

Epidemiology of viral respiratory tract infections in an outpatient haematology facility

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Abstract Viral respiratory tract infections (VRTI) are an important cause of morbidity and mortality in haematology patients, particularly after haematopoietic stem cell transplantation (HSCT). The incidence, clinical presentation and outcome of symptomatic and asymptomatic VRTI in HSCT outpatient unit were prospectively evaluated during a single influenza season (January–March 2011). Pharyngeal swabs were performed at the first visit and if new symptoms were present. Molecular multiplex assay for 12 respiratory viruses was performed by the regional reference laboratory. Among 264 swabs from 193 outpatients, 58 (22 %) resulted positive for 61 viruses (influenza, $n=20$; respiratory syncytial virus [RSV], $n=21$; rhinovirus, $n=12$; coronavirus, $n=4$; adenovirus, $n=3$; parainfluenza, $n=1$). VRTI were detected more frequently in the presence of symptoms than in asymptomatic patients: 49 out of 162 (30 %) vs. 9 out of 102 (9 %), $p<0.001$. Influenza-like illness syndrome (ILI) was significantly associated with a VRTI if compared to other presentations (42 %), while the European Centre for Disease Prevention and Control definition was not (30 %). Positive predictive value (PPV) of ILI for influenza was 17 %. Influenza and RSV peak periods were contemporary. Influenza prophylaxis was given to 25 patients following exposure. Low rate of progression from upper to lower respiratory tract infection (approximately 5 % for influenza and RSV), no nosocomial epidemics and no VRTI-related

deaths were observed. VRTI are very frequent in high-risk haematology outpatients, but symptoms are aspecific and PPV of ILI is low. Symptoms of influenza and RSV overlap. Thus, microbiological diagnosis and contact preventive measures are crucial. Rather than universal influenza prophylaxis, prompt diagnosis and treatment of only documented infections could be pursued.

Keywords HSCT · Influenza · RSV · Influenza-like illness · Parainfluenza · Rhinovirus

Introduction

Viral respiratory tract infections (VRTI) are an important cause of morbidity and mortality in patients with hematologic malignancies, particularly in allogeneic haematopoietic stem cell transplantation (HSCT) recipients [1–3]. In immunocompromised patients, VRTI are usually more severe, with an increased risk of progression from upper to lower respiratory tract infections and more frequent presence of bacterial or fungal co-pathogens than in immunocompetent patients [4–7]. Moreover, long-term sequelae of VRTI, such as restrictive or obstructive airway disease, have been reported [8, 9]. During the last decade, rapid and highly sensitive molecular tests have been developed and made available, with the most recent multiplex polymerase chain reaction (PCR) platform that can detect multiple viral pathogens [10–12]. Based on data from observational studies, it is believed that most VRTI in patients with haematological malignancies present with fever and/or upper respiratory tract symptoms, while less is known about the asymptomatic circulation of respiratory viruses, even though prolonged viral shedding has been observed [4, 12–20].

For influenza infection, the management strategy based on the presence of influenza-like illness syndrome (ILI) has been successfully used in epidemiological and treatment studies in

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immunocompetent patients. For HSCT recipients who are at an increased risk of developing severe influenza complications, post-exposure and general chemoprophylaxis during an influenza season have been recommended [21–23]. Nevertheless, the efficacy and impact of these strategies, particularly when compared to early diagnosis and treatment, remain unknown.

The aims of this study were to prospectively evaluate the incidence, morbidity and severity of VRTI in outpatients of an HSCT unit during the influenza season of 2011. Additionally, the clinical usefulness of the presence of an ILI for diagnosing and treating VRTI and the possible occurrence of nosocomial transmission or microepidemics were evaluated.

