



Human Metapneumovirus İnfeksiyonu

Dr. Şiran Keske

VKV Amerikan Hastanesi

İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji

25 Mart 2017

21 yaş, Kadın

05/01/2017

Ateş

Halsizlik

Nefes darlığı

Bilinç açık

Ateş: 38.2, SS: 25/dk, TA: Normal

Akciğerde bilateral bazallerde solunum sesleri azalmış, yer yer ronkus var.

Obez (VKİ: 35.9 kg/m²)

O₂ sat: %86

Akciğer grafisi

01:00

WBC: 4.83

Hb: 11.0

PLT: 116

CRP: 12.9

PCT: 0.07

Kre: 0.7

Na: 140

K: 4.6

06:00



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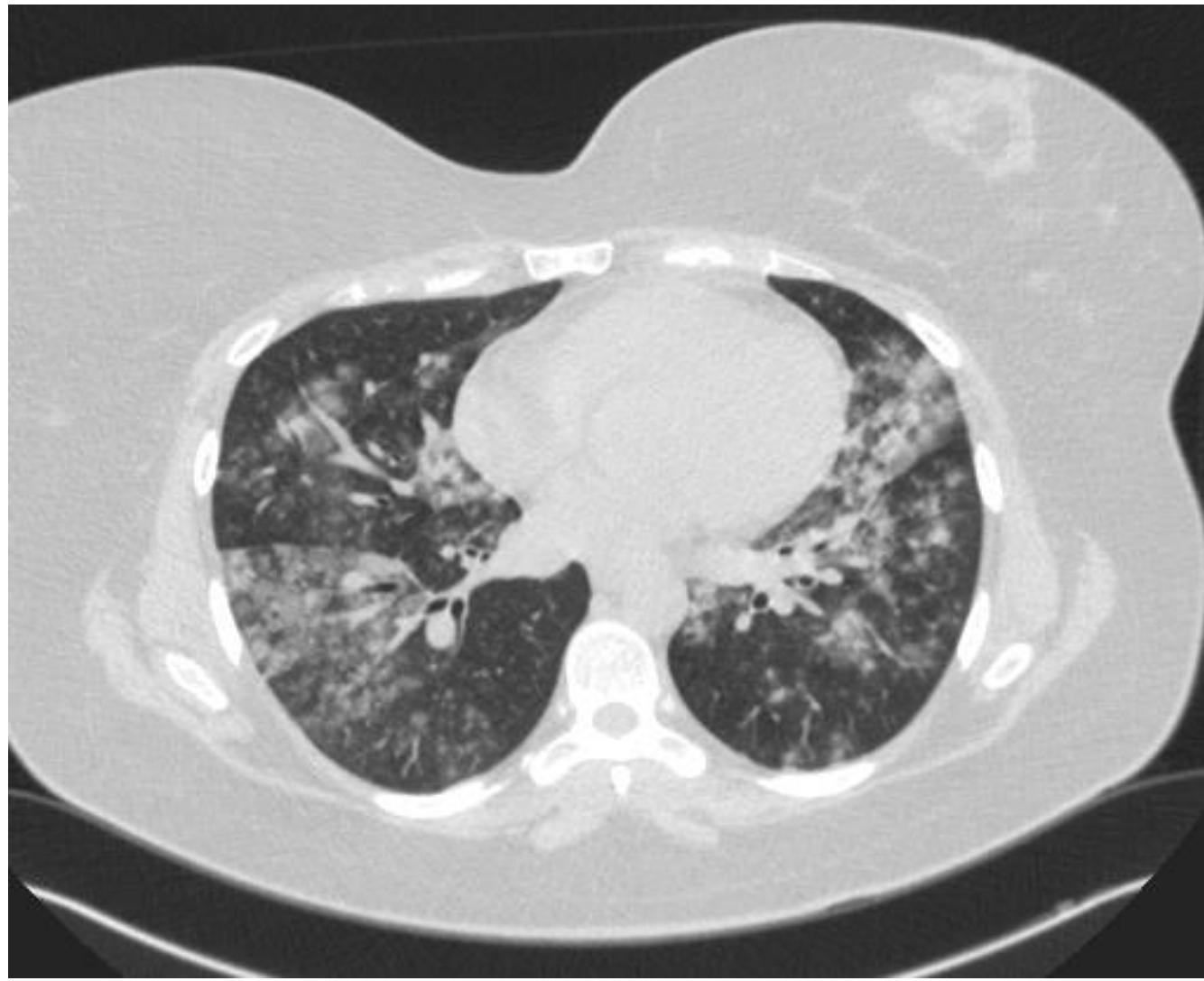
PCT: 0.07

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SOLUNUM PANELİ (PCR)

Toraks BT

Kan-balgam
kültürü

Akciğer grafisi

VİRAL ASYE

01:00

WBC: 4.83
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06:00

08:00

Oseltamivir
IV Hidrasyon

Cinsiyet / Yaş : K / 19.09.1990
Protokol No. : 697234
Örnek Tarihi/Saati : 05.01.2017 08:00

Doktor : ACİL SERVİS
Bölümü : KLİNİK LABORATUVAR
Rapor Tarihi : 05.01.2017 14:19

36180	Solunum Yolları Virüsleri (multiplex-PCR)	
Adenovirus	Negatif	
Coronavirus 229E	Negatif	
Coronavirus HKU1	Negatif	
Coronavirus NL63	Negatif	
Coronavirus OC43	Negatif	
Human Metapneumovirus	POZİTİF	
Human Rhinovirus/Enterovirus	Negatif	
Influenza A	Negatif	
Influenza B	Negatif	
Parainfluenza Virus 1	Negatif	
Parainfluenza Virus 2	Negatif	
Parainfluenza Virus 3	Negatif	
Parainfluenza Virus 4	Negatif	
Respiratory Syncytial Virus	Negatif	
Bordetella pertussis	Negatif	
Chlamydophila pneumoniae	Negatif	
Mycoplasma pneumoniae	Negatif	

21 yaş, Kadın

05/01/2017

Ateş Halsizlik Nefes darlığı

Bilinç açık

Ateş: SS: TA:

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Obez (VKİ: 35.9 kg/m²)

O₂ sat: %86

Nefes darlığı
Oks. Sat. %88

SOLUNUM PANELİ (PCR)

Toraks BT

Kan-balgam
kültürü

18:00

VİRAL ASYE

01:00
WBC: 4.83
Hb: 11.0
PLT: 116
CRP: 12.9
PCT: 0.07
Kre: 0.7
Na: 140
K: 4.6

06:00

08:00

Oseltamivir
IV Hidrasyon

Ribavirin
IV Hidrasyon

05/01/2017

06/01/2017

Nefes darlığı
Oks. Sat. %88

Ateş

Halsizlik

Nefes darlığı

Bilinç açık
Ateş devam ediyor.
Akciğerde bilateral
bazallerde SS azalmış, yer
yer ronkus var.
O₂ sat: %89 (O₂'siz)

PANELİ (PCR)

Igam

18:00

Ribavirin
IV Hidrasyon

08:00

WBC: 5.7
Hb: 12.1
PLT: 149
CRP: 92
PCT: 0.07
Kre: 0.7

06/01/2017

07/01/2017

10/01/2017

Ateş Halsizlik Nefes darlığı

Bilinç açık
Ateş devam ediyor.
Akciğerde bilateral
bazallerde SS azalmış, yer
yer ronkus var.
 O_2 sat: %89 (O_2 'siz)



08:00

WBC: 5.7
Hb: 12.1
PLT: 149
CRP: 92
PCT: 0.07
Kre: 0.7

Ateş yok Halsizlik

Nefes darlığı azaldı

O_2 sat: %90 (O_2 'siz)

08:00

WBC: 4.7
Hb: 11.7
PLT: 163
CRP: 52
PCT: 0.04
Kre: 0.5

Halsizlik

O_2 sat: %94 (O_2 'siz)

