AMCLI associazione microbiologi clinici italiani

Fondazione IRCCS Policlinico San Matteo

Sistema Socio Sanitario

Regione Lombardia

XLVIII CONGRESSO NAZIONALE AMCLI

2019

9-12 NOVEMBRE 2019
PALACONGRESSI RIMINI

Impatto dei virus respiratori come causa di infezioni severe in pazienti ricoverati in terapia intensiva

Sessione 15

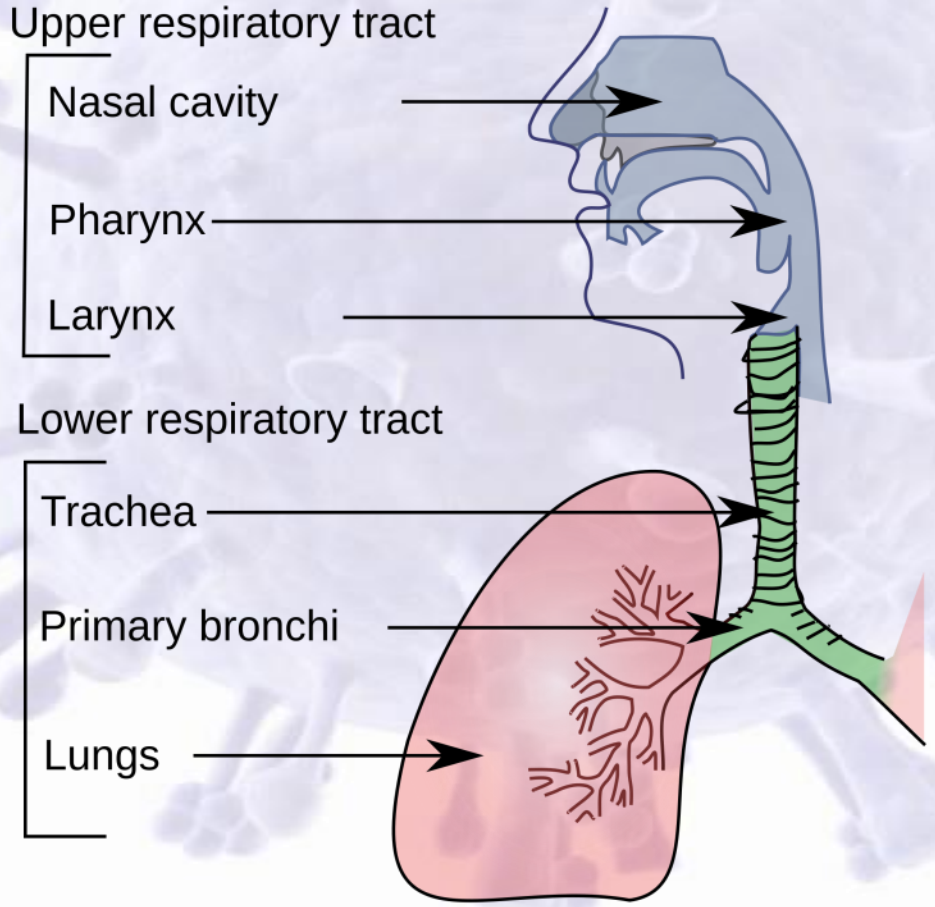
INFEZIONI VIRALI RESPIRATORIE

Antonio Piralla

Respiratory system

- The upper respiratory tract:
  - is continuously exposed to potential pathogens.
  - Nasal cavity, sinuses, pharynx, and larynx
  - Infections are fairly common.
  - Usually nothing more than an irritation

- The lower respiratory tract:
  - Lungs and bronchi
  - is essentially a sterile environment
  - Infections are more dangerous
  - Can be very difficult to treat



Lower respiratory tract infection

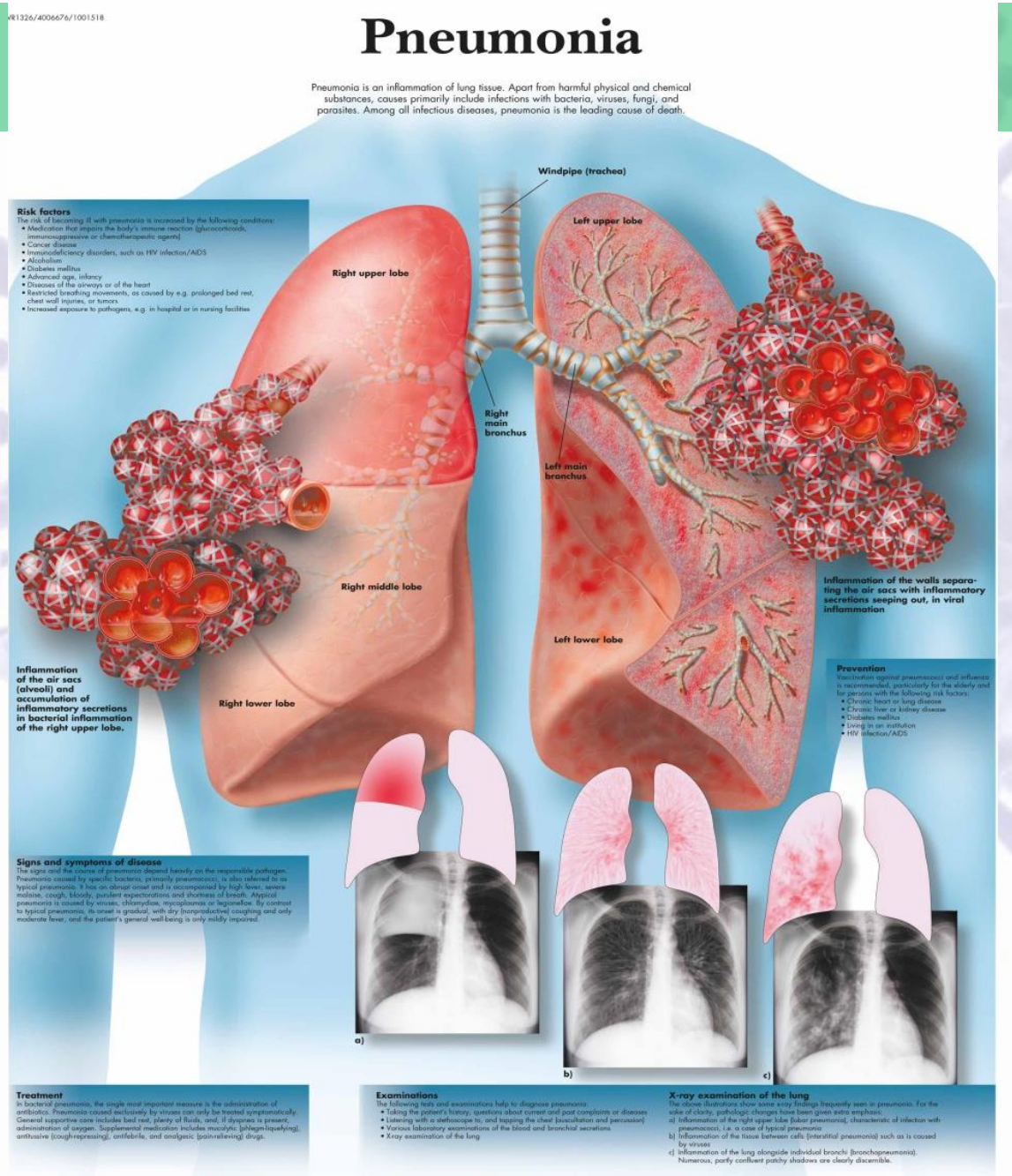
Essentially, it is inflammation of the airways/pulmonary tissue, due to viral or bacterial infection, below the level of the larynx.