Materials and methods

Patients and study protocol

A 3-month prospective study during the seasonal influenza outbreak, i.e. from 1 January 2011 to 31 March 2011, included all adult outpatients seen at least once a month in the HSCT unit. Most of the subjects were allogeneic HSCT recipients, while the other patients either received an autologous HSCT or chemotherapy for haematological diseases. The following data were recorded: demographics, type of the underlying disease and the date and type of HSCT, including conditioning regimen.

Informed consent was obtained in accordance with the Declaration of Helsinki. Both the asymptomatic and symptomatic for VRTI patients underwent clinical evaluation at every visit to the outpatient unit and were invited to contact their physician if any new symptoms developed. Additionally, influenza vaccination status of the patient and household contacts was noted. Pharyngeal swabs, which are specimens considered suitable and easily collected by recent WHO recommendations, were collected for viral testing at the first visit and then only in case of new VRTI symptoms [24]. Additional swabs were obtained in patients with VRTI in order to document the resolution of the infection or prolonged viral shedding but were not included in the analysis. Bronchoalveolar lavage (BAL) fluid and other clinical respiratory specimens were collected when clinically indicated.

The distribution of influenza cases, i.e. the beginning, the peak and the end of epidemic, in this cohort was compared to data available for Italy reported weekly by the Italian Network for Influenza Surveillance of Superior Health Institute.

Definitions

ILI syndrome was defined as the presence of fever plus at least one of the following symptoms: cough, sore throat, rhinorrhoea and/or systemic symptoms as headache, asthenia, malaise and arthromyalgia, in the absence of other documented causes.

VRTI was considered as detection of a respiratory virus from the upper or lower respiratory tract [25]. Similar to the European Centre for Disease Prevention and Control (ECDC) definition, in haematology patients, a confirmed case of viral respiratory tract infectious disease was defined as new onset of symptoms, and at least one of the following: cough, coryza, sore throat and shortness of breath, and the clinician's judgment that the illness is due to an infection [25].

A repeated detection of the same virus in a patient was considered as the same infection episode, and only the first positive swab was considered. Co-infection was defined as simultaneous detection of more than one virus, while separate infection episodes were diagnosed if a new virus was detected at the onset of new respiratory symptoms. Asymptomatic infection was defined as detectable virus in the patient's upper respiratory tract sample without symptoms of respiratory illness. Upper VRTI was defined as a respiratory viral isolation from a pharyngeal swab and included both symptomatic and asymptomatic infections. Upper VRTI symptoms included sore throat, cough, rhinorrhoea or nasal congestion. Lower VRTI was defined as a clinically and radiologically confirmed pneumonia with detection of virus from the lower respiratory tract (BAL fluid). A direct contact for a period of at least 1 h with a patient with an upper or lower VRTI was regarded as an exposition to VRTI case.

Microbiological methods

Molecular assay was performed by the regional reference laboratory operating from Monday to Friday. All specimens were transported in universal transport medium (COPAN Italia S.p.A., Brescia, Italy), collected and subjected to RNA extraction. According to the manufacturer's instructions, viral RNA was extracted by spin columns (QIAamp Viral RNA Mini Kit, Qiagen, Valencia, CA, USA), converted to random hexamer-primed cDNA by the RevertAid System (Fermentas, York, UK), and then stored at -20°C until use. Each cDNA preparation was subjected to the Seeplex RV12 ACE Detection PCR Kit procedure (Seegene, Seoul, South Korea). The multiplex PCR assay allowed the simultaneous detection of 12 respiratory viruses: influenza A/B, human adenovirus, respiratory syncytial virus (RSV) A/B, human metapneumovirus virus, human parainfluenza virus 1/2/3, human rhinovirus A/B, human coronavirus 229E/NL63–OC43/HKU1.

Samples positive only for the M gene of flu A by the Centers for Disease Control and Prevention (CDC) real-time reverse transcription polymerase chain reaction (RT-PCR) were typed using the real-time RT-PCR-based kit, established by the CDC, specific for detecting and characterizing A/H1N1p. Given the higher sensitivity of the CDC RT-PCR system than the Seeplex Kit for detecting A/H1N1p and influenza A viruses in general, throughout this paper, all results pertaining to influenza A virus should be considered

to have been obtained by the former method. A small number of influenza A virus positive samples were untypeable because of low viral loads. The performance of this multiplex assay has been determined elsewhere [26].