TABURCU

08:00

WBC: 5.22
Hb: 11.9
PLT: 175
CRP: 12

GİRİŞ ve EPİDEMİYOLOJİ



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ARTICLES

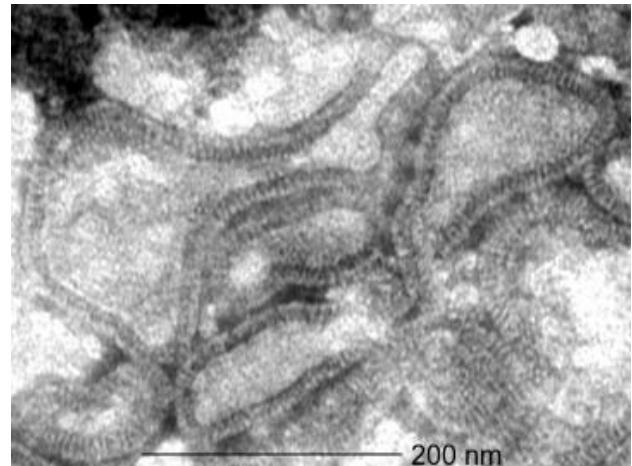
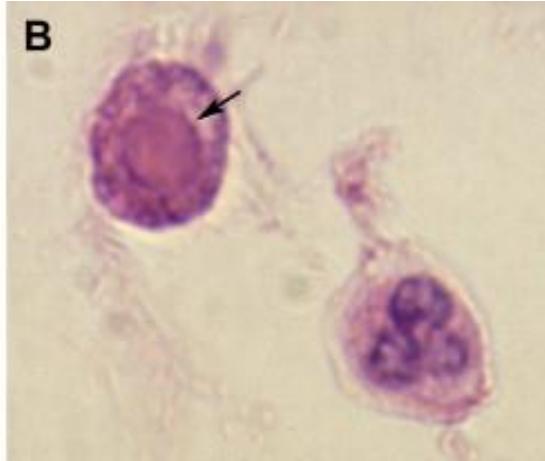
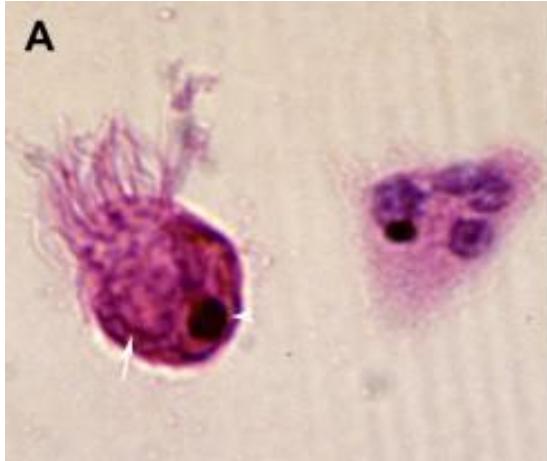
A newly discovered human pneumovirus isolated from young children with respiratory tract disease

BERNADETTE G. VAN DEN HOOGEN¹, JAN C. DE JONG¹, JAN GROEN¹, THIJS KUIKEN¹, RONALD DE GROOT², RON A.M. FOUCHEIR¹ & ALBERT D.M.E. OSTERHAUS¹

¹Departments of Virology and ²Pediatrics, Erasmus Medical Center, Rotterdam, the Netherlands

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From 28 young children in the Netherlands, we isolated a paramyxovirus that was identified as a tentative new member of the *Metapneumovirus* genus based on virological data, sequence homology and gene constellation. Previously, avian pneumovirus was the sole member of this recently assigned genus, hence the provisional name for the newly discovered virus: human metapneumovirus. The clinical symptoms of the children from whom the virus was isolated were similar to those caused by human respiratory syncytial virus infection, ranging from upper respiratory tract disease to severe bronchiolitis and pneumonia. Serological studies showed that by one age of five years, virtually all children in the Netherlands have been exposed to human metapneumovirus and that the virus has been circulating in humans for at least 50 years.



- hMPV zarflı, tek zincirli bir RNA virusu
- *Metapneumovirus* cinsi,
- *Paramyxoviridae* ailesi
- *Pneumovirinae* alt ailesinde yer alır

**Kızamık
Kabakulak
Parainfluenza 1-4
RSV
hMPV**

Wen SC, et al. *Clin Vaccine Immunol.* 2015;22:858-66
Hermos CR. *Clin Lab Med.* 2010;30(1):131-48
van den Hoogen BG et al. *Nat Med.* 2001;7(6):719-24.

Table 1 Seroprevalence of hMPV antibodies in humans categorized by age group

Age (years)	Immunofluorescence assays		Virus neutralization assays		Titer range
	<i>n</i> tested	<i>n</i> positive (%)	<i>n</i> tested	<i>n</i> positive (%)	
0.5–1	20	5 (25)	12	3 (25)	16–32
1–2	20	11 (55)	13	4 (31)	16–32
2–5	20	14 (70)	8	3 (38)	16–512
5–10	20	20 (100)	4	4 (100)	32–256
10–20	20	20 (100)	4	3 (75)	32–128
> 20	20	20 (100)	4	3 (75)	32–128
8–99*	72	72 (100)	11	11 (100)	16–128

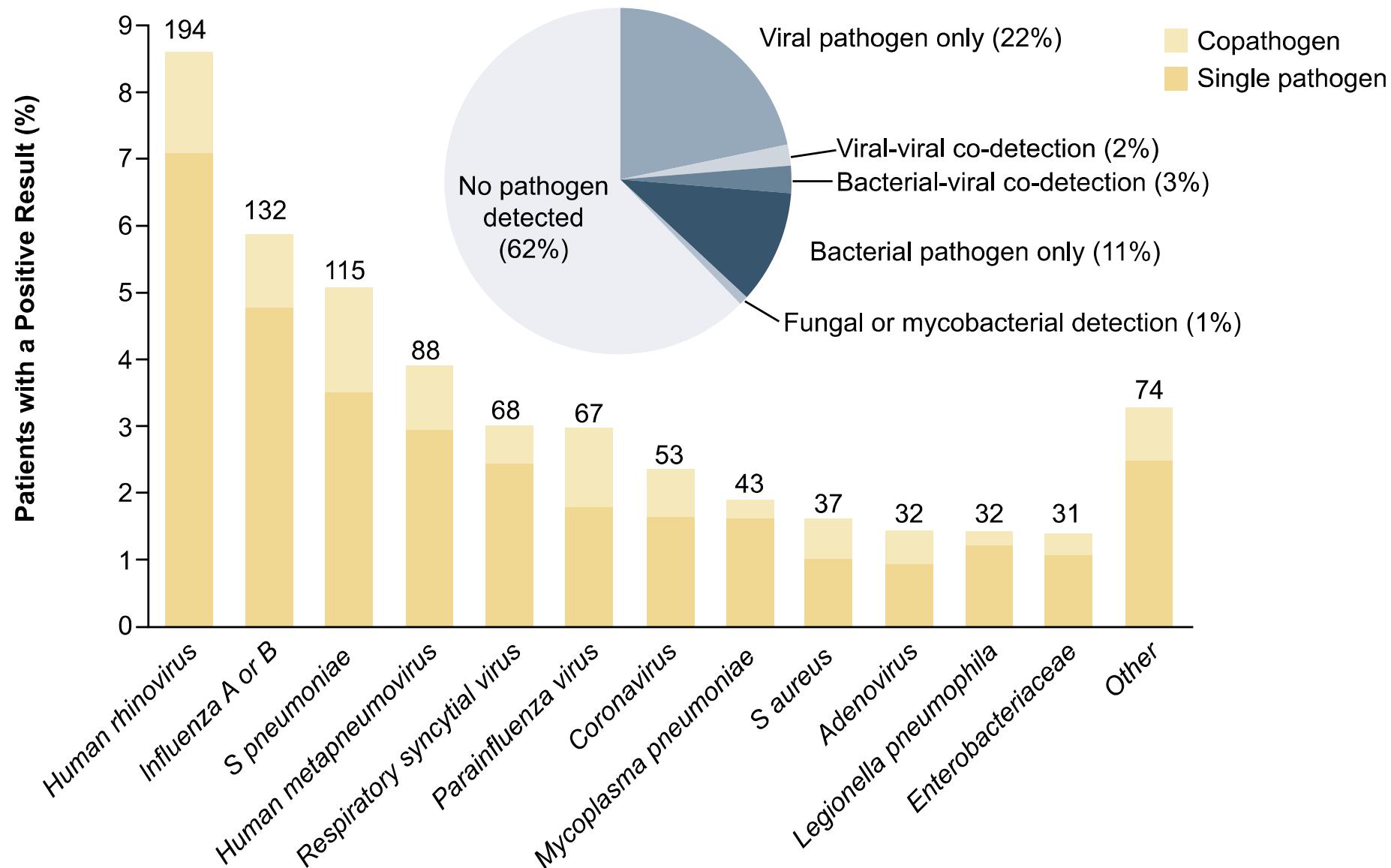
*, Sero-archeological analysis using sera collected in 1958 (refs. 16,17).

