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Review

Community acquired respiratory virus infections in cancer patients—Guideline on diagnosis and management by the Infectious Diseases Working Party of the German Society for haematology and Medical Oncology



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Abstract Background: Community acquired viruses (CRVs) may cause severe disease in cancer patients. Thus, efforts should be made to diagnose CRV rapidly and manage CRV infections accordingly.

Methods: A panel of 18 clinicians from the Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology have convened to assess the available literature and provide recommendations on the management of CRV infections including influenza, respiratory syncytial virus, parainfluenza virus, human metapneumovirus and adenovirus.

Results: CRV infections in cancer patients may lead to pneumonia in approximately 30% of the cases, with an associated mortality of around 25%. For diagnosis of a CRV infection, combined nasal/throat swabs or washes/aspirates give the best results and nucleic acid amplification based-techniques (NAT) should be used to detect the pathogen. Hand hygiene, contact isolation and face masks have been shown to be of benefit as general infection management. Causal treatment can be given for influenza, using a neuraminidase inhibitor, and respiratory syncytial virus, using ribavirin in addition to intravenous immunoglobulins. Ribavirin has also been used to treat parainfluenza virus and human metapneumovirus, but data are inconclusive in this setting. Cidofovir is used to treat adenovirus pneumonitis.

Conclusions: CRV infections may pose a vital threat to patients with underlying malignancy. This guideline provides information on diagnosis and treatment to improve the outcome.

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1. Introduction

The importance of community acquired respiratory virus (CRV) infections is increasingly recognised. CRV are responsible for respiratory infections, which usually present as a common cold in the immunocompetent individual but may be life-threatening in the immunocompromised host. Usually, orthomyxoviridae (influenza A, B and C), paramyxoviridae (including parainfluenza 1–4 [PIV], respiratory syncytial virus A and B [RSV], and human metapneumovirus [hMPV]), coronaviridae, picornaviridae (including >100 different serotypes of rhinovirus and enterovirus), adenoviridae, polyomavirus type 1 and bocavirus are regarded as potential causes of CRV infection. This guideline is intended to give haematologists and oncologists a broad overview with regard to clinical relevance and diagnosis of CRV infection and management of cancer patients affected by CRV. Detailed information on respective viruses including emerging resistance is not the scope of this guideline. Most data on this topic originate from patients following allogeneic stem cell transplantation (allo-SCT), and we know little about CRV infections in

cancer patients outside the setting of allo-SCT. However, in recent years increasing evidence has been gathered about other cancer patients, revealing clinical relevance of CRV infections in non-transplant patients. Therefore, this guideline discusses CRV infections in all cancer patients with ongoing relevant immunosuppression. It is left to the treating physician to assess the degree and relevance of immunosuppression in the individual patient.

2. Methods

This guideline has been developed by a panel from the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology including 17 experts certified in internal medicine, haematology/oncology, infectious diseases, microbiology/virology or radiology and one medical student. First, predefined topics were delivered by the designated coordinator (MvLT) to all participants of the panel to form subgroups. Data were extracted and tabulated after a systematic literature search by subgroup members and revised in several steps by the

members of the panel on the basis of an email-based discussion process and a face-to-face meeting. Finally, preliminary recommendations of the panel were discussed, revised and approved by the AGIHO assembly.

In May 2014, the first literature search was performed for CRV and immunosuppression using the terms ‘-virus’ and ‘immunocompromised’ (for example: ‘adenovirus immunocompromised’). This search was performed for adenovirus, bocavirus, coronavirus, enterovirus, hMPV, influenza, PIV, parechovirus, RSV and rhinovirus. The references were then screened by the subgroup members and relevant articles retrieved as full papers. Wherever applicable, additional papers were identified in the reference lists and treated as described. In February 2016, an update of the literature search was performed.

For grading, the system applied by the European Society of Clinical Microbiology and Infectious Diseases as proposed by Ullmann *et al.*, in 2012 [1] was used (Table 1) with one modification: other than Ullmann *et al.*, we used the same grading of the strength of

recommendation for diagnostic measures as for interventions (Table 1). The results of the literature search and the following grading process were used to develop recommendations wherever possible. Recommendations and evidence were then presented at and approved by the AGIHO assembly during the spring meeting on 6th March 2015. Following the update of the literature search in February 2016 no relevant changes were made.