Infection control measures

At the outpatient unit, all patients, visitors and healthcare workers are required to use a surgical mask and to wash their hands before and after all patient contact. Routinely, the outpatients received intravenous treatment in three-patient or five-patient rooms. In order to reduce the possibility of nosocomial transmission and to facilitate the evaluation of potential microepidemics, the patients were always placed in the same room, unless VRTI was detected. Patients with VRTI were placed in individual rooms until they were asymptomatic and, if feasible, negative for respiratory viruses. Yearly influenza vaccination of patients, hospital staff and family members was recommended [21, 27].

Statistical analysis

The differences between the groups were assessed by means of the chi-square test for heterogeneity or Fisher's exact test when appropriate. All *p* values are two-sided; a *p* value of ≤ 0.05 was considered to be statistically significant. The analyses were performed using the SPSS version 13.0 statistical package (SPSS, Inc., Chicago, IL, USA).

Results

Clinical presentation of virologically documented infections

A total of 193 patients were screened and 264 pharyngeal swabs were performed. Among them, 136 patients had 1 swab performed, 45 had 2, 11 had 3 and 1 had 5. Fifty-six percent of patients were male, and the majority (68 %, 132 out of 193) received HSCT (127 allogeneic and 7 autologous), at a median of 306 days before entry in the study (range, 30–7, 712 days). In particular, 26 % (35 out of 132) received transplant within 90 days, 14 % (18 out of 132) within 90–180 days and 60 % (79 out of 132) within 180 days or more.

Among 264 pharyngeal swabs, 162 (61 %) came from symptomatic patients and 102 (39 %) from asymptomatic patients. A total of 58 (22 %) swabs positive for 61 viruses were recovered. In case of symptoms, the virological documentation of infection was significantly more frequent: 30 % (49 out of 162) of swabs performed during symptoms were positive, compared to 9 % (9 out of 102) of swabs in asymptomatic subjects ($p < 0.0001$). The main viruses detected were influenza (20 out of 58 samples, 34 %), RSV (21 out of 58, 36 %) and rhinovirus (12 out of 58, 21 %), and influenza and

RSV infections were significantly more frequent in symptomatic subjects (Table 1). The symptoms of VRTI were divided into three main categories, and the rate of positive virological results was as follows: ILI 38 % (25 out of 65), fever only 30 % (9 out of 30) and upper VRTI symptoms 22 % (15 out of 67) (Fig. 1). The classical ILI presentation was significantly more frequently associated with virologically documented infection as compared with the upper VRTI symptoms group (38 vs. 22 %, $p = 0.04$). Considering the ECDC definition, it was less specific than ILI, with 30 % of patients (40 out of 132) fulfilling the criteria of a viral respiratory tract infectious disease having a microbiologically confirmed infection.

In case of influenza, 11 out of 20 patients presented with ILI (55 %), 4 with fever only (20 %), 3 with upper VRTI symptoms (15 %) and 2 (10 %) were asymptomatic (both patients had been vaccinated). When evaluating the predictive value of ILI for the diagnosis of influenza in symptomatic patients during the epidemic season, only 17 % (11 out of 65) of cases presenting with ILI had influenza. The other 14 patients with ILI and VRTI had RSV (9 patients, 14 %), rhinovirus (4 patients, 6 %) and coronavirus (1 patient, 1.5 %) infection, while in 40 other patients with ILI (61.5 %), no virus was detected. Thus, the sensitivity of ILI for influenza in our population was 55 % (95 % confidence interval [95 % CI], 32–77), specificity was 69 % (95 % CI, 61–76) and positive predictive value (PPV) was 17 % (95 % CI, 8–28). Among HSCT recipients, the predictive value of ILI for influenza was 15 % (7 out of 46 cases presenting with ILI).

