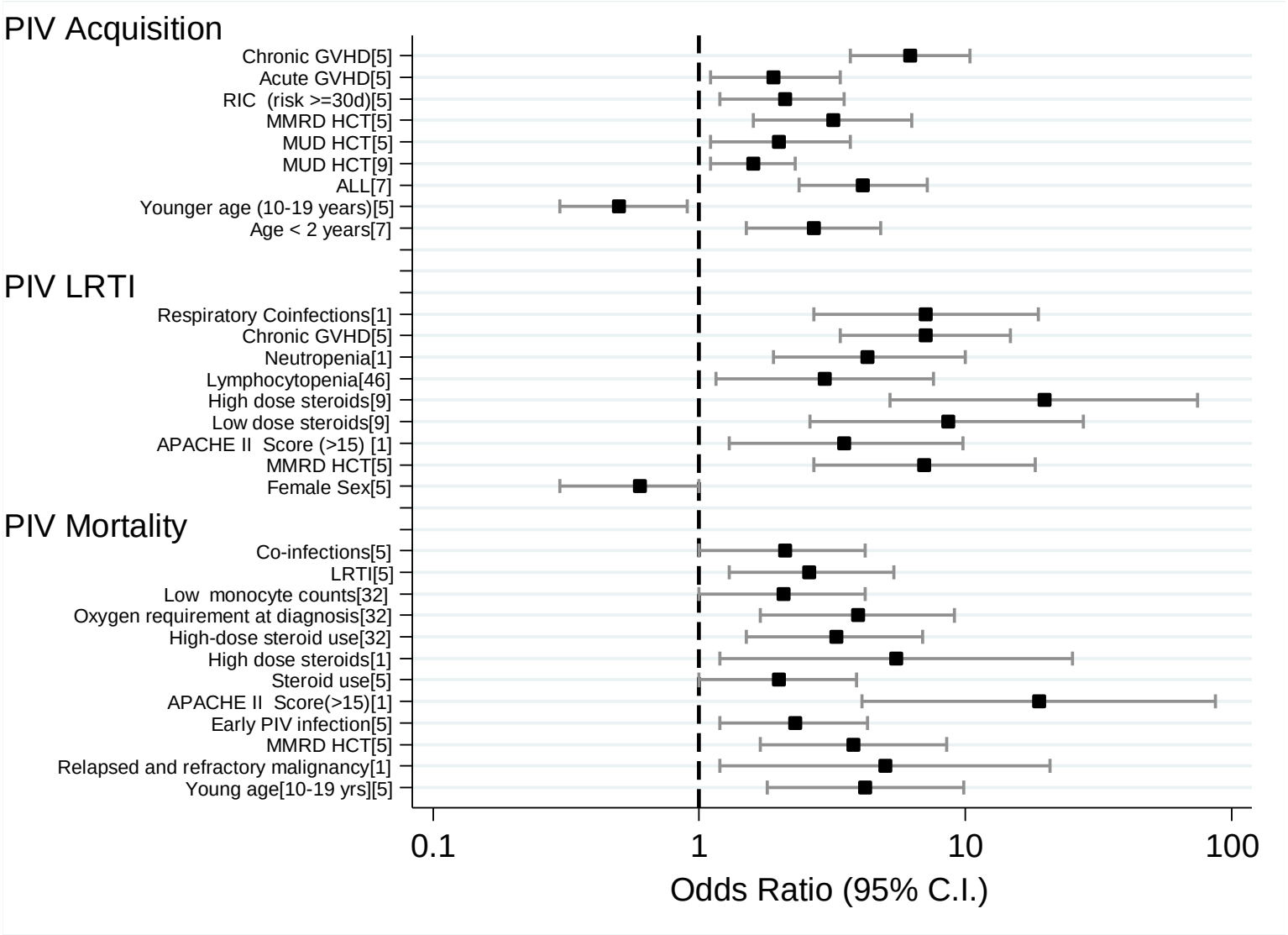
Table 2: Effect of antiviral therapy on PIV-LRTI and PIV mortality in HCT recipients and HM patients, no. (%)