3. Diseases caused by CRV

CRVs cause respiratory tract infections, which can be divided into upper respiratory tract infection (URTI), influenza-like illness (ILI) and lower respiratory tract infection/pneumonia (LRTI). Commonly, URTI can be assumed, if a patient has a new onset of symptoms including at least one of cough, coryza, sore throat or shortness of breath which is deemed to be due to an infection by the treating physician. LRTI requires clinical or radiological evidence of pneumonia [2]. ILI is diagnosed in patients with a sudden onset of new symptoms including at least one of fever or feverishness, malaise, headache or myalgia and at least one of the respiratory symptoms cough, sore throat or shortness of breath [3]. To be certain of the viral origin, the detection of the virus from respiratory samples like swabs, nasopharyngeal aspirates or bronchoalveolar lavage fluid is required. Of note, surveillance studies showed some patients to be asymptomatic but still shedding the virus [2,4–7]. For that reason, some authors distinguish between respiratory infection (detection of virus independent of symptoms) and respiratory infection disease (detection of virus and respective symptoms) [8]. However, for the purpose of this guideline, we omit this distinction and define URTI, LRTI and ILI as described above.

4. Epidemiology and clinical relevance

Some CRV like influenza or RSV have a seasonality with most infections occurring during the winter months [2,9,10]. Others like rhinovirus or parainfluenza are independent of seasonality [11]. Thus, an appropriate diagnostic work-up and clinical management is warranted in any patient presenting with typical symptoms regardless of the time of the year. As may be expected considering the nature of the disease, CRV frequently cause outbreaks in health care settings [7,12–15]. Importantly, outbreaks may also occur in outpatient settings [16] emphasising the need for awareness during all periods of cancer treatment.

Generally, viral URTI in cancer patients has some impact on the clinical course because the patients are symptomatic to a degree that frequently requires postponement of chemotherapy [17]. However, critical

Table 1
Grading of evidence as suggested by the ESCMID [1].

Strength of recommendation	
A	Strongly support a recommendation for use
B	Moderately support a recommendation for use
C	Marginally support a recommendation for use
D	Support a recommendation against use
Quality of evidence for interventions—level	
I	Evidence from at least one properly designed randomized, controlled trial
II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort- or case-control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinion of respected authorities, based on clinical experience, descriptive case studies, or report of expert committees
*Added index	
R	Meta-analysis or systematic review of randomized controlled trials
T	Transferred evidence, i.e. results from different patients' cohorts or similar immune status situation
H	Comparator group is a historical control
U	Uncontrolled trial
A	Abstract published at an international meeting
Quality of evidence for diagnostic measures—level	
I	Evidence from at least one properly designed multicentre cross-sectional or cohort study
II	Evidence from <ol style="list-style-type: none"> (1) At least one well-designed prospective singlecentre cross-sectional or cohort study or (2) A properly designed retrospective multicentre cross-sectional or cohort study or (3) From case-control studies
III	Evidence from opinion of respected authorities, based on clinical experience, descriptive case studies, or report of expert committees

illness and mortality due to viral URTI are rare. In contrast, most patients who died were suffering from LRTI, which thus poses the biggest threat to cancer patients. Rates of LRTI and mortality differ amongst the respective CRV [18] and exact estimation is hampered by the fact that fatal cases are probably over-reported. We have tried to deduce reliable information on LRTI and mortality from the literature for various CRV: influenza appears to have a high rate of LRTI with approximately 30% and an associated mortality rate of approximately 25% [19–22]. RSV appears to be at least as dangerous with a rate of LRTI of approximately 33% and an associated mortality rate of 27% [16]. However, it has to be kept in mind, that most data regarding RSV originate from SCT-recipients and very little is known regarding patients with other forms of malignancy. On the other hand, there are several reports of outbreaks in general haematology/oncology units, which showed a significant disease burden even in patients not undergoing stem cell transplantation [12].