Six patients had pneumonia; thus, BAL was performed and four viruses were detected (co-pathogens are reported in Table 2): one influenza A, two RSV and one coronavirus. In two cases (influenza and RSV), progression from upper to

Table 1 Viruses detected in our cohort, with the comparison of the incidence of single viruses in symptomatic and asymptomatic episodes

Virus	Total, 58 ^a	Symptomatic, 49 (30 % of 162 swabs)	Asymptomatic, 9 (9 % of 102 swabs)	<i>p</i> value
Influenza	20 ^b	18 (11 %)	2 (2 %)	0.007
RSV	21 ^c	18 (11 %)	3 (3 %)	0.018
Rhinovirus	12	10 (6 %)	2 (2 %)	NS
Coronavirus	4	3 (2 %)	1 (1 %)	NS
Adenovirus	3	2 (1 %)	1 (1 %)	NS
Parainfluenza	1	1 (1 %)	0	NS

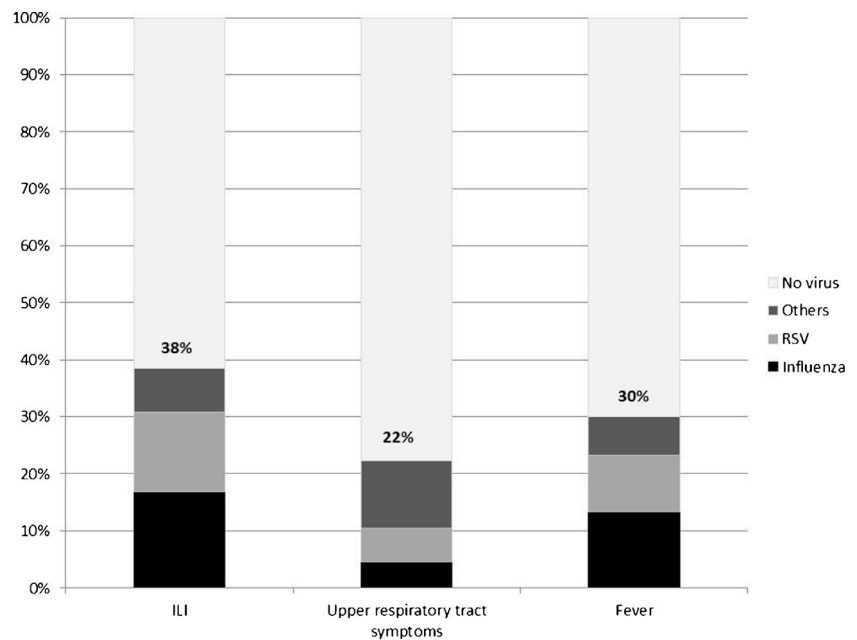
Data are presented as the number (percentage), unless otherwise indicated

^a The total number of detected viruses is superior to the number of positive swabs because, in three symptomatic infections, two viruses were detected in the same sample: influenza A+RSV in two cases and influenza A+coronavirus in one case

^b Influenza viruses were distributed as follows: 16 type A (10 H1N1, 5 H3N2 and 1 unknown) and 4 type B

^c RSV were distributed as follows: 10 type A and 9 type B

Fig. 1 The rate of positive virological results in the three categories of symptoms. *ILI* influenza-like illness, *URTI* upper respiratory tract infection



lower respiratory tract infection was diagnosed (progression rate for influenza, 1 out of 20; progression rate for RSV, 1 out of 19). These three patients with influenza and RSV pneumonia were successfully treated with oseltamivir and ribavirin, respectively. The other two patients were diagnosed with pneumonia due to other pathogens.

