Community-acquired respiratory virus (CARV) Infections other than influenza and adenovirus: RSV, MPV, PIV, Rhino, and Corona

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Overview

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- Definitions of CARV respiratory tract infection and disease
- Adapted ECDC definition of CARV RTID
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CARV Introduction

- Community-acquired respiratory virus (CARV) infections are caused by a range of diverse viral agents with RNA genomes (Orthymyxo-, 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 hematological disorders and those undergoing hematopoietic stem cell transplantation (HCT).

CARV covered in this Slide Set

- Respiratory Syncitial Virus
  - RSV-A and -B
- Human Parainfluenza Virus (HPIV)
  - PIV-1, -2, -3, and -4
- Human Metapneumo-Virus (HPMV)
- Human Coronavirus (HCoV)
  - Group I-like (HCoV-229E and HCoV–NL63)
  - Group II-like (HCoV-OC43 and HCoV-HKU1)
- Human Rhinovirus
  - Three groups A, B. and C, more than 100 serotypes
- Enterovirus (EnV)
  - Multiple types with predilection for oropharngx 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 laryngx e.g. in samples from nose, pharyngx, sinuses, laryngx
- Lower respiratory tract infection (LRTI)
  - Detection of CARV below laryngx e.g in samples from trachea, bronchus, bronchioli
- Symptomatic URTI = URTI disease (URTID)
  - Detection of CARV in upper respiratory 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)
  - Pathologic 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 of human to human transmission

Laboratory Criteria

- Detection of CARV in a clinical specimen by at least *one* 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 (RTID)
- **Probable case**
  - Any person meeting the clinical criteria (RTID) and with an epidemiological link
- **Confirmed case**
  - Any person meeting the clinical (RTID) and the laboratory criteria

Respiratory Syncytial Virus (RSV) Characteristics

- RSV A and B infections occur throughout the year, but increase in children during the cold season with bronchiolitis and penumia in neonates.
- RSV infection of patients with HCT and/or other hematological diseases coincides with the community activity suggesting community-acquired, household or nosocomial transmission.
- RSV infection occurs in 0.3% - 2.2% of in pediatric patients with acute myeloid leukemia and in 1%-12% of adult HSCT 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, preengraftment, and lymphopenia
- Treatment options are limited by the lack of RCTs, but the pooled published evidence suggests that treating URTID in patients at risk and LRTID 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 Bllod 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 mostly mild URTID throughout the year with varying seasonal increases in fall and spring in children and laryngotracheitis, bronchiolitis and pneumonia in 15% of cases.
- In HSCT recipients, HPIV infections range from 2% - 7% and may be as high as 17.9% if testing asymptomatic patients by NAT
- Persistent subclinical shedding may contribute to nosocomial outbreaks.
- HPIV-3 is most commonly detected in HSCT recipients (c. 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 LRTID include higher dose steroids, lymphopenia <200 cells/mL.
- The role of treatment is limited by the lack of RCTs, although some centers consider treating HPIV URTID in patients at risk and many centers consider treating LRTID.

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 months
- HMPV infection rates in HCT patients range from 5%-9% during the first 2 years posttransplant and include nosocomial transmission
- Asymptomatic and prolonged shedding has been reported in HCT patients
- Progression to HPMV 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 role of treatment is limited by the lack of effective agents and RCTs, although some centers consider treating HMPV LRTID

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 be reflect in part increasing testing for CARVs
- URTID with rhinitis, pharyngitis and laryngitis is the common manifestation, but LRTID with bronchitis, bronchiolitis, pneumonia may occur rarely in very young (age <1 year) and in immunodeficient patients
- In HCT patients, HCoV has been detected in 6.7% - 15.4%, but asymptomatic shedding was seen in 41%. In symptomatic HCT patients, co-infections with other pathogens was frequent.
- LRTID and pneumonia with fatal outcome occurs rarely in HCT
- The role of treatment is limited in view of the largely benign course, the lack of effective agents and RCTs, and only few centers consider treating HCoV LRTID