With regard to hMPV and PIV, exact information on the clinical relevance is even more difficult to obtain. However, although both viruses may cause asymptomatic infection [6,23], the available evidence suggests a similar overall rate of LRTI and mortality [7,11,13,24–28] compared with influenza and RSV. In contrast, despite case reports of fatal outcomes of infections with rhinovirus and coronavirus, these viruses as well as bocavirus appear to be rarely the cause of LRTI and dangerous only when patients are coinfecting with other pathogens [2,5,29]. Herpesviridae like herpes simplex virus, human herpes virus 6, cytomegalovirus, varicella zoster and Epstein–Barr virus as well as polyomaviruses or parechoviruses usually do not cause CRV infection. Pneumonia due to reactivation of herpesviridae in severely immunocompromised patients is not an infection by CRV and thus not covered by this guideline.

In CRV infection, coinfection with bacteria, fungi or even other viruses appears to occur in approximately 30% of the patients [10,11,28]. They play a vital role with regard to outcome of patients since patients with bacterial or fungal superinfection have a dramatically higher mortality rate than those with viral infection only [11,28]. Therefore, possible co- or superinfection should be considered when managing cancer patients with CRV. In addition to LRTI and bacterial or fungal superinfection, other risk factors for adverse outcome include haematological malignancy [22], severe immunosuppression such as steroid use or graft versus host disease or cytopenias [30–32] or low immunoglobulins [12].

Epidemiology of adenoviruses is somewhat different from the other CRV: often, the source of infection is a childhood infection in children under 5 years [33] and reactivation as well as new infection have been described to be the cause of disease [34,35]. Other than CRVs like

RSV or influenza, adenoviruses can cause a variety of symptoms such as conjunctivitis, haemorrhagic cystitis, gastroenteritis, and URTI in immunocompetent patients and hepatitis, colitis, nephritis, meningoencephalitis and LRTI in the immunocompromised host. In adult allo-SCT recipients, DNAemia occurs in up to 20% [36–38], but symptomatic disease by adenovirus is much less common with T-cell suppression being the predominant risk factor [36]. Again, coinfection is an important risk factor for severe illness [39].

5. Diagnosis of CRV infection

5.1. Virology—material

Cancer patients presenting with symptoms consistent with CRV infection should be diagnosed using material from the respiratory tract (Table 2). Serology is not useful to detect ongoing CRV infection and thus not recommended (D III). Regarding material used for microbiological diagnosis, a variety of approaches are used in various centres. As a general rule, a close collaboration with the local microbiology laboratory is highly recommended because this may determine which material should be used preferably since commercially available test kits are licensed for specific materials. For example testing for viral antigens usually requires more thorough sampling like combined nasal/throat swabs than testing for viral nucleic acids which can often be performed reliably on gargles alone. It is therefore essential for the clinician to be aware of the tests used in the respective laboratory. The overall evidence in the literature is best for combined nasal/throat swabs and nasopharyngeal aspirates (A II, Table 2).

5.2. Virology—test

The best evidence for reliable detection of a CRV present in respiratory samples exists for nucleic acid amplification based-techniques (NAT) like PCR. Therefore, the use of NAT is highly recommended (A II, Table 2) and any methods involving the detection of antigen appear to be second best in immunosuppressed cancer patients (C II [40–42]). Also, culture methods are not commonly used anymore and cannot be recommended for general diagnosis, but they are essential in individual cases in which no known virus can be detected or results of PCR-analysis are inconclusive (A II, [43]). In the era of multiplex-test kits, it is difficult to make a definite recommendation with regard to which viruses should be looked for. In the absence of any reliable data regarding this question, the panel feels that it is wise to search for influenza, RSV, PIV and viruses currently prevalent in the local environment in all immunosuppressed cancer patients presenting with symptoms. Patients with more severe disease (for

Table 2
Recommendations regarding diagnostic approaches in cancer patients with symptoms of CRV infection.

Population	Intention	Intervention	SoR	QoE	Reference
Symptomatic IS	To detect viral pathogen and diagnose infection	Serology	D	III	[94]
Symptomatic IS	To detect viral pathogen	Combined nasal/throat swabs or washes/aspirates	A	II	[95–103]
Symptomatic IS	To detect viral pathogen	NAT	A	II	[42,94,104–107],
Symptomatic IS	To detect LRTI in patients with CRV infection	Chest X-ray	D	II	[108]
Symptomatic IS	To detect LRTI in patients with CRV infection	CT scan	A	II	[44,46,47,69,108–115],

SoR, strength of recommendation; QoE, quality of evidence; IS, immunosuppressed cancer patients; NAT, nucleic acid amplification techniques; LRTI, lower respiratory tract infection; CRV, community acquired respiratory virus; CT, computer tomography.

example pneumonia or critical illness) may have the panel broadened to include hMPV and adenovirus and even viruses that only rarely cause LRTI like rhinovirus and coronavirus. However, evidence for this approach is low and it is strongly advisable to define local guidelines on this topic. It should be kept in mind, that herpesviridae are not the cause of CRV infection. Therefore, there is no rationale to look for cytomegalovirus, Epstein–Barr virus, herpes simplex virus or varicella zoster in patients with typical symptoms of CRV infection only.