Weekly incidence and distribution of VRTI due to different viruses

Weekly incidence of all VRTI was 3.11 per 100 patient-weeks, of influenza was 1.13 per 100 patient-weeks and of RSV was 1.07 per 100 patient-weeks. The analysis of weekly distribution of diagnosed VRTI documented that the peak activity for the main two viruses (influenza and RSV) was detected in the same period. The circulation of influenza virus in this cohort was detected later (detection from weeks 2 to 10, with peak activity in weeks 6 and 7), as compared to the general population (detection from week 50 of 2010 to week 9 of 2011, with peak activity from weeks 2 to 6). A similar delayed circulation was detected for RSV: in the study population in weeks 2–12, with peak activity in weeks 6 to 8, while in the general population from week 50 of 2010 to week 10 of 2011.

Clinical characteristics' of VRTI

A total of 58 VRTI with identification of 61 viruses occurred in 55 out of 193 outpatients (incidence 28 %). The incidence of influenza and RSV infections was 10 % (20 out of 193) and 11 % (21 out of 193), respectively. The incidence of VRTI was similar in HSCT recipients (40 out of 132, 30 %) than in patients with haematological malignancies and no transplant

(15 out of 61, 25 %; $p=0.49$). Three HSCT recipients developed a second episode of VRTI: (1) parainfluenza and 27 days later RSV, (2) influenza and 21 days later coronavirus and (3) coronavirus and 44 days later rhinovirus. The distribution of different VRTI is reported in Fig. 2. Patients' characteristics and outcome in four groups of VRTI are outlined in Table 2. In particular, approximately half of the patients with either of the following infections: influenza, RSV and rhinovirus, presented with ILI syndrome (11 out of 20, 55 %; 9 out of 19, 47 %; and 5 out of 12, 42 %, respectively).

Management of prevention of nosocomial transmission and evaluation of possible nosocomial outbreaks

The standard prevention measures that included facial masks and hand hygiene were applied to all the patients with VRTI. For influenza infection, the possibility of giving pharmacological prophylaxis with oseltamivir was evaluated for all the contacts of patients with a documented influenza infection. Among 20 influenza infections, 19 were treated with the full dose of oseltamivir and 1 patient was not treated because the positive result was available after 72 h and the patient was asymptomatic, vaccinated, with no previous allogeneic HSCT and well-controlled underlying disease.

Overall, 56 contacts of 20 cases were identified among outpatients: 6 were symptomatic and received oseltamivir treatment pending the results of viral testing, whereas 50 were asymptomatic. Among them, 19 received oseltamivir prophylaxis within 72 h of exposure to a contact patient, while the remaining 31 patients were closely monitored for the development of signs and symptoms of influenza infection, but no prophylaxis was given. The decision to withhold prophylaxis

Table 2 Patients' characteristics and outcome in four groups of VRTI

Variable	Influenza, 20 ^a	RSV, 19	Rhinovirus, 12	Other, 7 ^b
Gender, male	10 (50)	13 (68)	5 (42)	5 (71)
Underlying disease				
Acute leukaemia	5 (25)	5 (26)	8 (67)	2 (29)
Chronic myeloproliferative or lymphoproliferative disease	11 (55)	8 (42)	2 (17)	4 (57)
MS and SAA	4 (20)	6 (32)	2 (16)	1 (14)
HSCT, yes ^c	12 (60)	15 (79)	9 (82)	7 (100)
Time from HSCT to VRTI, months, median (range)	8 (0–75)	5 (0–86)	14 (1–31)	6 (1–109)
<6 months	6 (50)	7 (47)	4 (44)	4 (57)
>6 months	6 (50)	8 (53)	5 (56)	3 (43)
Donor type				
Matched related	7 (58)	8 (53)	8 (89)	5 (71)
MUD and MMR	4 (33)	6 (40)	–	–
Cord blood	1 (8)	1 (7)	1 (11)	2 (29)
Conditioning regimen				
Myeloablative/reduced	8/4	9/6	8/1	6/1
Symptoms				
ILI	11 (55)	9 (47)	5 (42)	1 (14)
Fever	4 (20)	3 (16)	1 (8)	1 (14)
URTI symptoms	3 (15)	4 (21)	5 (42)	3 (43)
Asymptomatic	2 (10)	3 (16)	1 (8)	2 (29)
LRTI	1 (5) ^d	2 (11) ^e	–	– ^f
Treatment	19 (95)	2 (11)	–	–
Alive at day 30 from virus detection	20 (100)	19 (100)	12 (100)	6 (86)

