

Community-acquired respiratory virus (CARV) infections other than Influenza and Adenovirus: Respiratory Syncytial -, Human Metapneumo- Parainfluenza-, Rhino-, and Coronavirus

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Overview

- Introduction
- Characteristics of CARVs other than influenza and adenovirus
- Definitions of CARV respiratory tract infection and disease (RTID)
- Adapted ECDC definition for CARV-RTID
- CARV diagnostic considerations
- CARV recommendations
 - Prevention
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- Outlook and research agenda
- Appendix



CARV Introduction

- Community-acquired respiratory virus (CARV) infections are caused by a range of diverse viral agents with RNA genomes (Orthomyxo-, Paramyxo-, Picorna-, Corona-) and DNA genomes (Adeno-, Boca-, Polyoma-)
- CARVs circulate in the general population throughout the year, but some CARVs show pronounced seasonality and cause epidemics.
- Respiratory tract infections (RTI) with CARVs may range from asymptomatic replication to significant disease, mostly affecting the very young, the very old, patients with chronic organ dysfunction and patients with some form of immunodeficiency.
- This slide set summarizes the ECIL-4 recommendations regarding CARV *other than influenza and adenovirus* for patients with haematological disorders and those undergoing haematopoietic stem cell transplantation (HCT).



CARVs covered in this Slide Set

- Respiratory Syncytial Virus
 - RSV-A and -B
- Human Parainfluenza Virus (HPIV)
 - PIV-1, -2, -3, and -4
- Human Metapneumovirus (HMPV)
- Human Coronavirus (HCoV)
 - Group I-like (HCoV-229E and HCoV-NL63)
 - Group II-like (HCoV-OC43 and HCoV-HKU1)
- Human Rhinovirus (HRhV)
 - Three groups A, B, and C, more than 100 serotypes
- Human Enterovirus (HEnV)
 - Multiple types with predilection for oropharynx and URTI
- Human Polyomavirus (HPyV)
 - Two related species KIPyV and WUPyV
- Human Bocavirus (HBoV)
 - Parvovirus detected in RTI



Definitions of CARV Infection and Disease

- Respiratory tract infection (RTI)
 - Detection of CARV in the respiratory tract
- Upper respiratory tract infection (URTI)
 - Detection of CARV above the larynx e.g. in samples from nose, pharynx, sinuses
 - Lower respiratory tract infection (LRTI)
 - Detection of CARV below the larynx e.g in samples from trachea, bronchus, bronchioli
- Symptomatic URTI = URTI disease (URTID)
 - Detection of CARV in upper respiratory tract fluid specimens together with symptoms and/or signs in the URT as defined by the *adapted* ECDC criteria for acute respiratory infectious disease (other causes excluded).
- Symptomatic LRTI or LRTI disease (LRTID)
 - Pathological sputum production, hypoxia or pulmonary infiltrates together with identification of CARV in respiratory secretions (other causes excluded).



Adapted ECDC Definitions of Respiratory Tract Infectious Disease (RTID)

Clinical criteria

- New onset of symptoms
AND
at least one of the following four
respiratory symptoms:
 - Cough
 - Sore throat
 - Shortness of breath
 - Coryza
- AND
- A clinician's judgement that the
illness is due to an infection

Epidemiological Criteria

- An epidemiological link with human to
human transmission

Laboratory Criteria

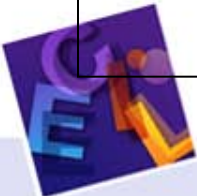
- Detection of CARV in a clinical
specimen by at least *one* of the
following:
 - Virus isolation by cell culture (VIC)
 - Direct virus antigen testing (DAT)
 - Nucleic acid amplification testing
(NAT)

Case Classification

- **Possible case**
 - Any person meeting the clinical
criteria of RTID
- **Probable case**
 - Any person meeting the clinical
criteria of RTID *and* with an
epidemiological link
- **Confirmed case**
 - Any person meeting the clinical of
RTID *and* the laboratory criteria

Adapted from ECDC definitions for influenza

http://ecdc.europa.eu/en/activities/surveillance/EISN/surveillance/Pages/influenza_case_definitions.aspx