5.3. Radiology

In patients with symptoms of LRTI, it is essential to determine the degree of pulmonary involvement. CRV can affect the tracheobronchial system or the lung parenchyma [44]. Generally, a chest X-ray has been proven to be unhelpful to diagnose pathologic changes in this setting because of lack of sensitivity. It is therefore not recommended (D II, see Table 2). In contrast, there is good evidence to recommend a CT scan of the chest to detect LRTI in patients with CRV infection (A II, see Table 2). Bronchial wall thickening as well as interstitial infiltrates presenting as ground-glass opacities may be detected. These are defined as increased lung density, whereas underlying lung architecture is still detectable. Ground-glass opacities may be patchy or diffuse [44–47] and can be well distinguished from consolidations, which show higher density obscuring e.g. the pulmonary vessels and which are typical for other differential diagnoses including bacterial infection. Affection of the terminal bronchioles might lead to visibility of those usually invisible structures at CT as small centrilobular nodules or ‘tree-in-bud’ sign [45] or evidence of bronchiolitis causing air-trapping. To reliably detect air-trapping while inspiratory CT is normal, a CT scan in expiration is necessary [44]. In addition to good diagnostic accuracy with regard to the diagnosis of a viral LRTI, the CT scan may also reveal evidence for an outbreak, since specific viruses tend to present with a typical pattern in the CT scan [45]. For an example see Fig. 1.

6. Management of CRV infection

6.1. Infection control

In the light of the danger of outbreaks with fatal consequences, the most important measure in the management of cancer patients with CRV infection is infection control (Table 3). Local authorities should give exact guidance on the necessary precautions in the respective institutions. The following statements intend to give a general overview.

There is sufficient evidence to recommend stringent hand hygiene (A II_t), the use of face masks (B II_t) and contact isolation (A III, Table 3). Importantly, shedding of CRV in cancer patients often lasts 2 weeks or longer [5,10,48]. It is therefore wise to perform follow-up testing of respiratory material in index patients and stop contact isolation only when they became negative. Of note, early implementation of infection control appears to be more effective than late implementation [49] which gives reason to recommend infection control as soon as symptoms appear and not only after evidence of CRV.

6.2. Supportive measures

Almost anybody who catches a cold applies some form of home remedies convinced that they ease the symptoms and positively influence the course of the disease. In contrast to this widespread use, there is very little evidence to recommend any such measures. In particular with regard to cancer patients, evidence is too poor to give a sound recommendation in favour of the use of vitamin C [50], echinacea [51], garlic [52], zinc [53], humidified hot air [54] or Chinese herbal medicine [55]. Surprisingly, even painkillers [56] and non-steroidal anti-inflammatory drugs [57] may ease the pain but have little influence on severity and duration of the CRV infection. However, as there is some evidence towards a considerable placebo effect [58], it can be argued that patients should be allowed to continue their home remedies provided there is no reason to assume harmfulness as may be the case for some Chinese herbal