Data are presented as the number (percentage), unless otherwise indicated

HSCT haematopoietic stem cell transplantation, ILI influenza-like illness, LRTI lower respiratory tract infection, MMR mismatched related donor, MS myelodysplastic syndrome, MUD matched unrelated donor, SAA severe aplastic anaemia, URTI upper respiratory tract infection, VRTI, viral respiratory tract infection

^a Three cases of co-infection were present: influenza A+RSV in two and influenza A+coronavirus in one, all reported in influenza column

^b Other: three adenovirus, three coronavirus and one parainfluenza virus infections type 3

^c All allogeneic HSCT, none of seven autologous HSCT recipients developed VRTI

^d No bacteria or fungi were detected, there were low levels of HSV-DNA positivity and lesions suggestive for BOOP, the patient responded to oseltamivir and high-dose steroids

^e BAL culture positive for *Stenotrophomonas maltophilia* and *Enterococcus* in one patient, and no co-pathogens in the other

^f In one patient, coronavirus was detected in BAL, but pulmonary lesions were most probably caused by Hodgkin's lymphoma or EBV

was based on either the fact that over 72 h elapsed between contact and notification or low risk of severe infection (no lymphopenia). None of 56 contacts developed microbiologically documented influenza infection.

Despite the high number of patients exposed to influenza, no nosocomial outbreak was detected. A cluster of influenza infection was observed in week 7 (five patients in 4 days), but the identified types of viruses were different (three type A H3N2, one type A H1N1 and one type B) and there was no evidence of any nosocomial contact with a patient infected with type A H3N2 4 days before. Transmission from healthcare workers or visitors could not be assessed as no swabs were performed among them, but no healthcare worker attending the outpatients unit had respiratory symptoms or

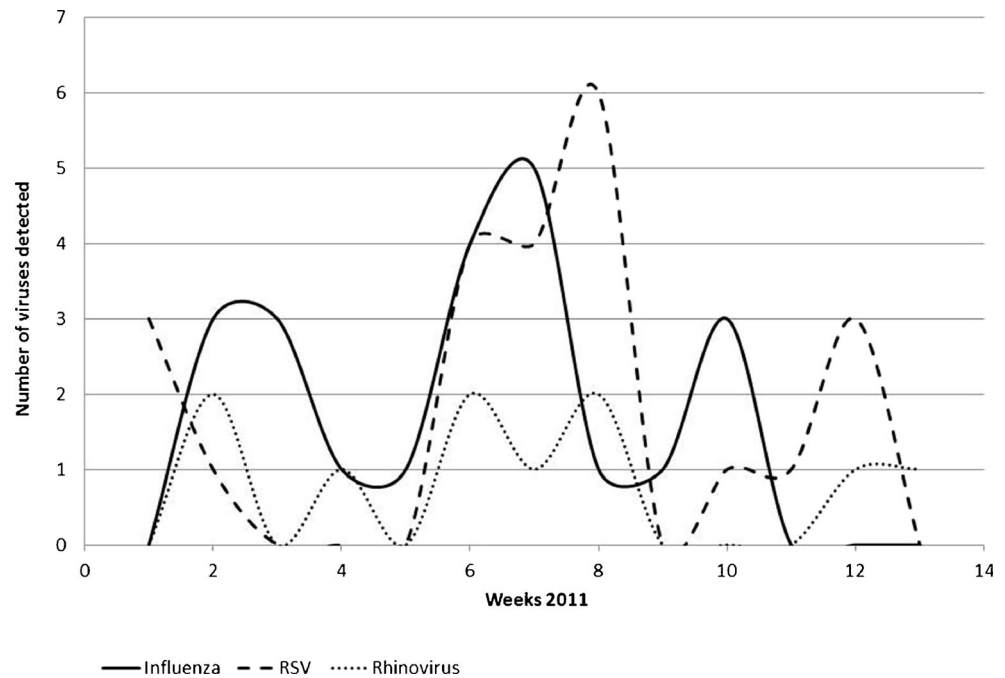
fever during the study period and visitors do not have access to outpatient therapy rooms.