- **Lobar Pneumonia**
- **Interstitial pneumonia**

in which the inflammatory process is confined within the alveolar walls, peribronchial & interlobular tissues

- **Bronchopneumonia**

Begins in the terminal bronchioles which become clogged with mucopurulent exudates to form consolidated patches in nearby lobules.



X-ray examination of the lung

The above illustrations show some x-ray findings frequently seen in pneumonia. For the sake of clarity, pathologic changes have been given extra emphasis:

a) Inflammation of the right upper lobe (lobar pneumonia), characteristic of infection with pneumococci, i.e. a case of typical pneumonia
b) Inflammation of the tissue between cells (interstitial pneumonia) such as is caused by viruses
c) Inflammation of the lung alongside individual bronchi (bronchopneumonia). Numerous, partly confluent patchy shadows are clearly discernible.

ICU admission and severe infections

Recommended ICU admission if either major or at least three minor criteria

Minor criteria	Major criteria
Respiratory rate 30 breaths/min	Invasive mechanical ventilation
PaO2/FiO2 ratio 250	Septic shock with the need for vasopressors
Multi-lobar infiltrates	
Confusion/disorientation	
Uremia (BUN level, 20 mg/dL)	
Leukopenia (WBC count, >4000 cells/mm^3)	
Thrombocytopenia (platelet count, !100,000 cells/mm^3)	
Hypothermia (core temperature, <36°C)	
Hypotension requiring aggressive fluid resuscitation	

ECMO

Acute Respiratory Distress Syndrome (ARDS) was defined:

- Acute onset (≤1 week) respiratory failure
- hypoxemia (pO_2/FiO_2 ratio <300 mmHg while on positive end-expiratory pressure or noninvasive CPAP ≥5 cmH_2O)
- bilateral opacities at chest imaging.

This Issue | Views 126,565 | Citations 2,656 | Altmetric 87

Special Communication | ONLINE FIRST

June 20, 2012

More

Acute Respiratory Distress Syndrome
The Berlin Definition

The ARDS Definition Task Force*

Author Affiliations

JAMA. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pao_2/Fio_2 × (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Respiratory viruses: How many??

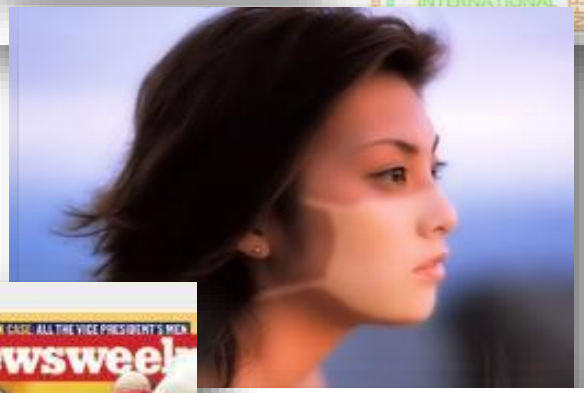
- **Influenza virus type A (Flu A)**
  - H1N1, H3N2, H1N1pdm09 (H5N1, H3N2v, H7N9)
- **Influenza virus type B (Flu B)**
  - Yamagata-lineage and Victoria-lineage
- **Human Respiratory syncytial virus (hRSV)**
  - type A, type B
- **human metapneumovirus (hMPV)**
  - type A, type B
- **Human parainfluenza viruses (hPIVs)**
  - hPIV1, hPIV2, hPIV3, hPIV4a/b
- **Human coronaviruses (hCoV)**
  - OC43, 229E, HKU1, NL63 (SARS, MERS)
- **Rhinoviruses (HRVs)**
  - 100 (A+B) and 60 types (C) in the last 15 years
- **Enteroviruses (EVs)**
  - more than 120 types (20 in the last 15 years)
- **Adenoviruses (AdV)** more than 55 types

New emerging or Re-emerging viruses

2003
SARS

2009 – Flu H1N1pdm09

2013 - H7N9



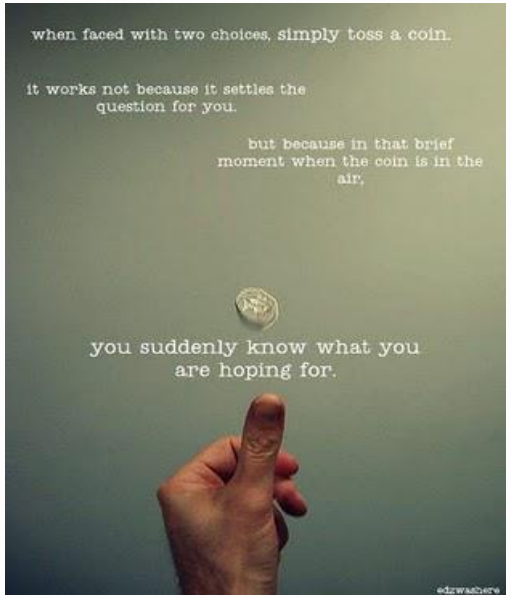
2012
MERS CoV

2005 – Flu H5N1

2016
EV-D68

Diagnosis of respiratory viruses in ICU pts

clinical



etiologic

Clinical diagnosis based upon better defined parameters:

- Symptoms
- Signs
- Imaging

Etiologic diagnosis often disregarded because of:

- Low awareness of the problem;
- restricted availability of diagnostic assays
- costs

Influenza virus A

HCoV SARS

Metapneumovirus

RSV

Clinical samples

- Suggestive clinical features combined with a **chest radiograph** or other **imaging technique** is required for the diagnosis of pneumonia.

- It is recommended that “patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues.”