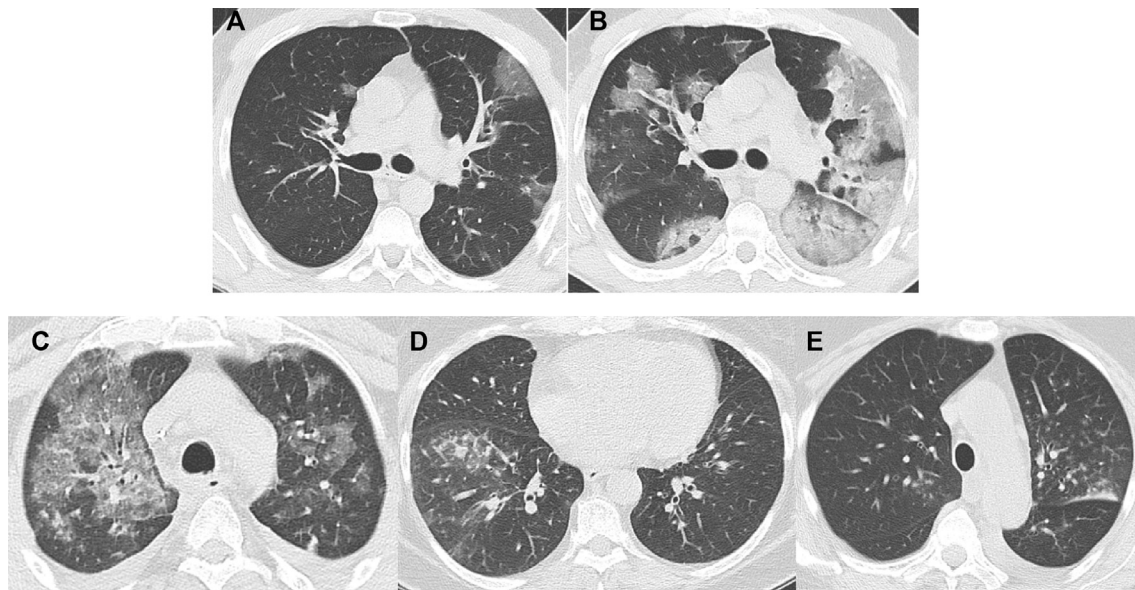


Fig. 1. A–B: pneumonia caused by influenza, first CT scan (A) and follow-up scan after 4 d (B). The bilateral diffuse ground-glass opacities progress over time to cover most parts of the lung. In addition, consolidations with positive bronchopneumogram develop, indicative of possible bacterial superinfection. C–E: CT scans from three different patients with pneumonia caused by RSV. Again, ground-glass opacities can be found but are of a more patchy character (Fig. 1C). They are often combined with centrilobular nodules (tree-in-bud, Fig. 1D). In some cases, only nodules with a ground-glass character are detected (Fig. 1E). RSV, respiratory syncytial virus.

Table 3
Recommendations regarding general management of cancer patients with CRV.

Population	Intention	Intervention	SoR	QoE	Reference
IS, infected persons, Contact persons	Infection control—prevent transmission	Hand hygiene	A	IIt	[49,116]
IS, Infected persons, Contact persons	Infection control—prevent transmission	Face mask	B	IIt	[49,116]
Infected persons	Infection control—prevent outbreak	Contact isolation	A	III	[117]
allo-SCT and evidence of CRV	Prevent disease, improve survival	Delay conditioning	A	II	[17]
All other chemotherapy and CRV	Prevent disease, improve survival	Delay chemotherapy if possible	C	III	[61]
allo-SCT and LRTI due to adenovirus	Prevent disease, shorten duration	Reduce immunosuppression	A	II	[36,62]
allo-SCT and LRTI due to CRV	Prevent disease, shorten duration	Reduce immunosuppression	A	IIt	[36,62]
allo-SCT and URTI	Prevent disease, shorten duration	Reduce immunosuppression	C	III	
IS with evidence of CRV	Reduce morbidity	Steroids >2 mg/kg	D	III	[10]
IS with evidence of RSV	Prevent LRTI, improve survival	IVIG	B	III	[30,82]
IS with evidence of influenza, PIV, hMPV	prevent LRTI, improve survival	IVIG	C	III	[69,92,118,119]

SoR, strength of recommendation; QoE, quality of evidence; IS, immunosuppressed cancer patients; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infection; CRV, community acquired respiratory virus; IVIG intravenous immunoglobulins; allo-SCT, allogeneic stem cell transplantation; RSV, respiratory syncytial virus; PIV, parainfluenza virus; hMPV, human metapneumovirus.

medicines contaminated with heavy metals [59] or the possibility to contract invasive fungal infection from inhaling contaminated air.

Needless to say, there is little to be gained from treating a viral infection with antibiotics [60], which is also true for cancer patients (D IIt,t for treating viral infections with antibiotics). However, having in mind the high rate of superinfection, cancer patients with viral LRTI and suspected or proven bacterial/fungal coinfection have to be treated accordingly (A III).