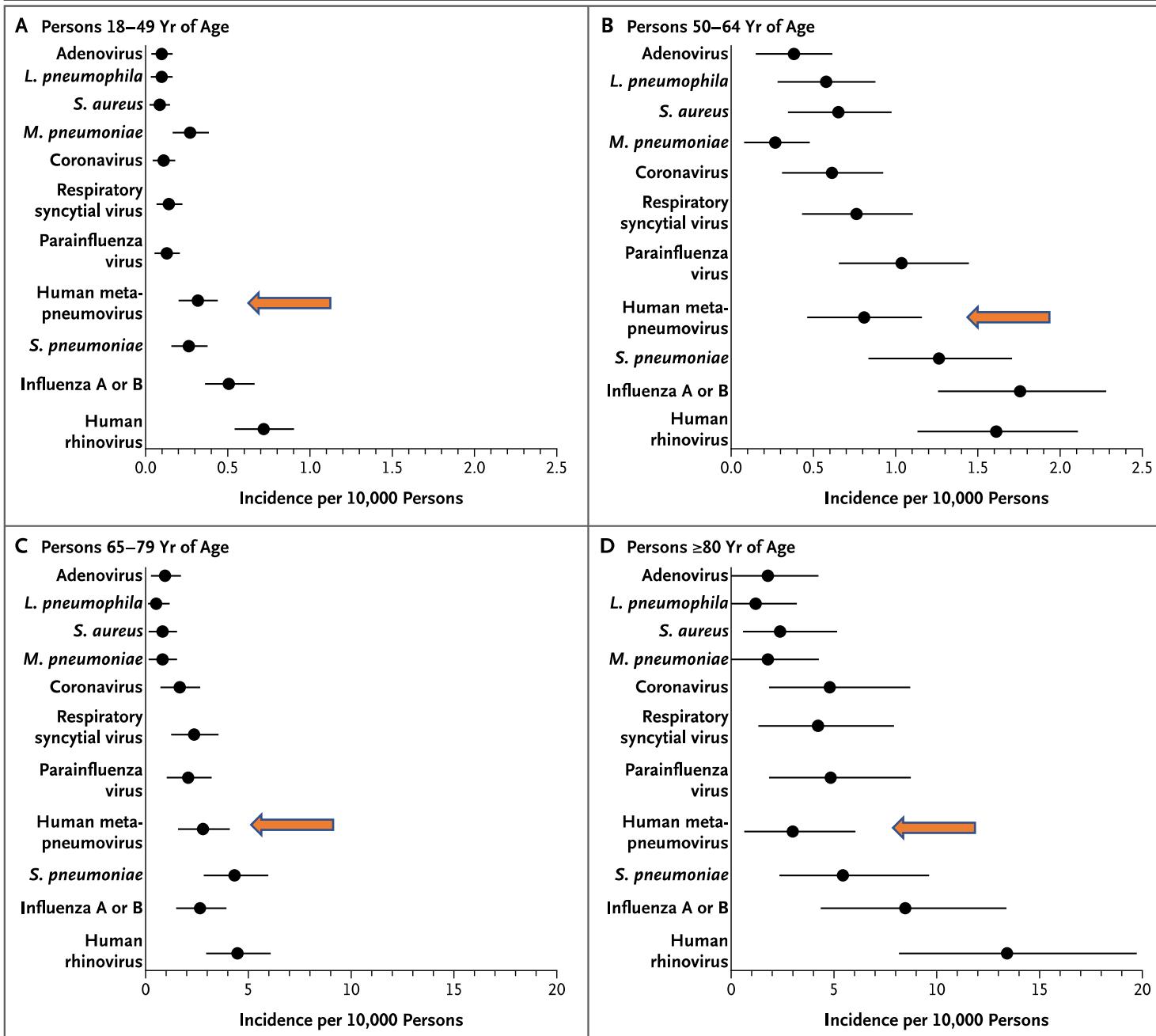
- İsrail:
 - 24 aylık çocuklarda %53
 - Okul çağındakilerin tamamında
- Japonya:
 - 2-5 yaş: %77
 - >10 yaş: %100

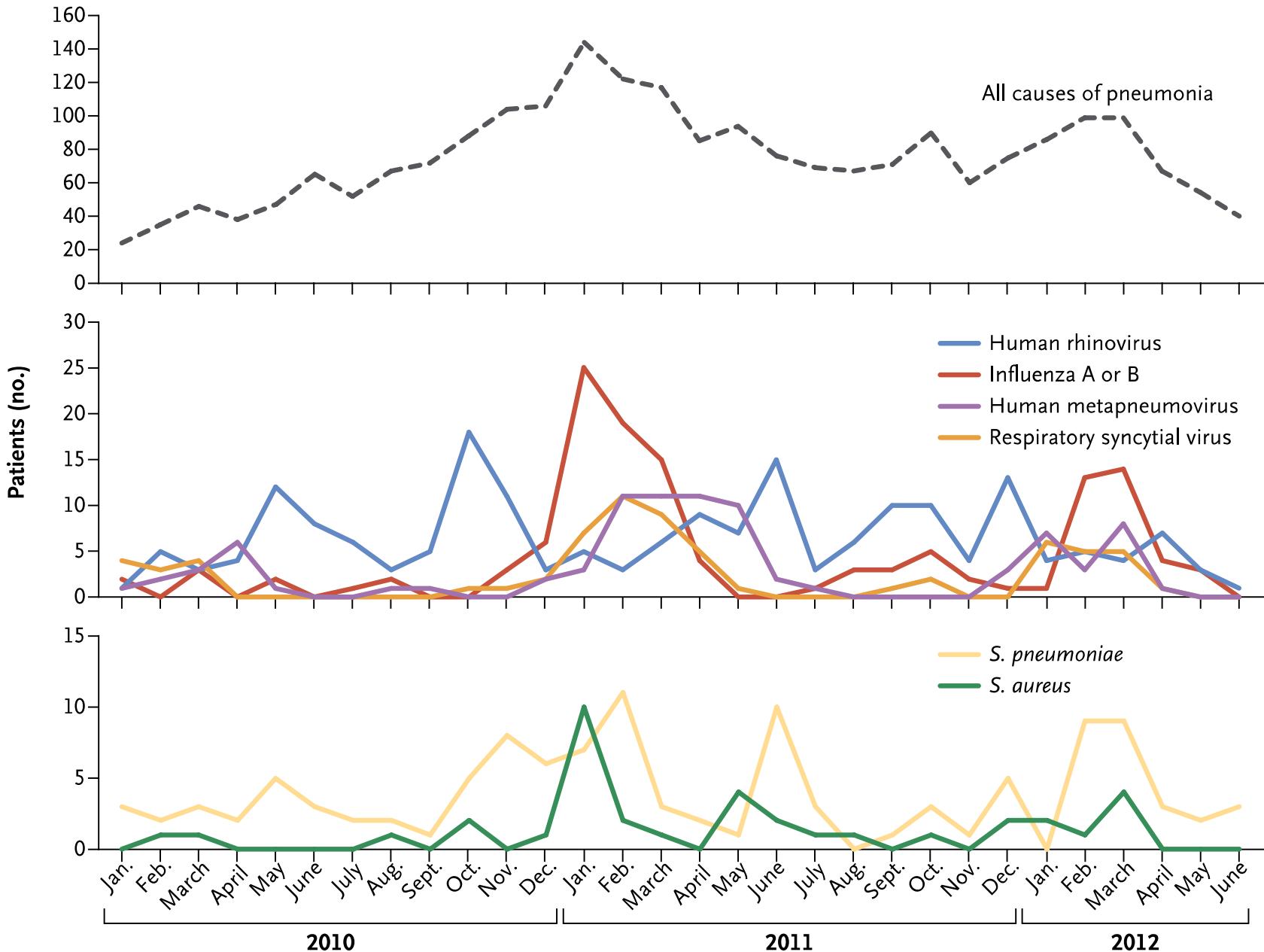
Wolf DG, et al. J Infect Dis. 2003;188:1865–7.