- Clinical samples:
  - ✓Pharyngeal swab
  - ✓Nasal swab
  - ✓Nasopharyngeal aspirates

  ] URT

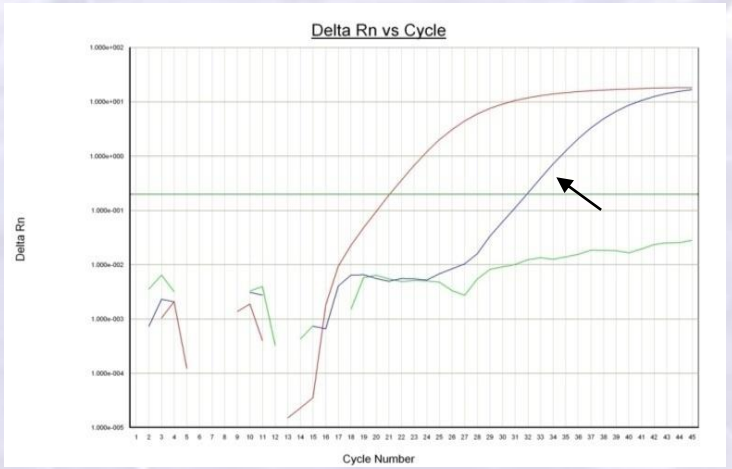
  - ✓Broncho aspirates
  - ✓Broncoalveolar lavage

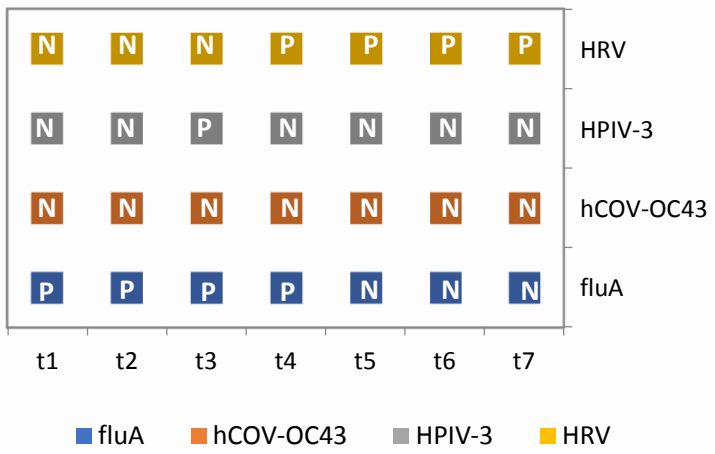
  ] LRT

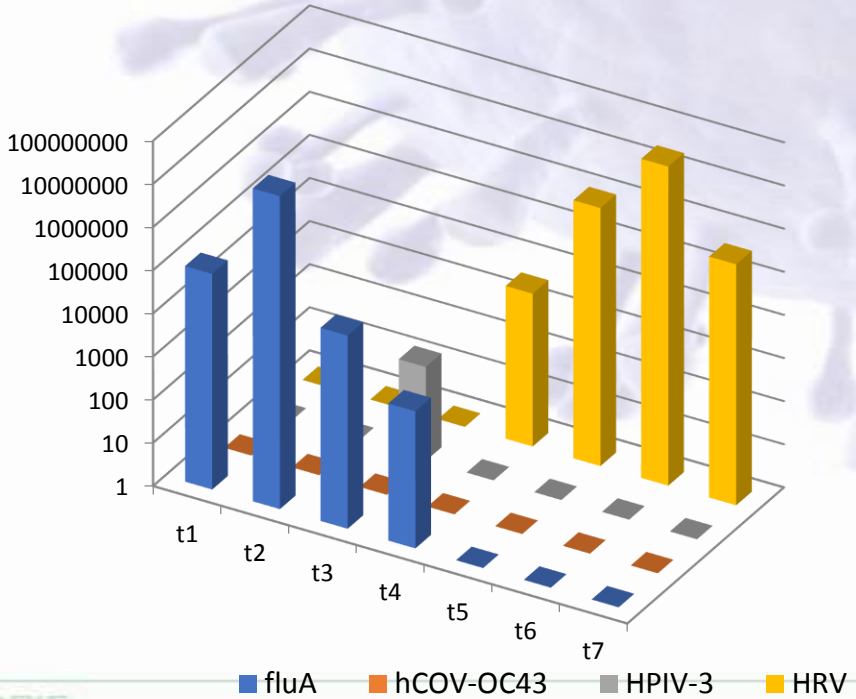
Diagnosis of respiratory viruses – gold standard

Molecular Assays - PCR and Real-time PCR

- Molecular technique using a clinical sample
- Extract and amplify nucleic acid (DNA or RNA) of specific pathogen
- Qualitative *vs* Quantitative?
- Singleplex *vs* Multiplex?
- Rapid response







LRT *vs* URT samples

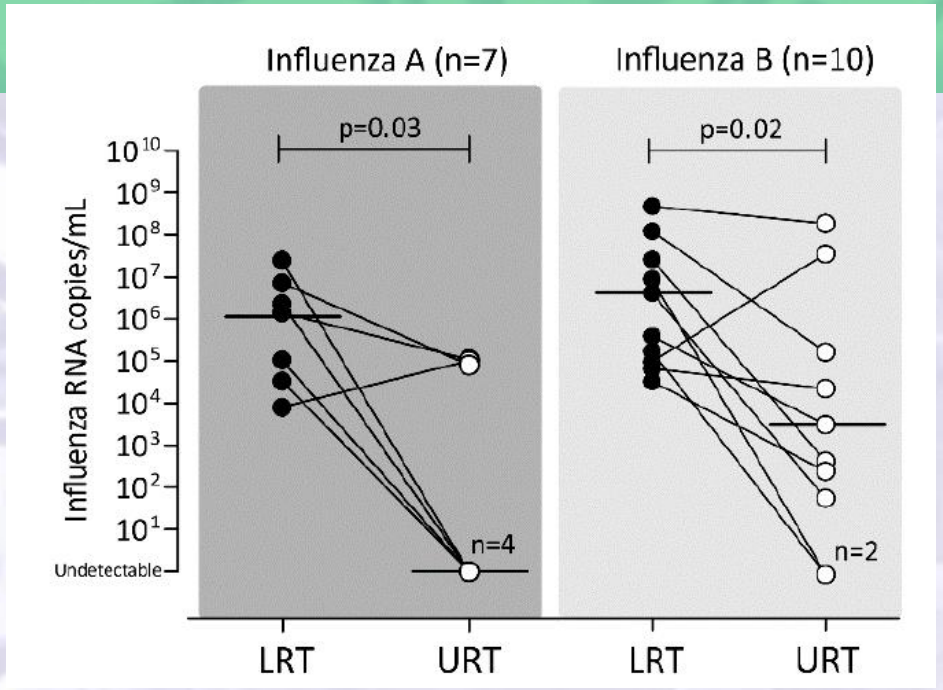
International Journal of *Molecular Sciences*

MDPI

Article

Molecular Characterization of Influenza Strains in Patients Admitted to Intensive Care Units during the 2017–2018 Season

Antonio Piralla [1,*,†], Elena Pariani [2,†], Federica Giardina [1], Cristina Galli [2], Davide Sapia [1], Laura Pellegrinelli [2], Federica Novazzi [1], Giovanni Anselmi [2], Francesca Rovida [1], Francesco Mojoli [3,4], Danilo Cereda [5], Sabrina Senatore [5] and Fausto Baldanti [1,3]



Influenza viruses were undetectable in 30-40% of paired URT samples.