Respiratory Syncytial Virus (RSV) Characteristics

- RSV A and B infections occur throughout the year, but increase in children and adults during the winter season with bronchiolitis and pneumonia in neonates.
- RSV infection of patients with HCT and/or other haematological diseases coincides with higher community activity suggesting an increased risk of community-acquired, household and/or nosocomial transmission.
- RSV infection occurs in 0.3% - 2.2% of in paediatric patients with acute myeloid leukaemia and in 1%-12% of adult HCT patients
- Progression from URTID to LRTID in adult HCT patients is observed in 20% - 68% of patients with an attributable mortality of 17-70%
- Risk factors for LRTID include severe immunodeficiency, pre-engraftment, and lymphopenia
- Treatment options are limited by the lack of randomized controlled clinical trials (RCTs), but the pooled published evidence suggests that treating URTID in HCT and leukemia patients at risk and LRTID with ribavirin and with intravenous immunoglobulins (IVIG) may improve outcome

Nichols et al. 2001 BBMT 7: 115
Martino et al. 2005 BBMT 11: 781
Chemaly et al. 2006 Medicine 85: 278
Khanna et al. 2008 CID 46: 402
Sung et al. 2008 Ped784 Blood Canc 51:
Avetysian et al. 2009 Transplant 88: 1222
Shah & Chemaly 2011 Blood 117: 2755

Human Parainfluenza Virus (HPIV)

Characteristics

- HPIV infections encompass 4 serotypes that cause mild URTID throughout the year, but varying increases of laryngotracheitis, bronchiolitis and pneumonia are seen in 15% of infected children during autumn and spring.
- In HCT recipients, HPIV infections range from 2% - 7% and may be as high as 17.9% if screening asymptomatic patients by NAT
- Persistent subclinical shedding may contribute to nosocomial outbreaks.
- HPIV-3 is most commonly detected in HCT recipients (up to 90% of cases) followed by HPIV-1 and -2
- URTI cause significant persistent air flow decline in 40% and progress to LRTID in 13-37% with a fatal outcome in 10-30%.
- Risk factors for HPIV-LRTID include higher dose steroids, lymphopenia <200 cells/mL.
- Treatment options are limited by the lack of effective agents and RCTs, although some centres consider treating HPIV-URTID in patients at risk and many centres consider treating HPIV-LRTID with ribavirin and/or IVIG.

Hall 2001 N Engl J Med 344:1917
Nichols et al. 2001 BBMT 7: 115
Erard et al. 2006 JID 193: 1619
Piralla et al. 2009 Haematologica 94: 833
Peck et al. 2007 Blood 110: 1681
Chemaly et al. 2006 Medicine 85: 278

Human Metapneumovirus (HMPV) Characteristics

- HMPV is a paramyxovirus closely related to RSV causing 5%-20% of URTID and tracheobronchitis in children and adults during the winter
- HMPV infection rates in HCT patients range from 5%-9% during the first 2 years post-transplant and include nosocomial transmission
- Asymptomatic and prolonged shedding has been reported in HCT patients
- Progression to HMPV-LRTID is rare, and rates and risk factors are not well described
- In HCT patients with pneumonia, co-detection of other pathogens has been reported
- The impact of HMPV in haemato-oncological patients is presently unclear.
- The role of treatment is limited by the lack of effective agents and of RCTs, although some centres consider treating HMPV-LRTID with ribavirin and/or IVIG

Machado et al. 2008 BBMT 14: 1348
Williams et al., 2005 JID 192:1061
Martino et al., 2005 BBMT 11:781-96
Campbell et al. 2010 JID 201:14114
Debur et al. 2010 TID 12. 173

Human Coronavirus (HCoV) Characteristics

- HCoVs circulate throughout the year with a predominance in winter, which may result in part from increased testing for CARVs
- URTID with rhinitis, pharyngitis and laryngitis is the common manifestation, but LRTID with bronchitis, bronchiolitis, and pneumonia may occur rarely in the very young (age <1 year) and in immunodeficient patients
- In HCT patients, HCoV has been detected in 6.7% - 15.4%, but asymptomatic shedding may occur in 41%. In symptomatic HCT patients, co-infections with other pathogens is seen frequently
- LRTID and pneumonia with fatal outcome occurs rarely in HCT patients
- The role of treatment is limited in view of the largely benign course, the lack of effective agents and clinical studies

Milano et al. 2010 Blood 115: 2088
Gerna et al. 2006 J Med Virol 78: 938
Oosterhof et al. 2010 BMT 45: 1115
Pene et al 2003 Clin Inf Dis 37: 929

Human Rhinovirus (HRhV) Characteristics

- HRhVs belong to the *picornaviridae* and consist of 3 genotypes (A,B,C) encompassing more than 100 serotypes.
- HRhV are throughout the year the most common cause of URTID (rhinorrhoea, postnasal drip, cough) and occasionally bronchitis
- In allogeneic HCT recipient, HRhVs are the most frequent CARV reaching a cumulative incidence of 22.3% by day 100.
- HRhV infection may be asymptomatic in 13% of HCT patients, and detection together with other CARVs may occur in 19%
- LRTID in allogeneic HCT is rare (<10%), and can be associated with a poor outcome in less than 10%
- The role of treatment is limited by the lack of agents and RCTs.