Ebihara T, et al. J Med Virol. 2003;70:281–3.

Specific Pathogens Detected





B Pathogens Detected, According to Month and Year

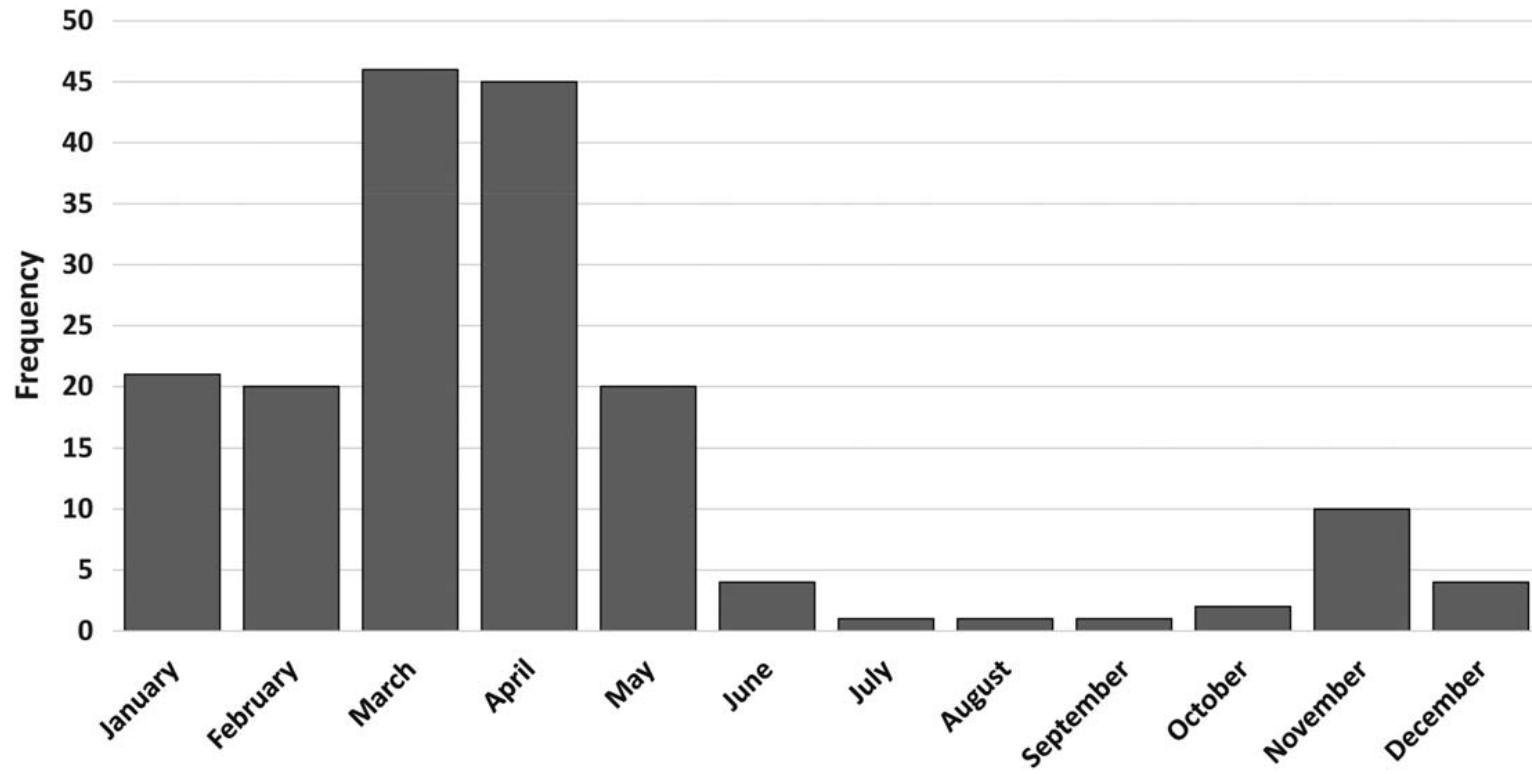


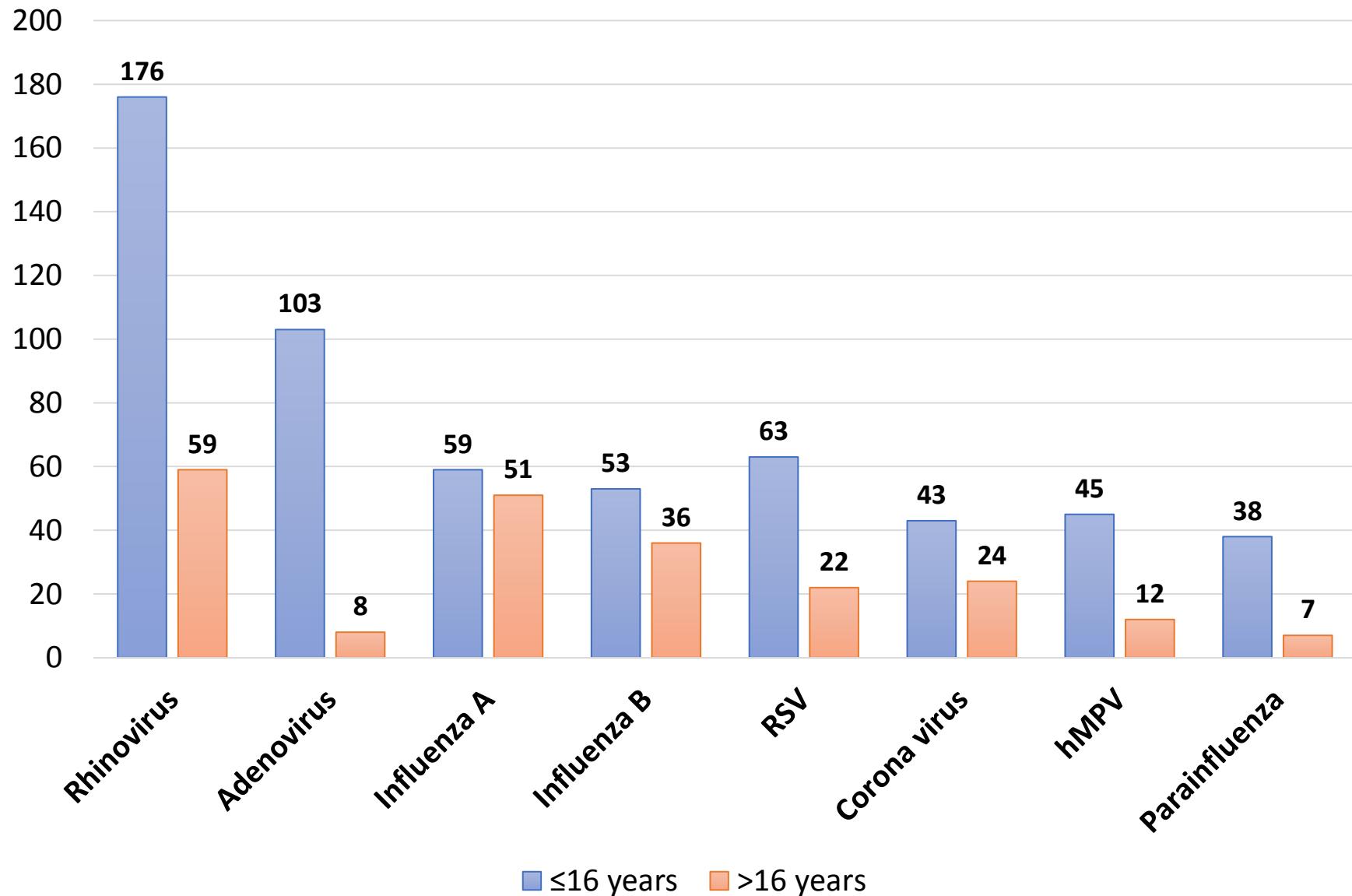
Figure 1. The seasonal distribution of human metapneumovirus infections between April 2012 and May 2015 is illustrated ($n = 181$).