RSV peak activity was observed from weeks 6 to 8 (seven infections). The equal circulation of the A (four) and B (three) subtypes and no contact between the patients involved make unlikely patient-to-patient transmission and large epidemic outbreak.

Influenza vaccination

Overall, 45 (23 %) patients were vaccinated with the seasonal strains, while among 148 non-vaccinated patients, 52 (35 %) reported that all or some household contacts had been vaccinated. There was no statistically significant difference in the

Fig. 2 The distribution of different VRTI



incidence of influenza between vaccinated (11 %, 5 out of 45) and non-vaccinated patients (10 %, 15 out of 148; $p=0.79$) and between patients with (13 %, 7 out of 52) and without vaccinated household contacts (8.6 %, 8 out of 96; $p=0.39$). Among 5 vaccinated patients (3 allogeneic HSCT recipients and 2 with no transplant), 2 had an asymptomatic infection, while 2 had classic ILI and 1 had fever only, as compared to 15 non-vaccinated patients, all of whom were symptomatic, in particular with ILI (9 out of 15, 60 %).

In the group of HSCT recipients, vaccination rate was 0 % (0 out of 53) within 6 months after transplant and 34 % (27 out of 79) among those over 6 months from transplant. Among seven autologous transplant recipients, one was vaccinated and none developed influenza. The incidence of influenza was 11 % (6 out of 53) among patient with <6 months from transplant, 7 % (2 out of 28) among those >6 months from transplant and vaccinated and 8 % (4 out of 52) among those >6 months from transplant and not vaccinated.

Discussion

This prospective study confirms that VRTI are a very common cause of morbidity, affecting during the observation period of 3 months almost one third of outpatients in an HSCT unit. Asymptomatic VRTI was not infrequent (9 %), but none of them developed a clinically significant disease. Symptoms of influenza, RSV and rhinovirus infection were similar and classic symptoms have low PPV for influenza (17 %). Thus, rapid and reliable diagnosis is crucial. Fortunately, no large outbreak was detected, and low rate of progression from upper

to lower respiratory tract infection and no VRTI-related mortality were observed.

The presence of any symptom was significantly associated with a confirmed VRTI, but in this population, classic ILI had low PPV for any VRTI (38 %), including influenza (17 %). Similar results were reported in another prospective observational study, where 25 % of patients had a VRTI, and respiratory viruses were detected more frequently in the presence of symptoms, but symptoms in case of influenza and other VRTI were similar [20]. ECDC definition adapted for the haematology population was even less specific than ILI. In immunocompetent individuals, ILI presentation is considered rather specific for influenza during the epidemic season. In fact, in generally healthy older adolescents and adults living in areas with confirmed influenza virus circulation, estimates of PPV, a simple clinical definition of influenza (acute onset of cough and fever), have been reported to be approximately 80–90 % and empirical anti-influenza treatment was recommended in such conditions [28–31]. However, even in an immunocompetent population, the accuracy of the clinical diagnosis of influenza on the basis of symptoms alone is being questioned (reported incidence of ILI in patients with influenza, 44–51 %) and is now considered limited because symptoms from illness caused by other pathogens can overlap considerably with influenza [29]. In immunocompromised patients, the association between ILI and influenza is even less pronounced, as systemic symptoms, such as fever or myalgia, are frequently lacking [32]. Therefore, considering the co-circulation of influenza, RSV and rhinoviruses in the same period and the similar clinical presentation of these infections, early use of rapid molecular testing to identify a specific virus, instead of universal empirical treatment with

anti-influenza drugs in patients with ILI, should be pursued. Initiating antiviral treatment at the onset of symptoms and then discontinuing it after diagnostic tests result negative for influenza is another feasible management strategy.