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) Characterisitics

- HRhV belongs to the picornaviridae and consists of 3 genotypes (A,B,C) encompassing more than 100 serotypes, which are, throughout the year, the most common cause of URTID (rhinorhea, postnasal drip, cough) and occasionally bronchitis
- In allogenic HCT recipient, HRhV is 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 19%
- LRTID in allogenic HCT is rare (<10%), with mortality in <10%
- The role of treatment is limited by the lack of agents and RCTs, and only few centers consider treating HRhV LRTID

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

Other CARVs Characeristics

- Human Bocavirus (HBoV), enterovirus (HEnV) and human polyomavirus (HPyV) have been detected in patients with hematologic malignancies or HCT, but risk factors for disease and 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 might indicate clinically significant replication.
- HEnV belong to the *picornavididae* is detected in <5% of hematological patients with URTID with progression to LRTID occuring 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%).
- Currently, there is 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 describing the use of molecular-genetic test such as PCR and others for the detection of microbial DNA and 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-labeled 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 including cell culture, shell vial etc.
- DAT and VIC have a good specificity. NAT is generally preferred because of a higher sensitivity, and a short turn-around time, yet may not be widely available.

CARV Diagnostic Considerations (2)

- Specimens are preferentially taken from sites of clinical involvement
  - Nasopharyngeal aspirates (NPA), nasopharyngeal wash (NPW), swabs (preferrably flocked swabs for nasal sampling), sputum, tracheal aspirates (TA) and bronchoalveolar lavage (BAL)
- For URTID, pooled bilateral nasopharyngeal and throat swabs rather than nasal wash is preferred in order to obtain respiratory specimens.
- For LRTID, BAL is preferred, but sputum or TA may be acceptable.
- Testing for Flu-A/B, RSV and PIV is recommended as a first priority
- Testing for MPV, RhV, CoV, EnV and AdV is recommended as a second priority,
  - if NATs of first priority are negative and if progression to LRTID is seen
- In many centers, NAT for CARV is performed in a multiplex format.

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)***

- Leukemia 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 access to patients and wards because of the higher risk of CARV exposure and transmission. ***(II-B)***

- Visitors and HCW with RTI should be restricted from access to patients and wards. ***(II-A)***

CARV Recommendations (2)

Prevention (2)

- To leukemia patients and patients after HCT with RTID, infection control measures should be applied which include should be isolation of patients and 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 e.g. in facilities and rooms separated from other HCT patients. ***(II-A)***

- Supplementing IVIG for patients with hypogammaglobunemia <4.5g/L may reduce the risk of CARV morbidity or mortality. ***(III-C)***

- The use of intravenous monoclonal antibody preparations targeting the RSV-F protein (palivizumab) may be considered for pediatric patients age <2 years as monthly prophylaxis during RSV epidemics ***(III-C).***

CARV Recommendations (3)

Diagnostic procedures

- HCT candidates or HCT recipients with symptomatic RTI (RTID) should be tested for CARVs to guide infection control measures, decisions regarding deferral of chemotherapy or HCT as well as treatment. ***(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 priority diagnostic testing should be performed for FLU-A/B, RSV, PIV. ***(II-A)***
- Testing for other CARVs (HMPV, HRhV, HCoV, HEnV, HAdV) should be considered according to risk of exposure, epidemiology, or if first priority CARV testing is negative. ***(III-B)***
- Patients with LRTID should be considered for BAL and broader diagnostic testing as clinically indicated. ***(II–B)***

CARV Recommendations (3)

Treatment (1)

- Patients with RSV URTID undergoing allogenic HCT, or recipients of allogenic HCT with risk factors for progression to RSV-LRTID and death should be treated with aerosolized or systemic ribavirin and IVIG. ***(II-B)***

- For allogenic HCT patients with PIV-LRTID, treatment with aerosolized or systemic ribavirin and IVIG may be considered. ***(III-B)***

- For allogenic HCT patients with CARV-URTID or CARV-LRTID other than RSV or PIV, systemic ribavirin and IVIG treatment cannot be generally recommended. ***(III-C)***

CARV Recommendations (3)

Treatment (2)

- For treatment of RSV, aerosolized ribavirin can be administered as 2 g for 2hours 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 potential teratogenic effects in pregnant HCW and visitors. ***(II-A)***.
- Patients on aerosolized ribavirin should be monitored and treated for adverse events including claustrophobia, bronchospasm, nausea, conjunctival irritation and declining pulmonary function ***(II-B)***.