Table 2. Distribution of Respiratory Viruses in Children and Adults^a

Respiratory virus	Children	Adults	Total
Influenza A virus	60 (18.9)	159 (31.5)	219 (26.7)
Influenza B virus	43 (13.6)	114 (22.6)	157 (19.1)
Rhinovirus/enterovirus	49 (15.5)	58 (11.5)	107 (13)
Human bocavirus	35 (11)	56 (11.1)	91 (11.1)
Respiratory syncytial virus A/B	43 (13.6)	21 (4.2)	64 (7.8)
Adenovirus	33 (10.4)	23 (4.6)	56 (6.8)
Coronavirus NL63/229E/OC43/HKU1	18 (5.6)	33 (6.5)	51 (6.2)
Parainfluenza virus 1-4	25 (7.9)	15 (3)	40 (4.9)
Human metapneumovirus	11 (3.5)	25 (5)	36 (4.4)
Total	317 (100)	504 (100)	821 (100)

AMERİKAN HASTANESİ

2013-2016



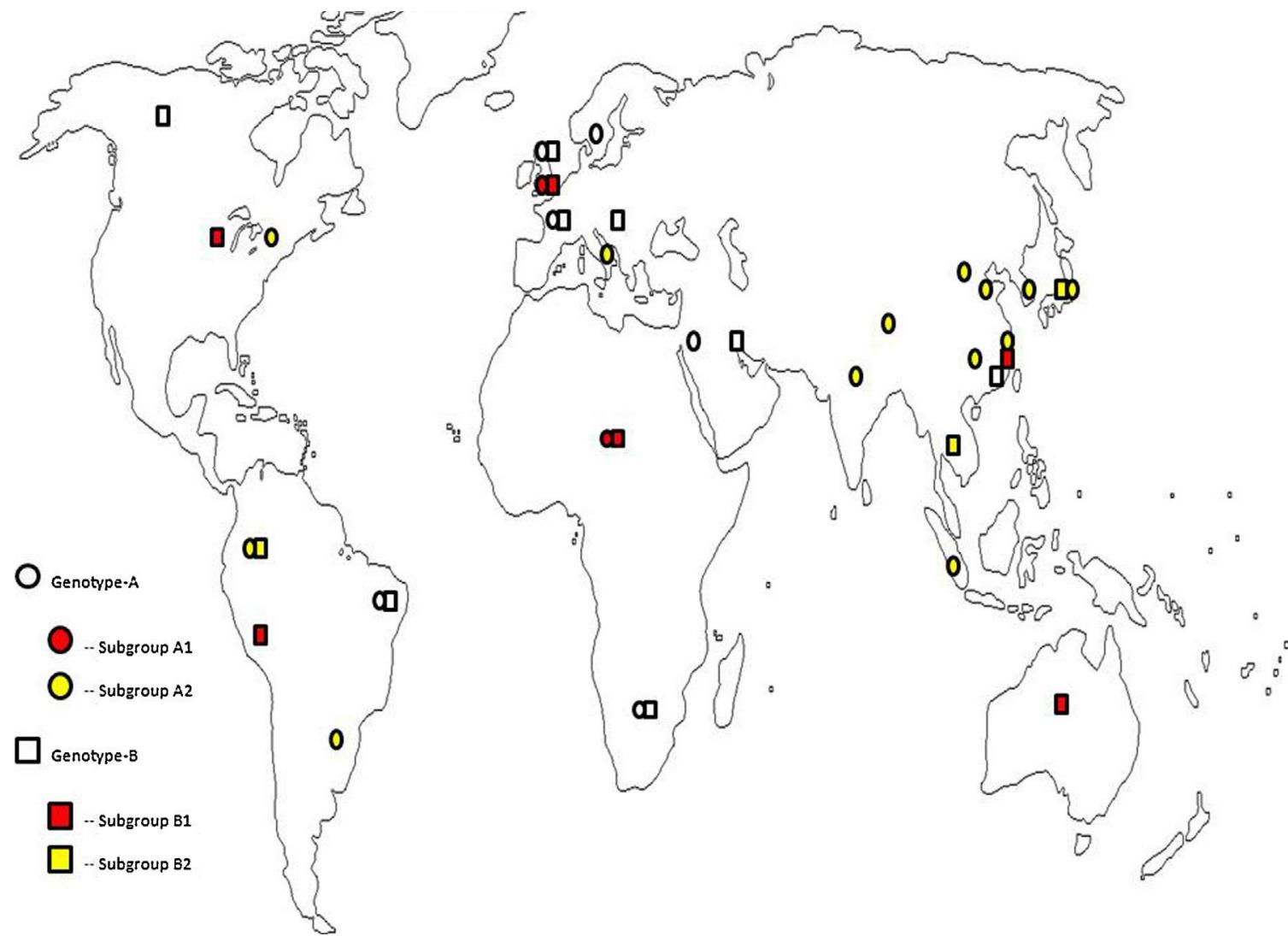


Figure 3. Geographical distribution of hMPV genotypes. Map showing the geographical distribution of hMPV genotypes among humans. Human metapneumovirus isolates are divided into four major subgroups (A1, A2, B1, and B2) and each has its own geographical localization.

Türkiye'de hMPV Genotip Özellikleri

Ocak 2011 ve Aralık 2013 arası,
Tüm örnekler içinde hMPV pozitifliği %2.6.

B2 genotipi %54.3.

B1 genotipi %17.4.

A1 genotipi %4.3.

A2a genotipi %4.3.

A2b genotipi %20.

2011'de A2b, 2012 ve 2013'te B2 ön planda.

KLİNİK

Asemptomatik

ÜSYE

ASYE

ARDS

Ölüm

335 hMPV
positive results



Case	Presentation
1	44-year-old man with remote Hodgkin disease
2	84-year-old man with diabetes mellitus, dementia
3	31-year-old woman, otherwise healthy
4	27-year-old woman with type 1 diabetes mellitus
5	54-year-old woman with mild intermittent asthma
6	58-year-old woman with COPD (severity unknown)

hMPV infeksiyonu olan hastaların mortalitesi %7

YBÜ gerektiren hastaların büyük bölümü immünsuprese ya da altta yatan ciddi akciğer hastalığı olan hastalar olsa da belirgin komorbid hastalığı olmayan hastalar da yoğun bakım gerektirebilmektedir.