For influenza, vaccination from 6 months after transplant is recommended for HSCT recipients [21, 27]. In this study, the incidence of influenza was similar in vaccinated and non-vaccinated patients. However, the only two patients with asymptomatic influenza infection had been vaccinated, suggesting that active immunization might significantly attenuate the course of infection, even if it is not prevented.

The role of chemoprophylaxis of influenza during the peak season remains controversial, even though it is universally recommended in case of nosocomial outbreaks and for the first 2 weeks after vaccination in case of community or nosocomial outbreak [21, 27]. However, in this population of immunocompromised patients, of whom <25 % was vaccinated, the incidence of influenza during the epidemic season was only 10 %. Such a low incidence might be a result of a strict isolation policy with daily use of surgical masks and particular attention to hand hygiene, together with a virus-specific attack rate that may vary annually. Additionally, a low progression rate to lower respiratory tract infection and low mortality in all VRTI was observed (approximately 5 %), possibly due to a rapid diagnosis and an early start of an antiviral therapy—usually 24–48 h after the onset of symptoms. Therefore, in a population with low incidence and mortality and in consideration of the possibility of acquiring resistance to antivirals, as reported during the 2009 H1N1 epidemics [33, 34], an early diagnosis and post-exposure prophylaxis for close contacts seem preferable to a general chemoprophylactic strategy.

Molecular assays are particularly convenient for the diagnosis of VRTI in immunocompromised patients because they are rapid, sensitive and may detect multiple pathogens, although there are always some viruses not included in the assay [26]. However, they may also detect viral genetic material from a resolved or subclinical infection, and the optimal management of these cases remains unclear. In this cohort, nine asymptomatic subjects had VRTI and isolation measures were applied in all cases, but only one patient was treated for influenza. It has been reported that, in asymptomatic patients, lower quantities of virus might be present [20, 35] and transmission might be improbable, as demonstrated by an observation that no transmission to household contacts occurred in asymptomatic immunocompetent subjects with rhinovirus [36]. Also, in this study, asymptomatic patients did not subsequently develop any clinical symptoms.

The strengths of this study include a prospective standardized diagnostic approach for all the outpatients, regardless of respiratory symptoms and the use of a very sensitive diagnostic method. The limitations are a single-centre experience and a short observation period, which did not include the last

weeks of 2010 when some infections could occur. Thus, data on the incidence cannot be extrapolated to other populations or seasons. Additionally, the sensitivity of detection of respiratory viruses may vary for oropharyngeal and nasopharyngeal specimens [37]. Although, nasopharyngeal aspirates may be the most sensitive, especially for conventional diagnostic methods, less invasive specimen collection techniques are also acceptable given the very high sensitivity of new molecular diagnostic methods [37], while recent guidelines recommend combined intranasal sampling using flocked swabs and the pharyngeal swabs in one virus transport medium [25]. Finally, other centres with different management strategies for outpatients, including different contact prevention measures, might experience different rates of nosocomial transmission or morbidity.

In conclusion, VRTI are frequent in patients with haematological malignancies and may occur both in the presence of classic symptoms and in those with fever only. There was a significant overlapping in both symptoms and circulation period for influenza, RSV and rhinovirus. Thus, empirical treatment of influenza in the presence of ILI might be reserved for severely ill patients. Rapid virological diagnosis and treatment only in case of a documented infection have been found feasible and successful in this setting of high-risk haematology outpatients.

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Conflict of interest The authors declare that they have no conflict of interest.

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