ORIGINAL ARTICLE VIROLOGY

Severe outcome of influenza A/H1N1/09v infection associated with 222G/N polymorphisms in the haemagglutinin: a multicentre study

F. Baldanti[1], G. Campanini[1], A. Piralla[1], F. Rovida[1], A. Braschi[2], F. Mojoli[2], G. Iotti[3], M. Belliato[3], P.G. Conaldi[4], A. Arcadipane[5], E. Pariani[6], A. Zanetti[6], L. Minoli[7] and V. Emmi[3]

1) *Molecular Virology Unit,* 2) *Intensive Care Unit I,* 3) *Intensive Care Unit II, Fondazione IRCCS Policlinico San Matteo, Pavia,* 4) *Institute of Microbiology and Virology,* 5) *Intensive Care Unit, ISSMET, Palermo,* 6) *Dipartimento di Sanità Pubblica-Microbiologia-Virologia, Università degli Studi di Milano, Milan and* 7) *Institute of Infectious Diseases, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy*

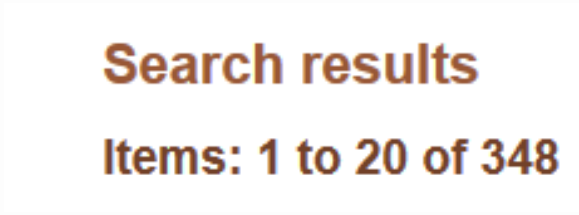
OPEN ACCESS Freely available online

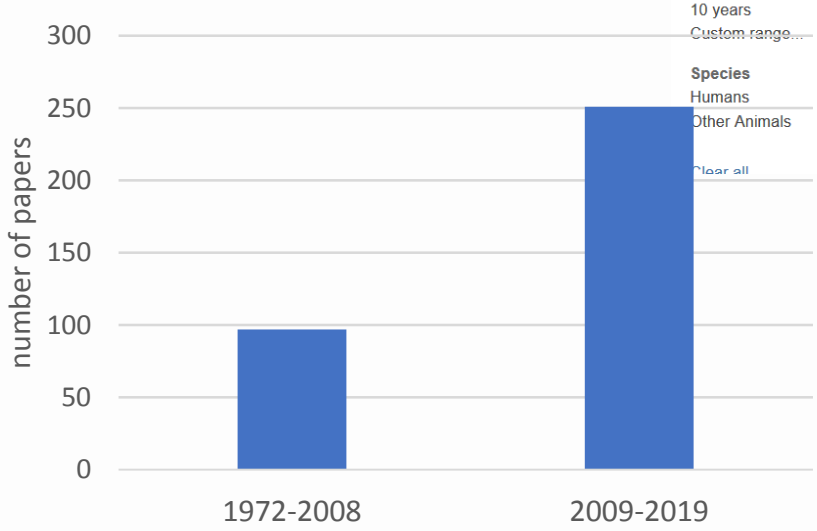
PLoS one

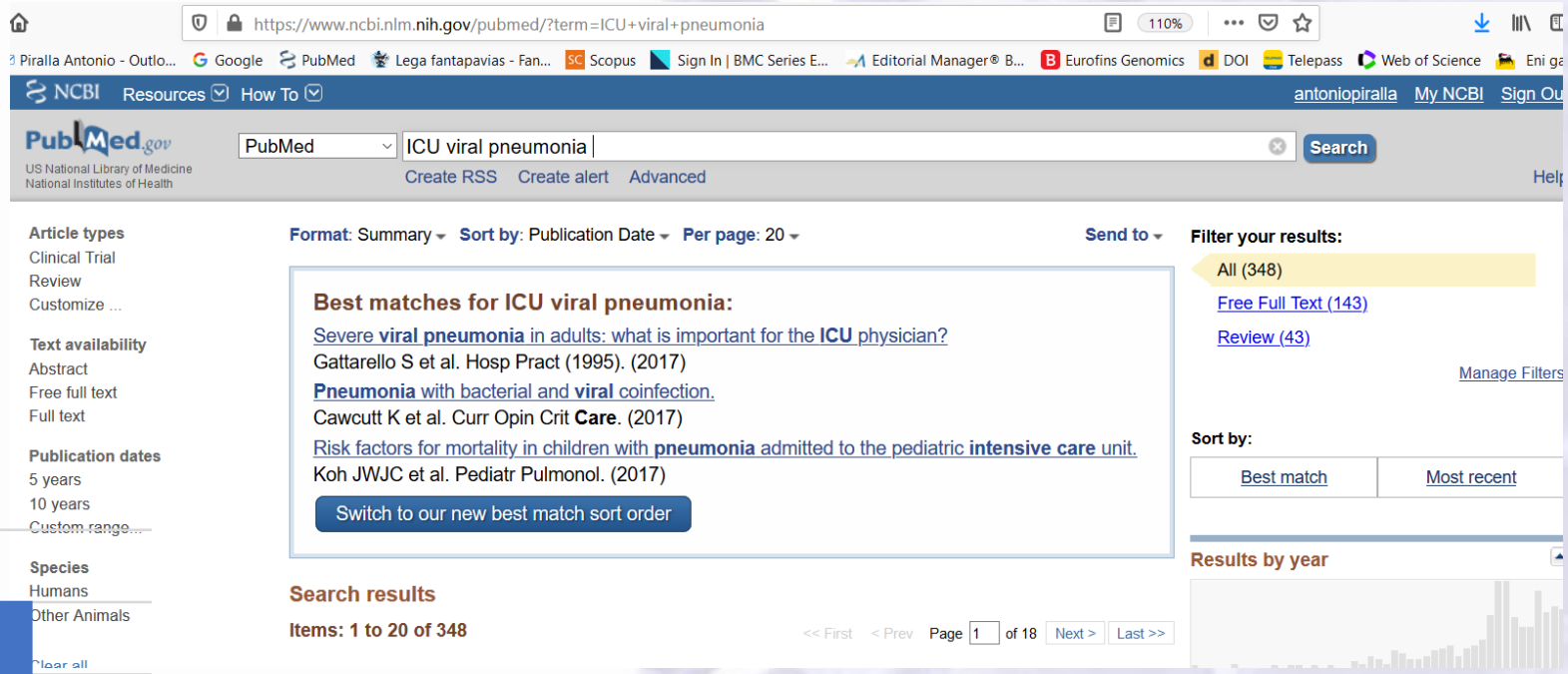
Segregation of Virulent Influenza A(H1N1) Variants in the Lower Respiratory Tract of Critically Ill Patients during the 2010–2011 Seasonal Epidemic