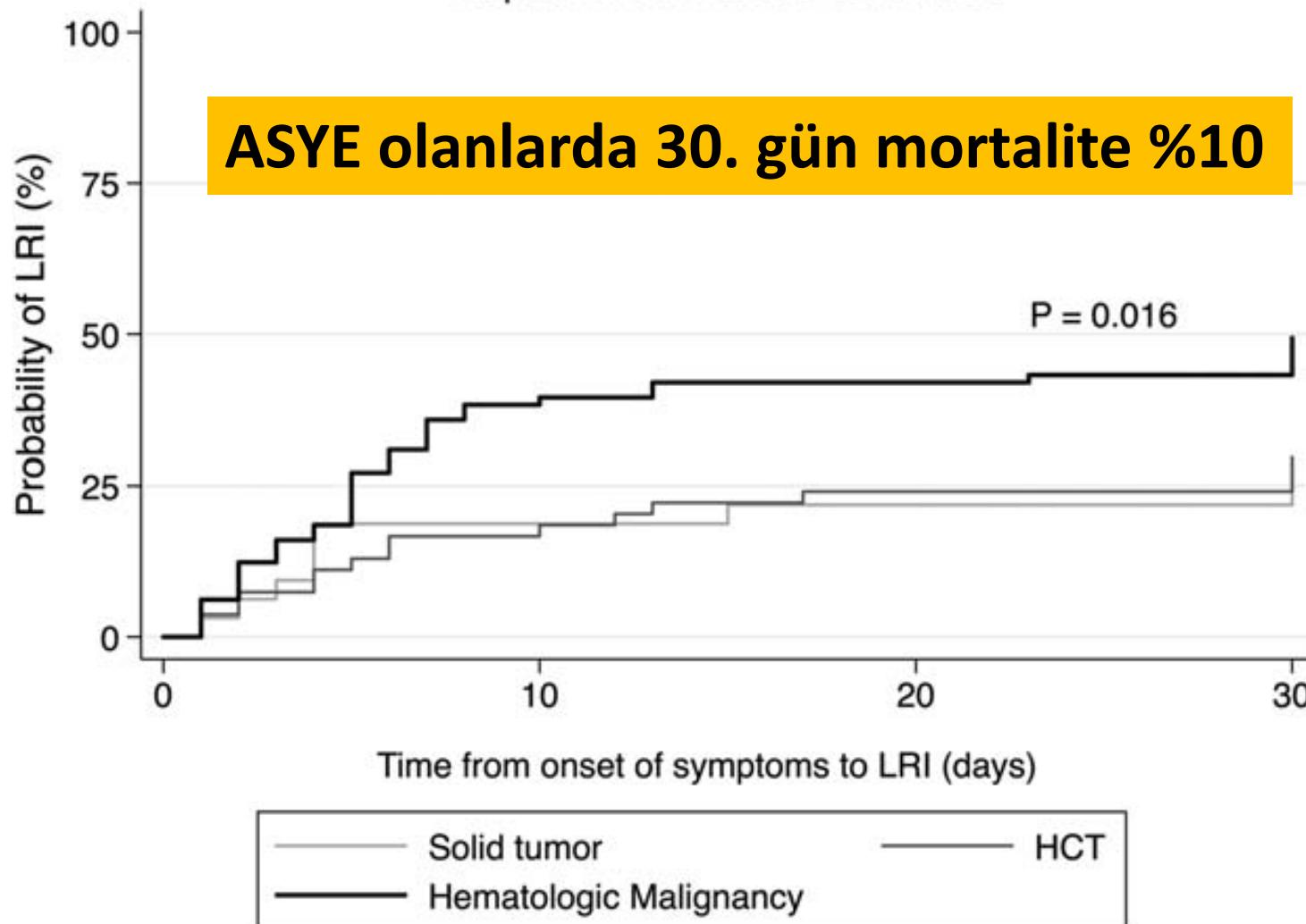


Figure 2. Kaplan-Meier failure curves illustrate the probability of progression to lower respiratory tract infection (LRI) over time (restricted to patients who presented with upper respiratory infection). HCT indicates hematopoietic cell transplantation.

Cerebrospinal Fluid Findings in an Adult with Human Metapneumovirus– Associated Encephalitis