Milano et al. 2010 Blood 115: 2088
Parody et al. 2007 Am J Hematol 82: 807
Gutman et al. 2007 BMT 40: 809
Hassan et al. 2003 BMT32: 73

Other CARVs Characteristics

- Human bocavirus (HBoV), enterovirus (HEnV) and human polyomavirus (HPyV) infections have been detected in patients with haematologic malignancies or HCT, but risk factors for disease and the need for therapy has been difficult to assess due to the lack of studies and co-detection of other pathogens
- HBoV belongs to the *parvoviridae* and is detected in 5% of children with RTI. In BAL from adult patients, HBoV was detected in 0% - 3% of cases. HBoV loads above 5 log₁₀ copies/mL in respiratory fluids has been proposed to indicate clinically significant replication.
- HEnV belong to the *picornaviridae* and are detected in <5% of haematological patients with URTID progressing to LRTID in 13%.
- HPyV include KIPyV and WUPyV that have been detected in 0.2% and 1.4% of children with RTI, respectively. KIPyV has been more frequently detected in respiratory fluids of HCT patients (17%) compared to other patients (5%). However, there are currently no data supporting the treatment of KIPyV- or WUPyV-LRTID

Gerna et al. 2007 NewMicrobiol 30: 383
Parody et al. 2007 Am J Haematol 82: 807
Hassan et al. 2003 BMT32: 73
Mourez et al. 2009 Emerg Inf Dis15: 107

CARV Diagnostic Considerations (1)

- Nucleic acid amplification testing (NAT) should be used as a generic term use in diagnostic laboratory medicine to describe the use of molecular genetic tests such as PCR and others for the detection of DNA or RNA
- Direct antigen testing (DAT) should be used as a generic term to describe the direct detection of antigens in a specimen using specific, often pre-labelled antibodies in different formats (direct fluorescent antigen; ELISA, immune chromatography etc.)
- Virus isolation by cell culture (VIC) should be used as a generic term to describe the use of cell culture for the isolation of infectious, replicating viruses.
- VIC is performed using conventional and shell vial cell culture techniques that can be combined with DAT for a specific diagnosis, but has a long turn-around time (TAT) of 2 – 5 days.
- DAT has a good specificity for RTID and a short TAT of <4 hours, but a lower sensitivity compared to VIC and NAT
- NAT is often preferred because of a higher sensitivity, and an acceptable TAT of <24 hours, and identification of a larger panel of infectious agents, but may not be widely available



CARV Diagnostic Considerations (2)

- Specimens are preferably taken from the sites of clinical involvement
 - Nasopharyngeal aspirates (NPA), nasopharyngeal wash (NPW), swabs (preferably flocked swabs for nasal sampling), tracheal aspirates (TA) and bronchoalveolar lavage (BAL)
- For URTID, pooled bilateral nasopharyngeal and throat swabs rather than nasal wash is preferred.
- For LRTID, BAL is preferred, but TA may be acceptable.
- Testing for Flu-A/B, RSV and HPIV is recommended as first line priority
- Testing for HMPV, HRhV, HCoV, HEnV and adenovirus (HAdV) is recommended as second line priority,
 - if first line testing is negative and if progression to LRTID is seen
- In many centres, testing for multiple CARVs is performed by a multiplex NAT.



CARV Recommendations (1)

Prevention (1)

- Good personal hygiene should be observed including frequent hand washing, cover the mouth when coughing & sneezing, and safe disposal of oral & nasal secretions. *(II-A)*
- Leukaemia patients and HCT patients should avoid contact with individuals with RTI in the hospital and in the community. *(II-A)*
- Young children should be restricted from visiting to patients and wards because of the higher risk of CARV exposure and transmission. *(II-B)*
- All visitors and health care workers (HCW) with RTI should be restricted from access to patients and wards. *(II-A)*



CARV Recommendations (2)

Prevention (2)

- Infection control measures should be applied to patients with RTI undergoing autologous or allogeneic HCT or undergoing chemotherapy for haemato-oncological diseases, which include the isolation of RTI patients and the application of strict protection measures (gloves, gowning, masks, eye protection) for HCW and visitors. **(II-A)**
- Outpatients with symptomatic RTI (RTID) should be seen and treated in accordance with infection control measures i.e. in facilities and rooms separated from other HCT and leukemia patients. **(II-A)**
- Administration of intravenous immunoglobulin (IVIG) preparations to HCT and leukemia patients with hypogammaglobulinaemia $<4.5\text{g/L}$ may reduce the risk of morbidity or mortality secondary to CARV-RTIDs. **(III-C)**
- The use of intravenous monoclonal antibody specific for the RSV-F protein (palivizumab) may be considered for paediatric patients age <2 years as monthly prophylaxis during RSV epidemics. **(III-C)**