In cancer patients who present with symptoms consistent with CRV infection prior to initiation of

chemotherapy, delaying treatment should be considered. Since a retrospective study with 2 groups showed a benefit, if treatment was delayed in patients undergoing allo-SCT, we clearly recommend delaying conditioning in those patients who are scheduled for allo-SCT and have evidence of CRV infection (A II, see Table 3). The situation is less clear for patients with less aggressive treatment, since there have been reports of uneventful courses of even high-dose chemotherapy in patients with initial CRV infection [61]. Therefore, the recommendation to delay the chemotherapy if possible to be on the safe side is merely a weak one (Table 3).

Similarly, reducing immunosuppression in patients with LRTI due to adenovirus-infection after allo-SCT is well founded [36,62] on retrospective cohort studies with 2 groups and is thus clearly recommended (A II, Table 3). Data can be transferred to the situation of other LRTI caused by CRV, therefore, reduction of immunosuppression is also recommended in allo-SCT recipients with LRTI caused by other CRV (A II, Table 3). In contrast, the situation is less clear in patients with URTI and therefore only a very weak recommendation can be made (C III, Table 3).

With regard to supportive application of systemic medication other than antivirals, no recommendation can be made for the use of steroids, since they show no effect and prolong viral shedding (D III, Table 3). In contrast, intravenous immunoglobulins (IVIGs) are a therapeutic option in RSV infection (B III) and may also be beneficial in influenza, PIV and hMPV infection (C III, Table 3). Because of lack of data, no recommendation can be made regarding the use of IVIG in other CRV infections.

7. Causal treatment

7.1. Influenza

If causal treatment was deemed necessary, influenza A was traditionally treated with amantadine or rimantadine. Nowadays, resistance rates are so high that neither can be recommended (D II [63–66]). In contrast, despite ongoing discussion regarding the balance of efficacy and side effects [67,68] the treatment of choice appears to be a neuraminidase inhibitor, be it oseltamivir, zanamivir or peramivir. They are recommended as prophylaxis as well as for treatment (for example http://www.rki.de/DE/Content/InfAZ/I/Influenza/IPV/IPV_Node.html or [63,69,70]). However, data regarding the efficacy of prophylactic use of neuraminidase inhibitors in cancer patients are very weak and almost exclusively in the setting of stem cell transplantation [71,72]. Therefore, the authors believe it is not justified to give any recommendation in favour of or against their use in cancer patients in general. Thus, prevention of influenza by application of neuraminidase inhibitors remains one of the unresolved issues requiring further study. Still, we

have included information on dose and duration in Table 5.

Treatment of influenza is usually recommended in symptomatic patients at high risk preferably <48h after the onset of symptoms [63]. Cancer patients might be regarded as high-risk patients per se, which is why neuraminidase inhibitors (usually oseltamivir) are often routinely given to patients with malignancies and influenza [69,70,73], since mostly retrospective data show a benefit of (early) antiviral treatment with regard to development of LRTI or further complications [10,20,74–76]. Thus, we do recommend the use of oseltamivir or zanamivir (B II, Tables 4 and 5). There is evidence to recommend early initiation of treatment, but that does not necessarily mean later treatment is futile [77] and therefore many authors recommend treatment regardless of timepoint [70]. However, we do not think either dose (150–300 mg/d) nor duration (5–10 d or longer) are well defined from the available evidence and need determination by local specialists. The reasons usually given for higher doses and longer treatment duration in high-risk patients is the prolonged viral shedding observed in cancer patients and a thus deduced susceptibility to develop resistances if not treated effectively [69,70].

Peramivir has received FDA approval during the 2009 pandemic and is recommended for patients with H1N1 infection unable to take oral medication [78]. It is not available in Germany but included in this guideline for the sake of completeness (Table 5). The authors advise its use in severe cases, when oral intake or inhalation is not possible (CIII). Another salvage option may be the combination of zanamivir or oseltamivir with ribavirin, since that has shown some efficacy in older studies [79].

7.2. RSV

RSV is usually treated with intravenous immunoglobulins (IVIG, B III, Table 3) and ribavirin. In Europe, the monoclonal antibody palivizumab is licensed for prevention of RSV in children only. In addition, the benefit over polyclonal IVIG is not entirely conclusive [80]. For these reasons, we do not make a clear recommendation for or against its use in cancer patients, since we regard

Table 4
Recommendations regarding causal treatment of influenza, RSV, parainfluenza and adenovirus.