**Natalie Jeannet, Bernadette G. van den Hoogen,
Joerg C. Schefold, Franziska Suter-Riniker,
Rami Sommerstein**

TANI

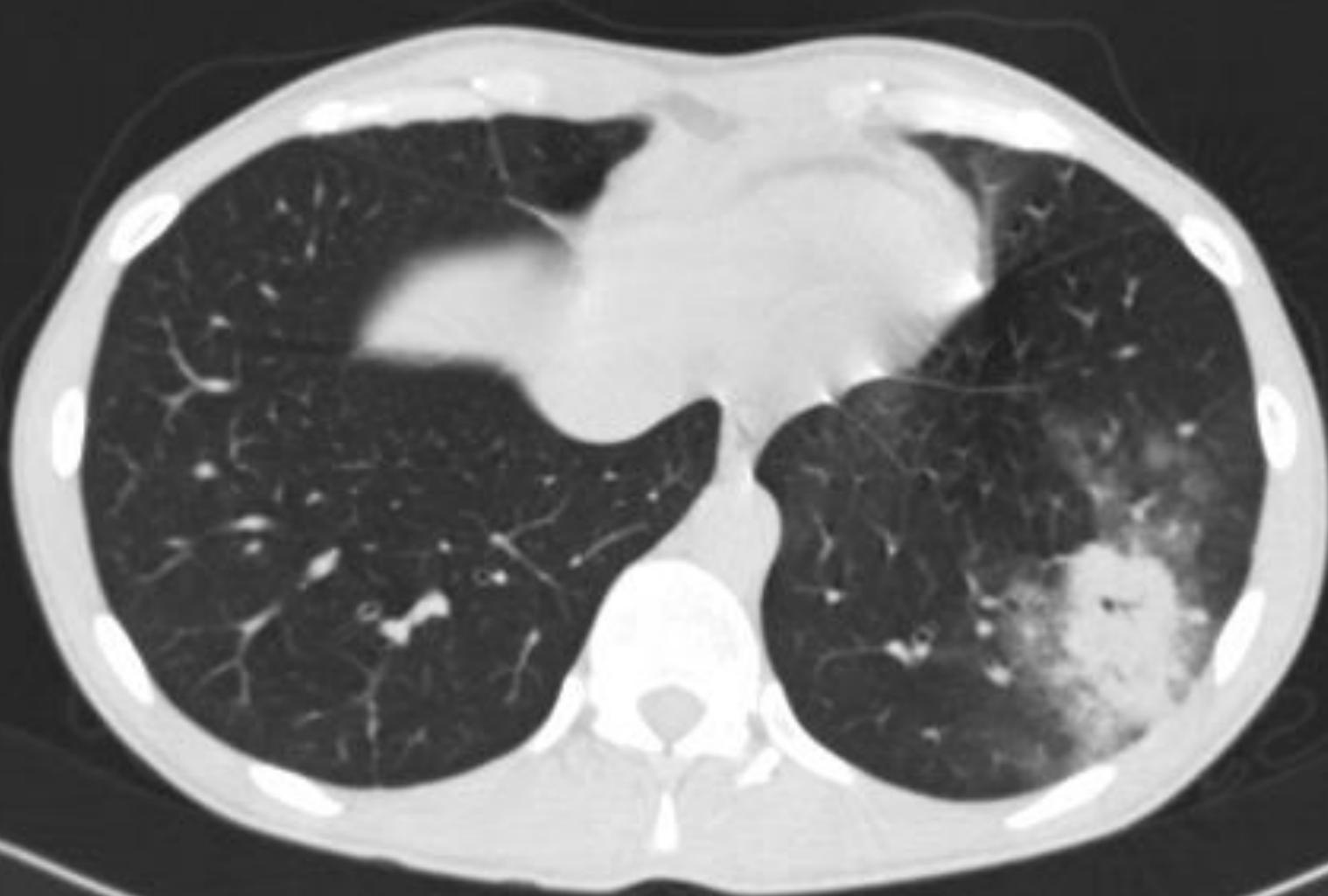
Laboratuvar

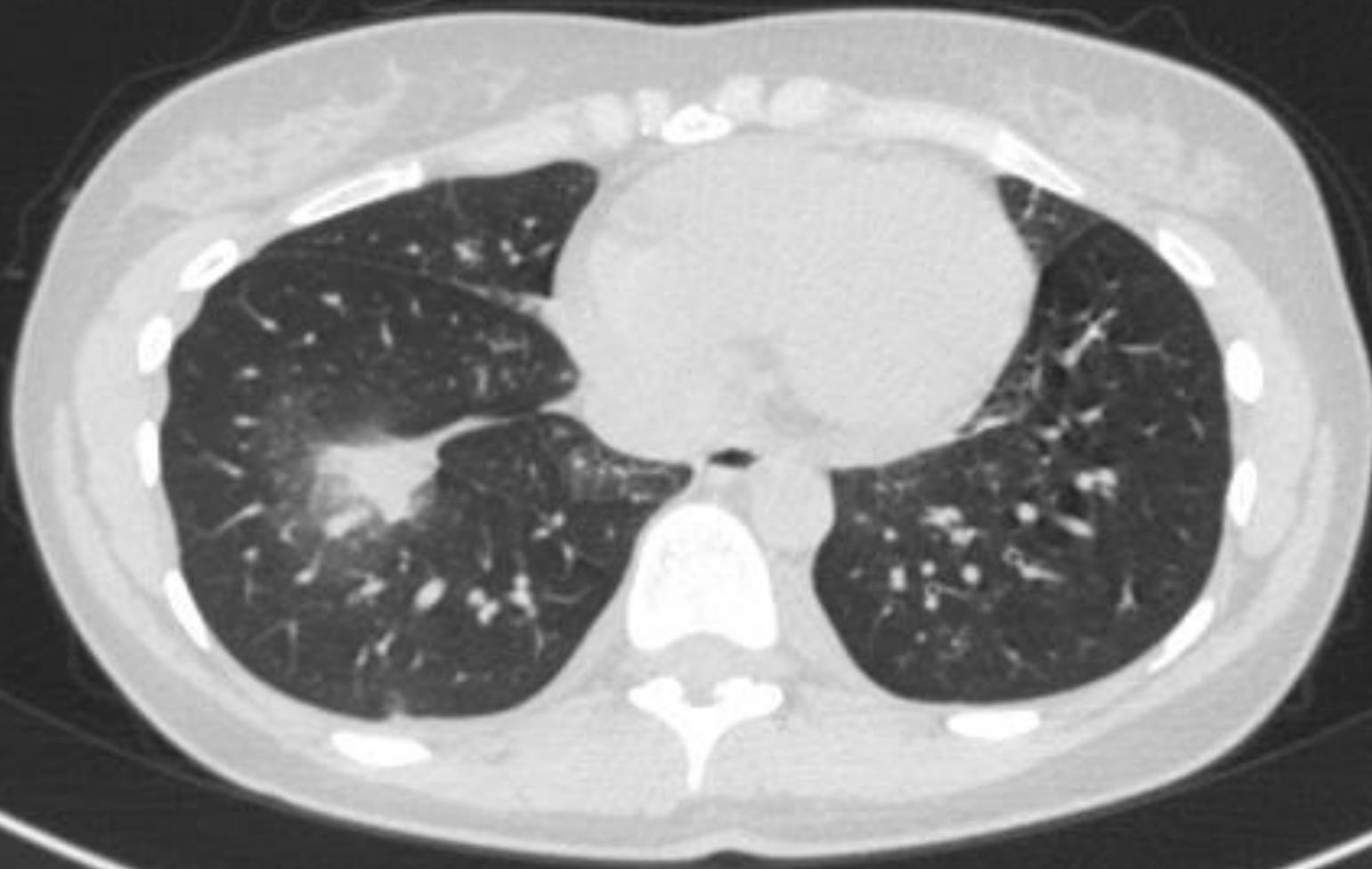
Radyoloji

Hücre kültürü

PCR

IFA





- Akciğer grafisinde peribronkovasküler infiltrasyon
- Unilateral veya bilateral multiple
- Akciğer tomografisinde nodüler konsolidasyon ve etrafında buzlu cam görünümü en sık rastladığımız bulgu

Culture and Serology

Pros

- Serology confirms true infection with host response

Cons

- Slow
- Resource-intensive
- Not all viruses can be cultured

High-throughput Sequencing

Pros

- Can look for any pathogen and do not need *a priori* knowledge of organism
- Not sensitive to sequence variation in known viruses

Cons

- Slow and expensive compared to PCR (but getting faster and cheaper)

Polymerase chain reaction assays

Pros

- Rapid
- Relatively inexpensive
- Highly sensitive and specific

Cons

- Sensitive to mutation at target site
- Must identify specific, expected target for assay

Goals for future assays

Pros

- Rapid
- Inexpensive
- Sensitive and specific
- Not sensitive to sequence variation
- Broad range of pathogens simultaneously assayed (beyond current multiplex panels)
- Include additional information about pathogens detected (eg, strain typing, drug resistance)
- May also assay host gene expression to characterize response type (eg, bacterial or viral) to inform treatment

Fig. 1. Methods for characterizing viruses in the respiratory tract. Current molecular methods, such as PCR and HTS, have clear advantages over older methods (culture and serology) in terms of cost, speed, and sensitivity. Future assays for research and diagnostics will be aimed at capturing and improving on the best features of the current methods.