CARV Recommendations (3)

Diagnostic procedures

- Patients with symptomatic RTI (i.e. RTID) should be tested for CARVs to guide infection control measures, treatment and decisions regarding deferral of chemotherapy or HCT. **(II-A)**
- Specimens should preferably be taken from the site of clinical involvement, and include pooled swabs, nasopharyngeal aspirates (NPA), nasopharyngeal wash (NPW), swabs, tracheal aspirates (TA), and bronchoalveolar lavage (BAL). **(II-B)**
- First line diagnostic testing should be performed for FLU-A/B, RSV, HPIV. **(II-A)**
- Testing for other CARVs (HMPV, HRhV, HCoV, HEnV, HAdV) should be considered according to risk of exposure, epidemiology, or if testing for the first line CARVs is negative. **(III-B)**
- Patients with LRTID should be considered for BAL and broader diagnostic testing as clinically indicated. **(II-B)**



CARV Recommendations (4)

Treatment (1)

- Deferral of conditioning therapy should be considered for patients with CARV-RTID planned for allogeneic HCT. **(II-B)**
- Deferral of conditioning/chemotherapy could be considered for patients with CARV-RTID scheduled for chemotherapy of haemato-oncological diseases. **(III-B)**
- Patients with RSV-URTID undergoing allogeneic HCT, or recipients of allogeneic HCT with risk factors for progression to RSV-LRTID and death should be treated with aerosolized or systemic ribavirin and IVIG. **(II-B)**
- For allogeneic HCT patients with HPIV-LRTID, treatment with aerosolized or systemic ribavirin and IVIG may be considered. **(III-B)**
- For allogeneic HCT patients with CARV-URTID or CARV-LRTID other than RSV or HPIV, aerosolized or systemic ribavirin and IVIG treatment cannot be recommended. **(III-C)**



CARV Recommendations (5)

Treatment (2)

- For treatment of RSV, aerosolized ribavirin can be administered as 2 g for 2 hours every 8 hours or as 6 g over 18 hours/day for 7-10 days. **(II-B)**
- For treatments using aerosolized ribavirin, appropriate precautions should be applied to avoid environmental exposure and thereby potentially teratogenic effects in pregnant persons including HCW and visitors. **(II-A)**.
- Patients on aerosolized ribavirin should be monitored and treated for adverse events including claustrophobia, bronchospasm, nausea, conjunctivitis and declining pulmonary function **(II-B)**.



CARV Recommendations (6)

Treatment (3)

- For treatment of RSV, systemic ribavirin can be administered orally (**III-B**) or intravenously for patients unable to take oral medication (10mg – 30mg/kg body weight in three divided doses). (**III-C**)
- Patients on systemic ribavirin should be monitored and treated for adverse events including haemolysis, abnormal liver function tests and declining renal function. (**III-B**)
- For allogeneic HCT patients with RSV-LRTID or at high risk for RSV-LRTID, aerosolized or systemic ribavirin therapy may be combined with IVIG (0.5 g/kg body weight) or anti-RSV-enriched antibody preparations. (**III-B**)
- Allogeneic HCT patients with RSV-LRTID or HCT and leukaemia patients at high risk for RSV-LRTID may be considered for treatment with intravenous monoclonal antibody specific for the RSV-F protein (e.g. palivizumab 15mg/kg body weight). (**III-C**)



CARV Recommendations (7)

Treatment (4)

- Withholding treatment for RSV infection should be considered for selected stable leukaemia, autologous and allogeneic HCT patients after careful evaluation of risk factors for morbidity and mortality and the possibility of appropriate follow-up visits e.g.
 - Remission of underlying disease
 - Absence immunosuppressive drug treatment
 - Absence of the risk factors associated with LRTID or mortality. **(III-C)**
- Treatment of CARV-RTID other than influenza is not generally recommended for patients undergoing autologous HCT or chemotherapy for haemato-oncological diseases. **(III-C)**