Antonio Piralla[1], Elena Pariani[2], Francesca Rovida[1], Giulia Campanini[1], Alba Muzzi[3], Vincenzo Emmi[4], Giorgio A. Iotti[5], Antonio Pesenti[6], Pier Giulio Conaldi[7], Alessandro Zanetti[2], Fausto Baldanti[1]* and the Severe Influenza A Task Force

State-of-art on viral pneumonia







1972-2008 → 2.6 papers/year

2009-2019 → 25.1 papers/year

In the last decade the Introduction of multiplexed nucleic acid amplification test (NAAT) has lead to improve the diagnosis of respiratory viruses.

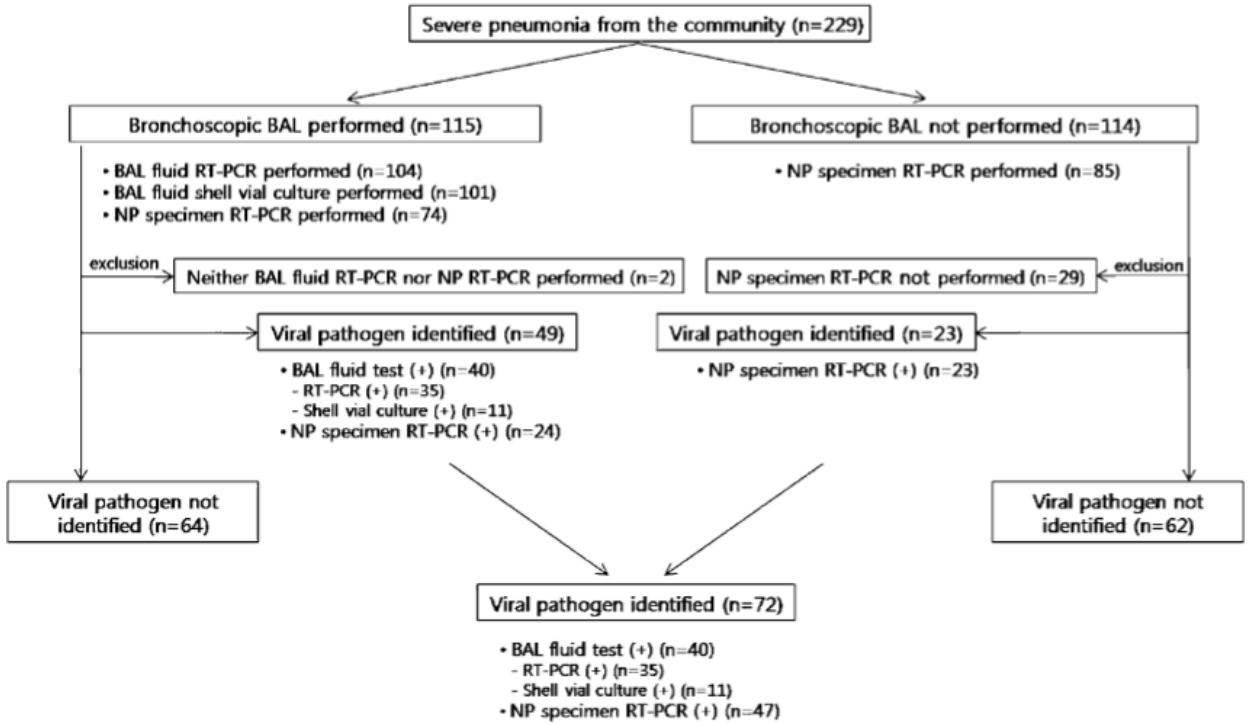
Viral Infection in Patients with Severe Pneumonia Requiring Intensive Care Unit Admission

Sang-Ho Choi[1], Sang-Bum Hong[2], Gwang-Beom Ko[1], Yumi Lee[1], Hyun Jung Park[1], So-Youn Park[1], Song Mi Moon[1], Oh-Hyun Cho[1], Ki-Ho Park[1], Yong Pil Chong[1], Sung-Han Kim[1], Jin Won Huh[2], Heungsup Sung[3], Kyung-Hyun Do[4], Sang-Oh Lee[1], Mi-Na Kim[3], Jin-Yong Jeong[1,5], Chae-Man Lim[2], Yang Soo Kim[1], Jun Hee Woo[1], and Younsuck Koh[2]

[1]Department of Infectious Diseases, [2]Department of Pulmonary and Critical Care Medicine, [3]Department of Laboratory Medicine, [4]Depa Radiology, and [5]Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Am J Respir Crit Care Med Vol 186, Iss. 4, pp 325–332, Aug 15, 2012

Originally Published in Press as DOI: 10.1164/rccm.201112-2240OC on June 14, 2012



- A total of 133 patients (67.2%) had one or more respiratory pathogens that were identified, and 113 patients (57.0%) underwent bronchoscopic BAL for etiologic diagnosis.
- 71 (35.9%) had a bacterial infection ,and 72 patients (36.4%) had a viral infection.
- Rhinovirus was the most common identified virus (23.6%), followed by parainfluenza virus (20.8%), human metapneumovirus (18.1%), influenza virus (16.7%), and RSV (13.9%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults

July 30, 2015
N Engl J Med 2015; 373:415-427
DOI: 10.1056/NEJMoa1500245

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Children

February 26, 2015
N Engl J Med 2015; 372:835-845
DOI: 10.1056/NEJMoa1405870

The NEW ENGLAND JOURNAL of MEDICINE

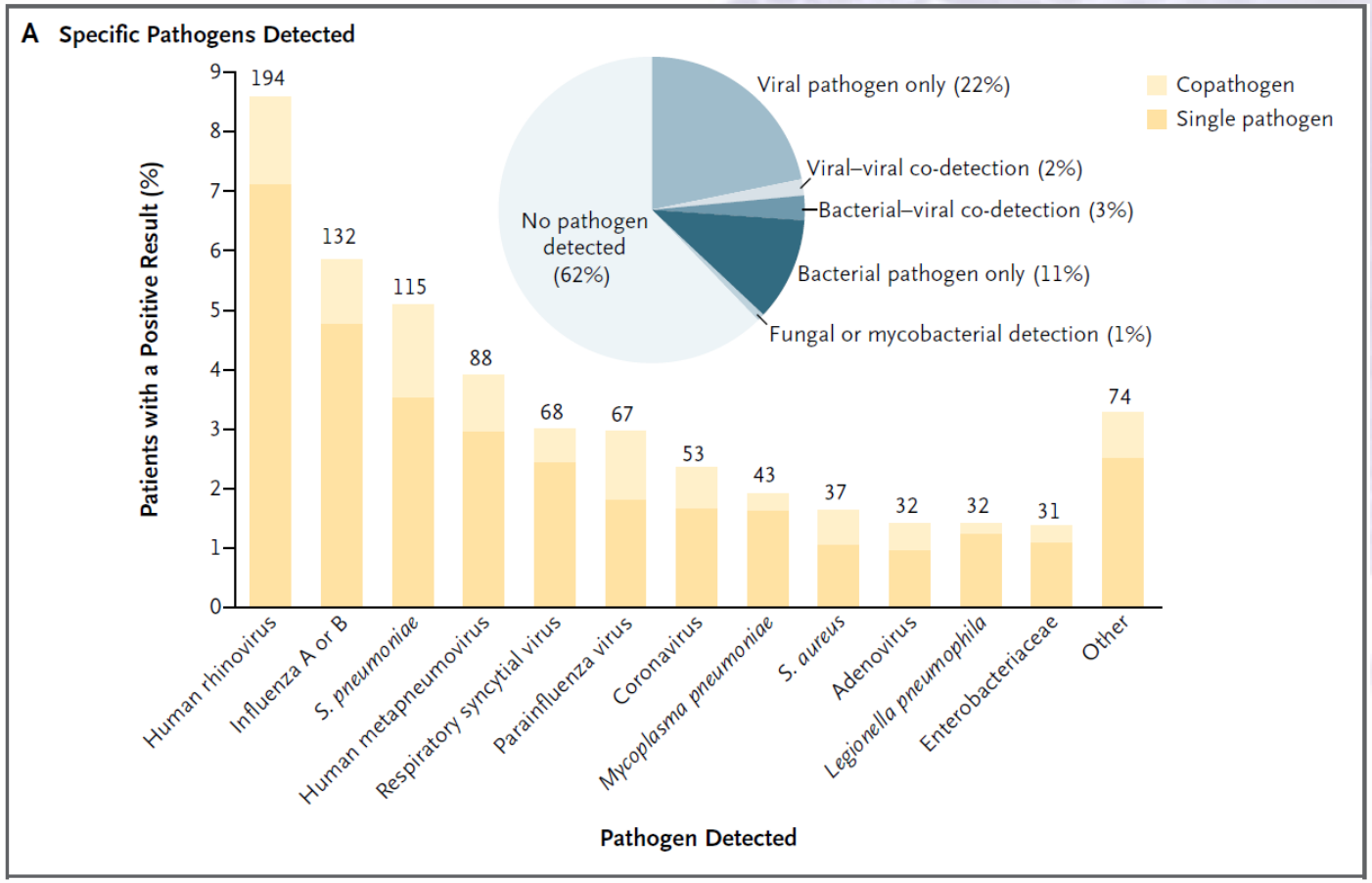
ORIGINAL ARTICLE

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults

CONCLUSIONS

The incidence of community-acquired pneumonia requiring hospitalization was highest among the oldest adults. Despite current diagnostic tests, no pathogen was detected in the majority of patients. Respiratory viruses were detected more frequently than bacteria. (Funded by the Influenza Division of the National Center for Immunizations and Respiratory Diseases.)