CARV Recommendations (4)

Treatment (3)

- For treatment of RSV, systemic ribavirin can be administered as oral drug ***(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 hemolysis, abnormal liver function tests and declining renal function ***(III-A)***.

- For allogenic HCT patients with RSV-LRTID or at high risk for RSV-LRTID treatment with intravenous antibody (IVIG) or anti-RSV enriched antibody preparations in combination with aerosolized or systemic ribavirin therapy may be considered ***(III-B)***.

- Allogenic HCT patients with RSV-LRTID or patients at high risk for RSV-LRTID may be considered for treatment with intravenous monoclonal antibody preparations targeting the RSV-F protein (Palivizumab 15mg/kg body weight) ***(III-C)***.

CARV Recommendations (5)

Treatment (3)

- *No treatment* for RSV infection should be considered for selected stable (out-)patients after careful evaluation of risk factors for morbidity and mortality and granted appropriate follow-up. ***(III-C)***
  - Remission of underlying disease
  - No immunosuppressive drugs
  - None of the risk factors associated with LRTID or death

Patients with autologous HCT and/or hemato-oncological disease

- Infection control measures should be applied to patients undergoing autologous HCT or chemotherapy for hemato-oncological diseases with symptomatic CARV-RTI (RTID) ***(III-B)***.

- Deferral of conditioning / chemotherapy should be considered for patients with CARV-RTID scheduled for autologous HCT or chemotherapy for hemato-oncological diseases ***(III-B)***.

- Treatment of CARV-RTID other than influenza is not generally recommended for patients undergoing autologous HCT or chemotherapy for hemato-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 of CARV-URTID, -LRTID and -attributable mortality
- Prospective randomized controlled trials comparing aerosolized RBV with systemic (oral) RBV
- Prospective randomized controlled trials comparing RBV with RBV plus IVIG
- Prospective randomized controlled trials determining the use of intravenous monoclonal antibody preparations targeting 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, PIV)
- Development of CARV-specific vaccines (especially RSV, PIV)

Appendix

RSV Risk factors

- RSV infection
  - Male gender (Nichols et al. 2001)
- Progression to LRT-ID
  - Lymphopenia <200/uL (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)
  - Allogenic HCT <1month (Whimbey et al. 1996)
  - Neutropenia <500/µL (Whimbey et al. 1997)
  - No therapy with aeRBV+ivIG (Whimbey et al. 1997)
- Mortality
  - Preengraftment (Hertz et al. 1989; Ghosh et al. 2001; Small et al. 2002; Khanna et al. 2008)
  - Lymphopenia ≤200/uL (Ljungman et al. 2001; Chemaly et al. 2006; Ghosh et al. 2001; Schiffer et al. 2009)
  - Allogenic HCT < 1 months (Whimbey et al. 1996)
  - Severe immunodeficiency (Khanna et al. 2008)
  - Older age >65 yrs (Chemaly et al. 2006)
  - Underlying disease ?

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 at 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% (89% treated)

- LRTID RSV-attributable mortality 17-70%
  - Avetisyian et al. 2009 (ret, HCT, n=14): 36% (86% treated)
  - Chemaly et al. 2006 (n=107): 17% (treated); [33% 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% (untreated 35%; treated 70%)
  - Sung et al. 2008 (ret n=40; ped AML): 10%
  - Ljungman et al. 2001 (ret, HCT, n=14): 34%

RSV Treatment (2)

- Review of outcome of combining *any* RBV treatment/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)