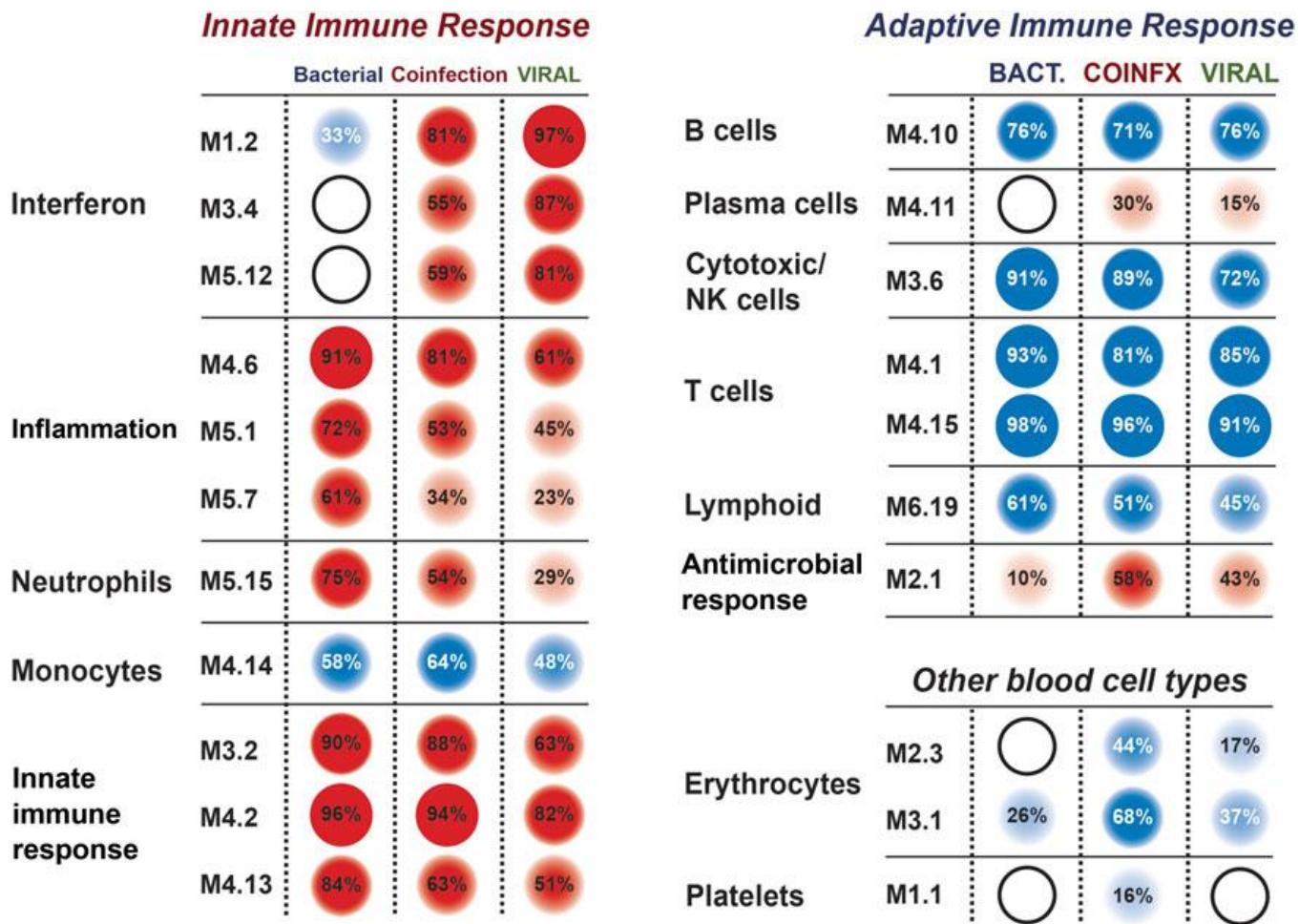


Figure 3. Modular transcriptional fingerprint comparison among the 3 lower respiratory tract infection groups. Mean modular transcriptional fingerprint for bacterial (22 patients and 18 matched controls), viral (25 patients and 18 matched controls), and bacterial-viral coinfection (25 patients and 18 matched controls). Modules are organized based on its relation to the innate and adaptive immune response. Abbreviation: NK, natural killer.

Molecular
test for
pathogen



Molecular
test for
host
response



Integrated
report to
inform
clinical
treatment

TEDAVI

Table 1

Molecules of therapeutic interest tested against hMPV infection. √: tests performed; ×: no test published.

Type of molecule/name	Mechanism of action	Tests <i>in vitro</i>	Animal model
Ribavirin	- Inhibition of IMP dehydrogenase or - Interaction with viral polymerases and introduction of mutation during transcription	√	√
Polyclonal antibodies		√ (not active)	×
Anti hRSV humanized monoclonal antibodies (Palivizumab)	Neutralization	√	×
Anti hMPV humanized monoclonal antibodies (mAb 338)	Neutralization	√	√
Heparin	Competitive inhibition of G protein with regards to cellular GAGs	√	×
NMSO3	Modulation of the binding force between protein G and GAGs	√	×
Peptide-derived fusion inhibitors	Inhibition of the fusion protein	√	√
RNA interference (siRNA)	Cleavage of mRNA before translation	√	×

Yazar	Yıl	Metot	Sonuç
Wyde PR	2003	In vitro	RBV + IVIG etkili
Hamelin ME	2006	Fareler	RBV etkili, steroid ?
Shahda S, et al.	2011	Çoğu akciğer transplantlı 9 hasta	2'sine oral + aerosolize RBV ve IVIG İkisi de iyileşmiş.
Egli A	2012	HSCT'lı 8 çocuk	RBV + IVIG. Mortalite %12.5
Park SY	2013	Hematolojik hastalığı olan çocuklar	RBV alan ve almayanlarda 30. gün mortalitede fark yok
Jochmans D	2016	In vitro + Fareler	Faviprevir'in antiviral etkinliği olduğu belirtilmiş.

Wyde PR, et al. Antiviral Res. 2003;60:51-9.

Hamelin ME, et al. Antimicrob Agents Chemother. 2006;50:774-7.

Shahda S, et al. Transpl Infect Dis. 2011;13:324-8.

Egli A, et al. Infection. 2012;40:677-84.

Park SY, et al. Antimicrob Agents Chemother. 2013;57:983-9.

Jochmans D. Antimicrob Agents Chemother. 2016;60:4620-9.

Table 5. Recommendations for Community-Acquired Respiratory Virus Treatment in Hematopoietic Stem Cell Transplantation and Leukemia Patients

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

ECIL-4: European Conference on Infections in Leukaemia

Table 7. Use of Systemic Ribavirin for Respiratory Syncytial Virus or Human Parainfluenza Virus Respiratory Tract Infectious Diseases^a

Oral or intravenous ribavirin maximal dosing 10 mg/kg body weight every 8 h for adults

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

Day 2: 400 mg every 8 h

Day 3: Increase the dose to a maximum of 10 mg/kg body weight every 8 h

In case of adverse events:

Decrease dose or discontinue ribavirin

Creatinine clearance:

Oral or intravenous administration

30–50 mL/min

Maximal 200 mg every 8 h

10–30 mL/min

No recommendation can be given^b

^a Modified after [14].

^b Some experts use 200 mg once daily under close clinical and laboratory monitoring.

korunma

Strategy	Vaccine(s)	Tested model(s)	Results
Inactivated virus	Formalin-inactivated HMPV	Cotton rats, macaques	Abs neutralized and protected but increased lung pathology after HMPV challenge in cotton rats Vaccinated macaques were not protected from challenge and their pulmonary disease was enhanced
	Heat-inactivated HMPV	BALB/c mice	Vaccine enhanced lung disease with eosinophilic infiltration and increased T _H 2 cytokines despite protection
Subunit protein	F protein	Cotton rats, hamsters, macaques	Vaccine elicited neutralizing Abs and protection against lung viral replication in all models Ab response waned rapidly in macaques
	F and M proteins	BALB/c mice	Mice vaccinated with F + M had lower lung viral titers than mice vaccinated only with F
Virus-like particles	F-VLPs and F/G-VLPs	C57BL/6 mice, BALB/c mice	F-VLPs and F/G-VLPs induced neutralizing Abs G-VLPs did not induce neutralizing Abs F-VLPs and F/G-VLPs protected from viral challenge in the lungs

Live attenuated virus

Cold-passaged tem-

Hamsters

Vaccine induced high titers of neutralizing Abs and

İnsanlarda aşı ile ilgili yapılan tek çalışma var

Rekombinan aşı teknolojisi.

Aşılanan kişilerin burun yıkama sıvısında viral yük düşük bulunmuş ve serum antikor düzeyi 4 kat yüksek saptanmış.
Lisans almaya en yakın aşı olarak kabul ediliyor.

	F protein RGD motif		protection against viral challenge
Chimeric virus	Live PIV3 vector expressing HMPV F Alphavirus-vectored F protein	Hamsters, African green monkeys	Vaccine induced neutralizing Abs and provided protection against viral challenge in both models Vaccine induced neutralizing Abs and provided protection against homologous and heterologous virus challenge
	Chimeric rHMPV with N and P of AMPV	Hamsters, African green monkeys	Vaccine elicited high levels of neutralizing Abs in hamsters Results are comparable to those of wild-type HMPV in providing protective efficacy in monkeys
Cytotoxic T cell epitope	Peptide vaccine	BALB/c mice, Rag1 ^{-/-} mice	Epitopes from N and SH reduced lung viral titers Adoptive transfer of CTL lines against dominant M2-1 and the subdominant N epitope reduced lung virus titers in Rag1 ^{-/-} mice
	TriVax (epitope peptide + anti-CD40 Ab + poly(I:C))	PD1 ^{-/-} mice (C57BL/6 background)	Vaccination induced CD8 ⁺ T cell responses and reduced lung virus titers

Marquez-Escobar. Expert Rev Vaccines. 2017 Jan 27:1-13

ÖZETLE

Hayatın çok erken dönemlerinde toplumda sık olarak karşılaşılan bir virus

PCR bazlı testlerin yaygınlaşması ile daha kolay tanı konmaya başladı

Radyolojik bulguları küf mantarları ve bakteriyel pnömoni ile karışabilir

İmmünsuprese konaklarda ağır seyrederek YBÜ'ye yatis gerektirebilir ve hatta ölümle sonuçlanabilir.

Etkin bir tedavisi yok ancak özellikle immünsuprese konaklarda ribavirin kullanımını öneren az sayıda çalışma mevcut.