Population	Intention	Intervention	SoR	QoE	Reference
IS and influenza	Shorten duration and prevent LRTI	Oseltamivir	B	II	[10,74,76,77]
IS and influenza	Shorten duration and prevent LRTI	Zanamivir	B	II	[75,76]
IS and RSV	Prevent LRTI and improve survival	Ribavirin	B	II	[12,30,80–82,86,87]
IS and PIV	Prevent LRTI and improve survival	Ribavirin	C	III	[11,24,79,86,88,89]
Adenovirus-associated pneumonitis	Cure	Cidofovir	B	II	[120–122]

SoR, strength of recommendation; QoE, quality of evidence; IS, immunosuppressed cancer patients; LRTI, lower respiratory tract infection; CRV, community acquired respiratory virus; RSV, respiratory syncytial virus; PIV parainfluenza virus.

Table 5
Information on specific drugs.

Name	Class	Indication	Dose	Application mode	Duration	Comment	Reference
Oseltamivir	Neuraminidase inhibitor	Prophylaxis influenza	75 mg/d	Oral	As needed in seasonal prophylaxis; 10d in post-exposure prophylaxis	Caveat: data too weak to make a recommendation, local strategies needed	[63,69,71]
Oseltamivir	Neuraminidase inhibitor	Treatment influenza	2 × 75-150 mg/d	Oral	5–10 d		[10,74,76,77]
Zanamivir	Neuraminidase inhibitor	Prophylaxis influenza	10 mg/d	Inhalation	As needed in seasonal prophylaxis; 10d in post-exposure prophylaxis	Caveat: data too weak to make a recommendation, local strategies needed	[63,69]
Zanamivir	Neuraminidase inhibitor	Treatment influenza	2 × 10 mg/d	Inhalation	Until negativity		[75]
Peramivir	Neuraminidase inhibitor	Treatment influenza	600 mg/d	Intravenous		Not available in Germany	[78]
Ribavirin	Nucleoside inhibitor	Treatment RSV, PIV, hMPV	Daily dose: 2 g for 2 h every 6 h or 6 g over 18 h	Inhalation	7–10 d	Be aware of potential teratogenic effect—special precautions needed	[82]
Ribavirin	Nucleoside inhibitor	Treatment RSV, PIV, hMPV	Different schedules ^a	Oral		Be aware of potential hepatic and renal toxicity, haemolysis	[12,30,80–82,86,87]
Ribavirin	Nucleoside inhibitor	Treatment RSV, PIV, hMPV	10–30 mg/kg/d	Intravenous		Be aware of potential hepatic and renal toxicity, haemolysis	[87]
Cidofovir	DNA polymerase inhibitor	Treatment adenovirus	Cidofovir 3–5 mg/kg iv once weekly for 2 weeks, then once every week	Intravenous		To reduce cidofovir toxicity, add at least 2 l of iv Prehydration and probenecid 2 g po 3 h prior and 1 g 2 and 8 h following cidofovir	[120–124]

RSV, respiratory syncytial virus; PIV, parainfluenza virus; hMPV, human metapneumovirus.

^a For example: loading dose: 10 mg/kg, then 3 × 400 mg d2, 3 × 600 mg from d3 [30]; 1800 mg/d [87]; <65 kg body weight: 2 × 400 mg/d; 65–80 kg body weight: 2 × 500 mg/d; >80 kg body weight: 2 × 600 mg/d [12]; <75 kg body weight: 2 × 600 mg/d and ≥75 kg body weight: 2 × 800 mg/d [81]; 20 mg/kg/d in four divided doses increasing every 24–48 h to 60 mg/kg/d in four divided doses, if tolerated [86].

the question whether to use palivizumab instead of IVIG as an unresolved question requiring further study.