Jain et al, NEJM 2015



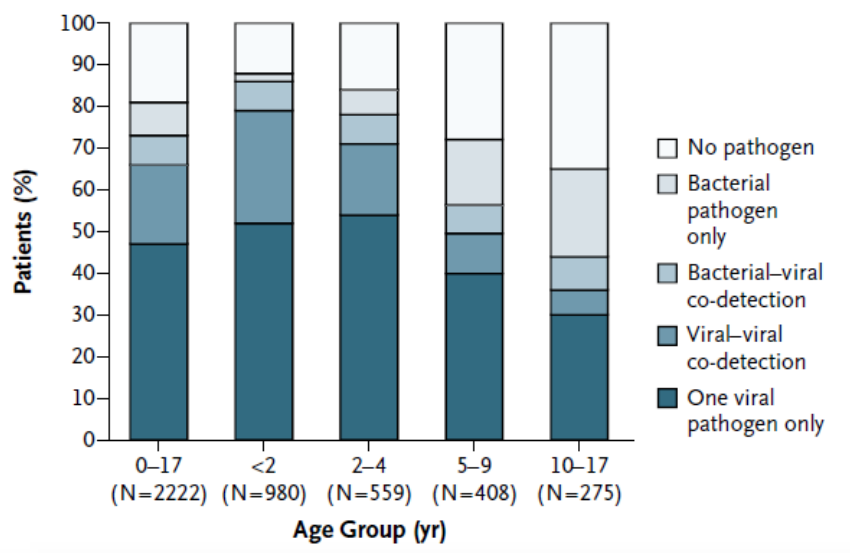
Recent past

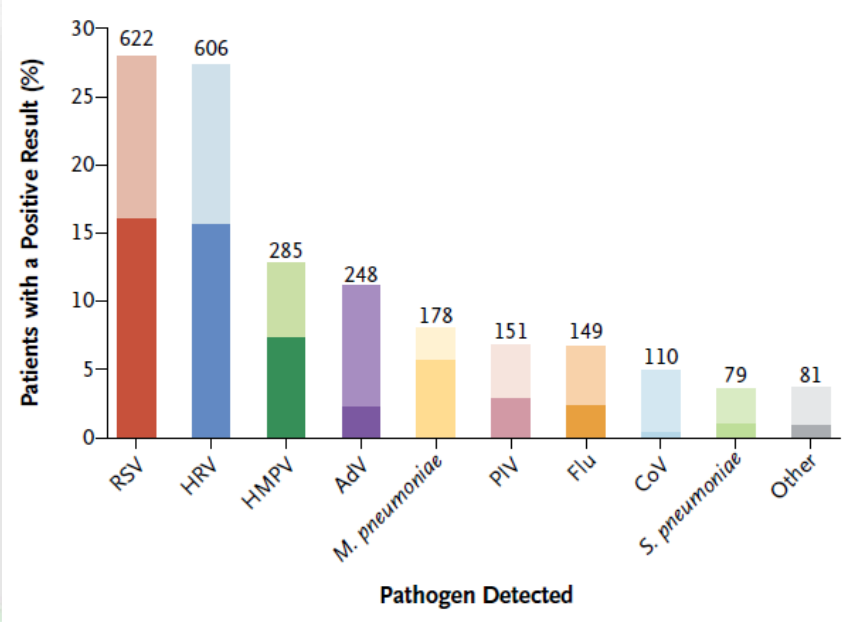
The NEW ENGLAND JOURNAL of MEDICINE

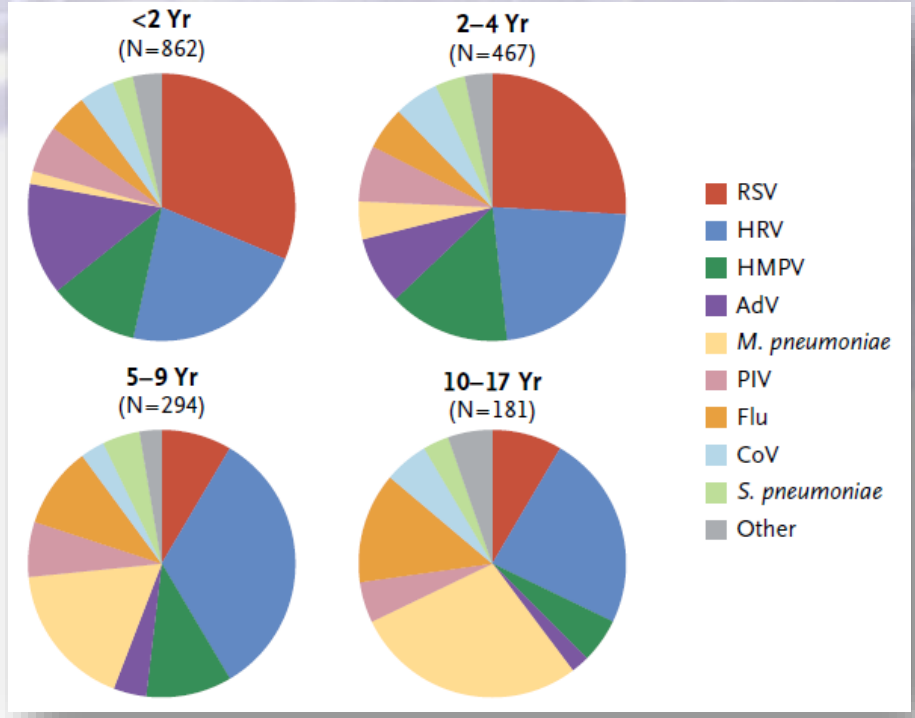
ORIGINAL ARTICLE

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Children

From January 2010 through June 2012, we enrolled 2638 of 3803 eligible children (69%), 2358 of whom (89%) had radiographic evidence of pneumonia.



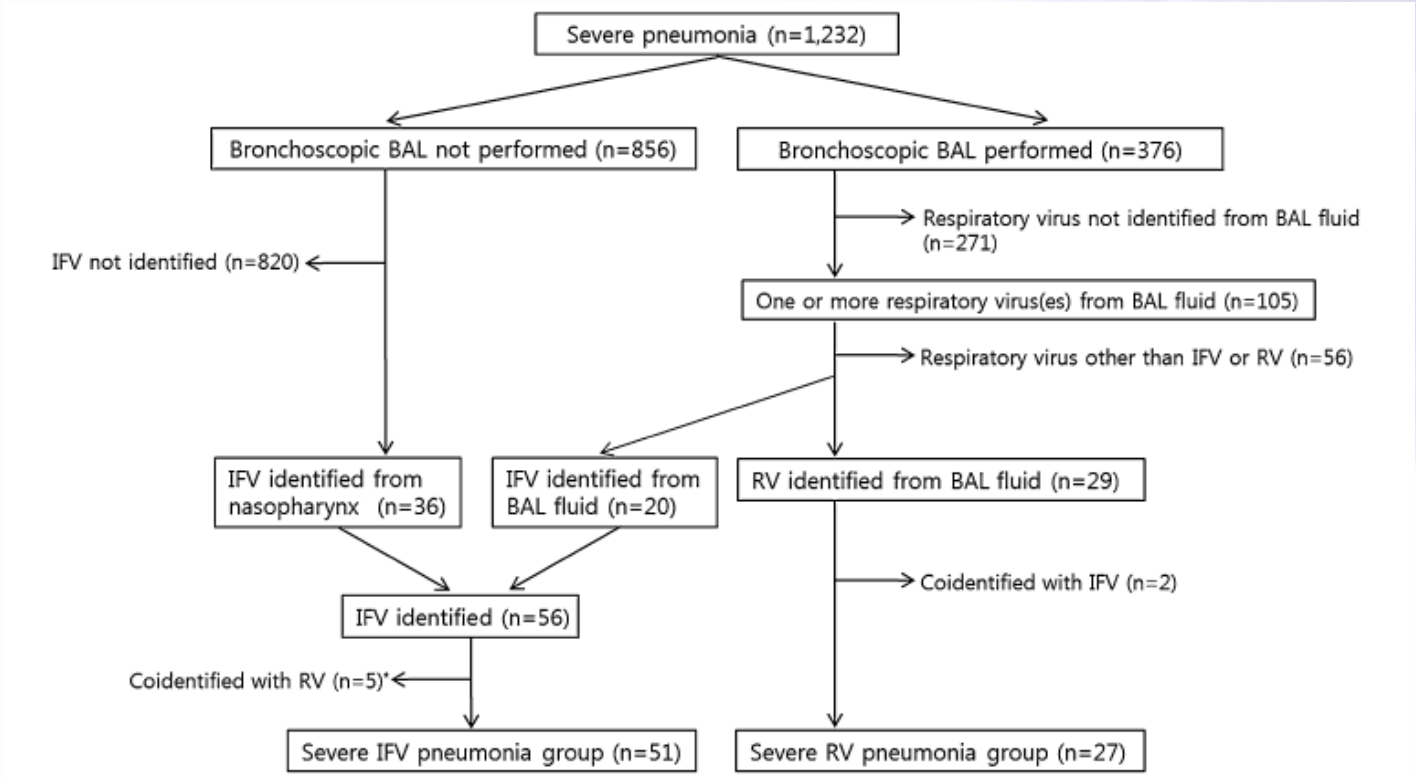




HRV and Pnemuon

Clinical characteristics and outcomes of severe rhinovirus-associated pneumonia identified by bronchoscopic bronchoalveolar lavage in adults: Comparison with severe influenza virus-associated pneumonia