Author, Year	PIV cases	Total treated	Antiviral therapy	Treated, URTI stage			Not treated, URTI stage			Treated, LRTI stage		Not treated, LRTI stage	
				No.	Progression to LRTI	Deaths	No.	Progression to LRTI	Deaths	No.	Deaths	No.	Deaths
HCT recipients													
Chemaly-A, 2012[1]	120	10 (8)	AR ± IVIG	5	3 (60)	0	115	43 (37)	8 (7)	5	1 (20)	38	7 (18)
Chemaly, 2006[54]	92	23 (25)	AR	7	4 (57)	0	85	30 (35)	4 (5)	16	2 (13)	18	2 (11)
Wendt, 1992[20]	27	9 (33)	AR	2	0	0	25	19 (76)	6 (24)	7	2 (29)	12	4 (33)
Chakrabarti, 2002[2]	16	14 (88)	AR or IR	1	0	0	15	13 (87)	2 (13)	13	2 (15)	0	0
Elizaga, 2001[28]	24	18 (75)	AR	8	1 (13)	0	16	13 (81)	8 (50)	10	6 (60)	4	2 (50)
Ustun, 2012[5]	173	51 (29)	AR ± IVIG	10	-	-	163	-	-	41	19 (46)	34	13 (38)
Lujan-Zilberman, 2001[34]	17	3 (18)	AR	0	-	-	17	-	-	3	1 (33)	4	0
Lewis, 1996[8]	61	5 (8)	AR	0	-	-	61	-	-	5	2 (40)	22	8 (36)
Dignan, 2006[43]	23	8 (35)	AR or IR	2	-	0	15	-	1 (6)	6	1 (17)	6	2 (33)
Total	553	141 (25)		35	8 (23)	0	512	118 (23)	28 (5)	106	36 (34)	138	38 (28)
HM patients													
Chemaly-B, 2012[1]	80	9 (11)	AR ± IVIG	6	6 (100)	1 (17)	74	43 (58)	7 (9)	3	1 (33)	40	7 (18)
Marcolini, 2003[10]	47	5 (11)	AR	0	-	-	47	-	-	5	1 (20)	21	6 (29)

Total for all studies combined	680	155 (23)	41	14 (34)	1 (2)	633	161 (25)	35 (6)	114	8 (7)	199	51 (26)

AR, aerosolized ribavirin; IR, intravenous ribavirin; and IVIG, intravenous immunoglobulin.

Figure 1: Risk factors significantly associated with PIV infection, PIV-LRTI and PIV-mortality in HCT recipients and HM patients



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Supplementary Tables

Table S1: Risk factors significantly associated with PIV infection, PIV-LRTI and PIV-mortality in HCT recipients and HM patients

Author, Year	Risk Factors	Odds Ratios (95% CI)	P value
Risk factors for associated with acquisition of PIV-infection			
Ustun[b], 2012[5]	Reduced intensity conditioning regimen (risk ≥30d)	2.1 (1.2- 3.5)	0.01
	MUD HCT	2.0 (1.1 – 3.7)	0.03
	MMRD HCT	3.2 (1.6 – 6.3)	< 0.01
	Younger age (10-19 years)	0.5 (0.3 – 0.9)	0.03
	Acute GVHD	1.9 (1.1 – 3.4)	0.03
	Chronic GVHD	6.2 (3.7 – 10.4)	< 0.01
Srinivasan[b], 2011[6]	Allogeneic HCT	N A	< 0.001
	TBI–based conditioning regimen	N A	< 0.001
Nichols[b], 2001[9]	HCT from unrelated donor compared to autologous HCT	1.6 (1.1 – 2.3)	0.01
Srinivasan[c], 2011[7]	Age < 2 years	2.69 (1.5 – 4.8)	0.002
	ALL	4.13 (2.37 – 7.2)	< 0.001

Risk Factors associated with PIV-LRTI			
Ustun[b], 2012[5]	MMRD HCT	7.0 (2.7 – 18.3)	< 0.01
	Female sex	0.6 (0.3 – 1.0)	0.04
	Chronic GVHD	7.1 (3.4 – 14.8)	< 0.01
Chemaly[a], 2012[1]	Neutropenia (ANC<500 cells/µL)	4.3 (1.9 – 10..0)	< 0.001
	APACHE II score >15	3.5 (1.3 – 9.8)	0.016
	Respiratory co-infections	7.1 (2.7 – 18.8)	< 0.001
Srinivasan[b], 2011[6]	First 100 days post-HCT	N/A	0.006
	Lymphocytopenia (ALC<100 cells/mL)	N/A	<0.001
	Neutropenia (ANC<500 cells/µL)	N/A	<0.001
	Steroid use	N/A	0.035
Nichols[b], 2001[9]	Steroids at the time of URTI diagnosis		
	1 to less than 2mg/kg/day	8.6 (2.6 – 27.8)	0.0003
	At least 2mg/kg/day	19.8 (5.2 – 74.6)	<0.001
Elizaga[b], 2001[28]	No difference between allogeneic HCT versus autologous HCT	N/A	-
Srinivasan[c], 2011[7]	Younger age (27 months vs. 56 months)	N/A	0.005
	Lymphocytopenia (ALC <100 cells/µL)	N/A	0.008

	Fever with severe neutropenia (ANC <500 cells/µL)	N/A	0.02
Schiffer[b] 2009[44]	Lymphocytopenia (ALC<300 cells/mL)	3 (1.2-7.6)	0.02
Risk factors associated with PIV-mortality			
Seo[b],2014[32]	Oxygen requirement at diagnosis	3.96 (1.7–9.1)	.001
	Low monocyte counts (<100 cells/µL)	2.07 (1.0–4.2)	.041
	High-dose steroid use (>2 mg/kg/day)	3.27 (1.5–6.9)	.008
Ustun[b], 2012[5]	LRTI	2.6 (1.3 – 5.4)	< 0.01
	Early PIV infection (<30 days post-HCT)	2.3 (1.2 – 4.3)	< 0.01
	Young age (10 - 19 years)	4.2 (1.8 – 9.9)	< 0.01
	MMRD	3.8 (1.7 – 8.5)	< 0.01
	Co-infections	2.1 (1.0 – 4.2)	0.04
	Steroid use	2.0 (1.0 -3.9)	0.05
Chemaly[a], 2012[1]	Relapsed and refractory malignancy	5.0 (1.2 – 20.8)	0.028
	APACHE II score >15	18.9 (4.1 – 86.9)	< 0.001
	High-dose steroids	5.5 (1.2 – 25.3)	0.028
Srinivasan[b], 2011[6]	African-American ethnicity	N/A	0.013
	LRTI	N/A	0.002