Ribavirin is the agent of choice in the treatment of RSV infection. Most available data concern allo-SCT recipients [80], but recent evidence also suggests a benefit in less severely immunosuppressed cancer patients [12,81]. It appears to lower the progression rate to LRTI [82] and is reported to have a positive influence on survival [12]. However, some authors report favourable outcome of RSV infections without any causal treatment [61,83,84]. Traditionally, it is used as an aerosol (see Table 5), but this application mode is cumbersome

and may be associated with a teratogenic effect [85]. Also, patients may not be able to inhale for such a long time or they may react with bronchospasm. Thus, oral application has been used increasingly with a similar efficacy [12,30,81,86,87] and even intravenous application is reported [87]. Despite some reports with a good outcome without treatment, we believe the available evidence justifies a recommendation for the use of ribavirin in cancer patients with RSV infection (B II, Table 4). Also, at least in high-risk patients the treatment should be given at the stage of URTI, since this has shown a benefit (B II [82]).

7.3. Parainfluenza (PIV)

Experience with antiviral therapy (generally ribavirin) in patients with parainfluenza infection is not very large and the efficacy is not entirely convincing [11,24,79,86,88,89]. This may be partly because causal treatment is started too late in the course of the disease and partly because the cause of death often is a coinfection requiring antibiotic therapy [7,28]. Nonetheless, it may be reasonable to attempt therapy with ribavirin in patients with parainfluenza infection (C III, Table 4).

7.4. Adenovirus

Causal therapy with cidofovir is justified in immunosuppressed cancer patients with LRTI caused by adenovirus (B II, Tables 4 and 5). More experimental therapies, which are employed in the setting of allo-SCT include donor-lymphocyte infusions [90] or adoptive transfer of specific T-cells [91]. However, to date evidence is too weak to justify a recommendation in favour of or against the use of these treatment modalities.

7.5. Human metapneumovirus (hMPV), rhinovirus, coronavirus and others

Causal therapy with ribavirin has been attempted in patients with infections caused by hMPV [92,93], albeit with unconvincing results. There is not enough evidence to make a definitive recommendation for or against the use of any specific antiviral drug or other causal treatment approaches like interferon for any of the CRV other than the ones discussed above.

8. Conclusion and outlook

Early diagnosis and general infection prevention may improve the outcome of cancer patients with CRV infections. Despite some data regarding some viruses (influenza, RSV) and patient populations (HSCT-recipients), there is still a lack of information on most CRV and on other patient populations (for example those with solid tumours). Also, almost no prospective randomised trials have been performed for the treatment of CRV infections in cancer patients. Thus, most recommendations have to be deduced from other populations and further study is urgently needed.

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Conflict of interest statement

MvLT has received honoraria and travel support from Gilead, MSD, Pfizer, Celgene and Janssen Cilag, has received travel support from Astellas Pharma and has received research support from MSD. She is member of the advisory board to MSD.

MC has received research funding from Deutsche Forschungsgemeinschaft (DFG) and Erich und Gertrud Roggenbuck Stiftung, been a speaker for MSD and Basilea, has been a consultant for MSD and Basilea, received travel grants from Celgene, Takeda, Gilead and MSD and is a recipient of the MSD stipend oncology 2013.

MH served on advisory boards of Gilead, Roche Pharma and Takeda and served on the speakers' bureau for Celgene, Novartis, Janssen and Amgen.

CPH is a stock owner of Stada and GSK and has received consultation fees and/or honoraria from Schering-Plough, Pfizer, Basilea, Boehringer Ingelheim, Novartis, Roche, Astellas, Gilead, MSD, Lilly, Inter-mune, Fresenius, Olympus, Gilead, AstraZeneca, Bracco, MEDA Pharma, Chiesi, Siemens, Covidien, Pierre Fabre, Grifols and research funding from Siemens, Pfizer, MeVis and Boehringer Ingelheim.

MK has received honoraria and travel support and served on the speakers' bureau for Gilead, MSD, Pfizer.

OP has received honoraria and travel support from Astellas, Gilead, Jazz, MSD, Neovii Biotech and Pfizer. He has received research support from Bio Rad, Gilead, Jazz, Neovii Biotech, Pierre Fabre, Sanofi and Takeda. He is member of the advisory board to Alexion, Jazz, Gilead and MSD.

MJGTV is a consultant to: Berlin Chemie, MSD/Merck and Astellas Pharma; has served at the speakers' bureau of: Pfizer, Merck/MSD, Gilead Sciences, Organobalance and Astellas Pharma; received research funding from: 3M, Astellas Pharma, DaVolterra and Gilead Sciences.

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