Sang-Ho Choi[a,1], Jin Won Huh[b,1], Sang-Bum Hong[b], Ju Young Lee[a], Sung-Han Kim[a], Heungsup Sung[c], Kyung-Hyun Do[d], Sang-Oh Lee[a], Mi-Na Kim[c], Jin-Yong Jeong[a,e], Chae-Man Lim[b], Yang Soo Kim[a], Jun Hee Woo[a], Younsuck Koh[b,*]



Journal of Clinical Virology 62 (2015) 41–47

Clinical characteristics and outcomes of severe rhinovirus-associated pneumonia identified by bronchoscopic bronchoalveolar lavage in adults: Comparison with severe influenza virus-associated pneumonia

Sang-Ho Choi[a,1], Jin Won Huh[b,1], Sang-Bum Hong[b], Ju Young Lee[a], Sung-Han Kim[a], Heungsup Sung[c], Kyung-Hyun Do[d], Sang-Oh Lee[a], Mi-Na Kim[c], Jin-Yong Jeong[a,e], Chae-Man Lim[b], Yang Soo Kim[a], Jun Hee Woo[a], Younsuck Koh[b,*]

	Total (n = 78)	Rhinovirus (n = 27)	Influenza virus (n = 51)	p-Value
Male sex	49 (62.8)	21 (77.8)	28 (54.9)	0.047
Age, median (interquartile range)	65.0 (53.8–71.0)	66.0 (57.0–70.0)	62.0 (53.0–73.0)	0.77
Underlying disease or condition[a]				
Structural lung disease	22 (28.2)	7 (25.9)	15 (29.4)	0.75
Chronic obstructive lung disease	10 (12.8)	3 (11.1)	7 (13.7)	1.00
Interstitial lung disease	7 (9.0)	4 (14.8)	3 (5.9)	0.23
Bronchiectasis	4 (5.1)	1 (3.7)	3 (5.9)	1.00
Destroyed lung due to tuberculosis	1 (1.3)	0	1 (2.0)	1.00
Pneumoconiosis	1 (1.3)	0	1 (2.0)	1.00
Hematologic malignancy	18 (23.1)	11 (40.7)	7 (13.7)	0.007
Diabetes mellitus	16 (20.5)	7 (25.9)	9 (17.6)	0.39
Solid cancer	10 (12.8)	3 (11.1)	7 (13.7)	1.00
End-stage renal disease	2 (2.6)	0	2 (3.9)	0.54
Congestive heart failure	4 (5.1)	0	4 (7.8)	0.29
Liver cirrhosis	1 (1.3)	1 (3.7)	0	0.35
Chronic renal failure	3 (3.8)	0	3 (5.9)	0.55
s/p cerebraovascular attack	1 (1.3)	0	1 (2.0)	1.00
Solid organ transplantation	3 (3.8)	2 (7.4)	1 (2.0)	0.27
Hematopoietic stem cell transplantation	9 (11.5)	4 (14.8)	5 (9.8)	0.71
Immunocompromised state[b]	39 (50.0)	22 (81.5)	17 (33.3)	< 0.001
Receipt of immunosuppressant	21 (26.9)	14 (51.9)	7 (13.7)	< 0.001
Recent chemotherapy	17 (21.8)	9 (33.3)	8 (15.7)	0.07
Active smoker	5 (6.2)	4 (14.8)	1 (1.9)	0.04
Ex-smoker	28 (35.9)	11 (40.7)	17 (33.3)	0.52
Recent surgery (within 1 month)	3 (3.8)	2 (7.4)	1 (2.0)	0.27
Neutropenia[c]	8 (10.3)	5 (18.5)	3 (5.9)	0.12

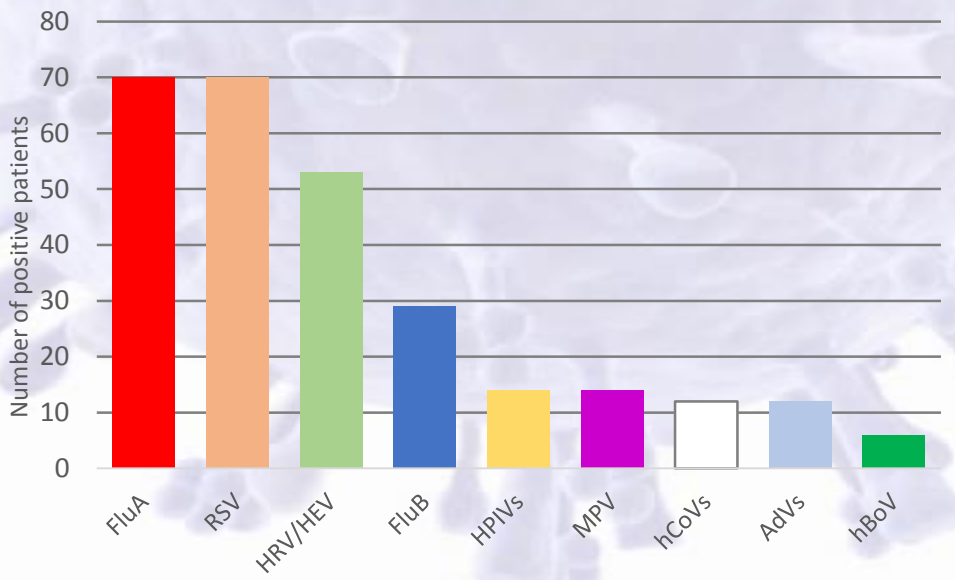
Journal of Clinical Virology 62 (2015) 41–47

RIAResp – Retrospective study

- Collection of Epidemiological data on respiratory viruses circulation among patients amditted to ICU with a diagnosis of Severe acute respiratory infection.
- Period: 1 Jan 2017 – 30 Dec 2018.

A total of 815 ICU-hospitalized patients with severe acute respiratory infections were analyzed.

- In 297/815 (36.4%) patients one or more respiratory viruses were detected, while 518/815 (63.6%) patients resulted negative.
- Flu A and RSV were the most detected viruses with at least 50% of cumulative positivity.
- HRV was detected in 53 cases (17,8% of the total)



Conclusions

- Viral infections were present in a large proportion of ICU-admitted patients with CAP (near 35%).
- In addition to influenza A and RSV, HRVs were shown to account for a significant number of ICU-infections.
- The introduction of multiplexed nucleic acid amplification test (NAAT) have improved the detection of HRV/EV and other non-influenza respiratory viruses leading to its implications in more serious respiratory disorders in both immunocompetent and immunocompromised patients.
- A more correct sampling collection results in a better diagnosis (LRT vs URT)
- Presence of bacteria and fungi should be investigated.

Aknowlodgements

AMCLI and GLIViRe

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