CARV Outlook & Research Agenda

- Prospective multicentre cohort studies determining the role of DAT, VIC and NAT for CARV diagnosis
- Prospective multicentre cohort studies determining the risk factors for CARV-URTID, -LRTID and -attributable mortality
- Prospective randomized controlled trials comparing aerosolized ribavirin with systemic (oral) ribavirin
- Prospective randomized controlled trials comparing ribavirin with ribavirin plus IVIG
- Prospective randomized controlled trials determining the use of intravenous monoclonal antibody specific for the RSV-F protein (palivizumab) as post-exposure prophylaxis in high-risk patients
- Identifying and testing new antivirals and specific antibody preparations for CARV (especially RSV, HPIV)
- Development of CARV-specific vaccines (especially RSV, HPIV)

Appendix



Risk factors for RSV in HCT patients

- RSV infection
 - Male gender (Nichols et al. 2001)
- Progression to LRTID
 - Lymphopenia $<200/\mu\text{L}$ (Nichols et al. 2001; Ljungman et al. 2001)
 - Older age (Nichols et al. 2001)
 - Mismatched/unrelated donor (McCarthy et al. 1999; Nichols et al. 2001)
 - Allogeneic HCT <1 month (Whimbey et al. 1996)
 - Neutropenia $<500/\mu\text{L}$ (Whimbey et al. 1997)
 - No therapy with aerosolised ribavirin+IVIG (Whimbey et al. 1997)
- Mortality
 - Pre-engraftment (Hertz et al. 1989; Ghosh et al. 2001; Small et al. 2002; Khanna et al. 2008)
 - Lymphopenia $\leq 200/\mu\text{L}$ (Ljungman et al. 2001; Chemaly et al. 2006; Ghosh et al. 2001; Schiffer et al. 2009)
 - Allogeneic HCT < 1 months (Whimbey et al. 1996)
 - Severe immunodeficiency (Khanna et al. 2008)
 - Older age >65 yrs (Chemaly et al. 2006)



RSV Disease and Mortality in HCT patients

■ Progression from URTID to LRTID in HCT patients is observed in 20% - 68% of patients

- Chemaly et al. 2006 (n=107): 29% (treated 20%; untreated 59%)
- Martino et al. 2005 (n=12): 25%
- Khanna et al. 2008 (review n=465): 38% (untreated 68%; treated 32%)
- Shah et al. 2011 (review n=185): 30% (untreated 45%; treated 16%)
- Ljungman et al. 2001 (ret, HCT, n=8): 25%
- Nichols et al. 2001 (ret, HCT; n=54): 32%
- Avetysian et al. 2009 (ret, HCT; n=18): 0% (16 treated [89%])

■ LRTID RSV-attributable mortality 17-70%

- Avetysian et al. 2009 (ret, HCT, n=14): 36%
- Chemaly et al. 2006 (n=107): 17% (if treated [33% if untreated])
- Martino et al. 2005 (n=12): 25%
- Khanna et al. 2008 (review n=437): 32%
- Schiffer et al. 2009 (ret n=12): 25%
- Shah et al. 2011 (review n=265): 52%
- Sung et al. 2008 (ret n=40; paed AML): 10%
- Ljungman et al. 2001 (ret, HCT, n=14): 34%

*review, review of the literature;
ret, retrospective study*



Review of RSV Treatment

■ Outcome of *any* ribavirin treatment incl. combinations

		P	OR (95% CI)
– URTI treated (n=161)			
• Progression to LRTID (n=26)	16%		
– URTI untreated (n=342)			
• Progression to LRTID (n=150)	44%	<.001	4.1 (2.5 – 6.5)
– LRTI treated (n=240)			
• Mortality (n=87)	36%		
– LRTI untreated (n=35)			
• Mortality (n=28)	80%	<.001	7.0 (2.9 – 16.8)

(Shah & Chemaly 2011, Blood 117: 2755; selected from Table 4)



Off-label use of Systemic Ribavirin for RSV- or HPIV-RTID

■ Oral

- maximal dosing 10 mg/kg body weight every 8 hours (= TID)

e.g. for adults

Day 1: Start with 600 mg loading dose, then 200mg every 8h

Day 2: 400mg every 8h

Day 3: increase to maximal dose of 10mg/kg body weight every 8h

■ Check for adverse events

- Decrease dose stepwise or discontinue ribavirin

■ Creatinine clearance

- Same as for oral administration
- 30-50 mL/min maximal 200mg every 8h
- 10-30 mL/ min 200mg once a day

■ Intravenous ribavirin is dosed similarly

modified after Hirsch et al. 2004 SwissNoso 11 (3)

www.swissnoso.ch/de/bulletin/articles/article/respiratorisches-syncytial-virus-rsv-infektion-massnahmen-beim-immunsupprimierten-patienten%22

Khanna et al. 2008 Clin Inf Dis 46: 402)