	Steroid use	N/A	< 0.001
	Mechanical ventilation	N/A	< 0.001
	Lymphocytopenia (ALC <100 cells/μL)	N/A	0.01

a HM patients and HCT recipients combined
b HCT recipients only
c HM patients only

NA, not available; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; MUD, matched unrelated donor; MMRD, mismatched related donor; GVHD, graft versus host disease; TBI, total body irradiation; HCT, hematopoietic cell transplant; LRTI, lower respiratory tract infection

Table S2: Randomized, double-blind interventional clinical trials on safety and efficacy of drugs for the treatment of PIV infections (www.clinicaltrials.gov, US National Institutes of Health)

NCT number	Objective	Phase	Intervention model	Intervention	Enrollment	Start date	Status
NCT00876161	Single-dose escalation study in healthy adults	1	Single	DAS181 dry powder inhalant	45	Apr 2009	Completed
NCT00527865	Single-dose escalation study of DAS181 in adults	1	Single	DAS181	36	Oct 2007	Completed
NCT01441024	DAS181 in patients with parainfluenza (adults)	2	Parallel	DAS181	50	Jul 2011	Recruiting
NCT01651494	Influenza antiviral DAS181-F04 in healthy adults	1	Parallel	DAS181	9		Recruiting
NCT01173224	Influenza antiviral DAS181-F03	1	Parallel	DAS181	27	Nov 2010	Recruiting
NCT01644877	DAS181 in immunocompromised patients with PIV infection	2	Parallel	DAS181 dry powder, formulation F02	0	Dec 2012	Withdrawn
NCT00938353	Efficacy of nebulized beclomethasone dipropionate for moderate croup in children	3	Parallel	BDP suspension for nebulization 800 mcg	6	Apr 2010	Terminated

Table S3: Randomized, double-blind interventional clinical trials on safety and efficacy of vaccines for prevention of PIV infections (www.clinicaltrials.gov, US National Institutes of Health)

NCT number	Objective	Phase	Intervention	Intervention model	Enrollment	Start date	Status
NCT00345670	Safety of MEDI-534 vaccine against RSV and PIV-3 in healthy children	1	MEDI-534	Single	120	Jun 2006	Completed
NCT00686075	Safety, tolerability, immunogenicity, and vaccine-like viral shedding of MEDI-534 against RSV and PIV3 in healthy children	1,2	MEDI-534	Parallel	720	Jul 2008	Active, not recruiting
NCT00493285[a]	Safety and tolerability of MEDI-534 in children (6 to < 24 months)	1	MEDI-534	Parallel	49	Jul 2007	Completed
NCT00508651[a]	Safety, immunogenicity, and shedding of MEDI-560 in infants (1 to < 12 months)	1,2	MEDI-560	Parallel	30	Oct 2007	Terminated
NCT01139437	Safety of a live, attenuated PIV-2 vaccine for adults, children, and infants	1	Standard-dose PIV2 vaccine vs. low-dose PIV2 vaccine vs. placebo	Parallel	90	Jun 2010	Recruiting
NCT00641017	Safety of and immune response to recombinant live-attenuated PIV-1 vaccine	1	rPIV1 84/del170/942A, Lot PIV1 #104A vaccine	Parallel	110	Mar 2008	Recruiting
NCT00366782	Safety of and immune response to a cow/human parainfluenza virus vaccine (rb/PIV-3) in healthy infants, children, and adults	1	rB/PIV3	Parallel	51	Mar 2007	Completed
NCT01254175	Safety and immunogenicity of a PIV-3 vaccine in infants and children	1	rPIV3cp45 vaccine	Parallel	28		Active, not recruiting

NCT00308412	Safety of and immune response to a PIV vaccine (rPIV3cp45) in healthy infants	1	rPIV3cp45	Parallel	45	Jun 2006	Completed
NCT01021397	Safety of and immune response to recombinant live attenuated PIV-3 vaccine in healthy infants and children	1	rPIV3cp45	Parallel	30	Nov 2009	Completed
NCT00186927[b, c]	Safety of live intranasal Sendai virus vaccine in children and toddlers	1	Sendai virus vaccine	Parallel	30	Mar 2005	Active, not recruiting

a study has results

b open label

c non-randomized

Supplementary Figure S1: Flow diagram of study selection of PIV infections in HM patients and HCT recipients