Infecciones Respiratorias Virales en UCI

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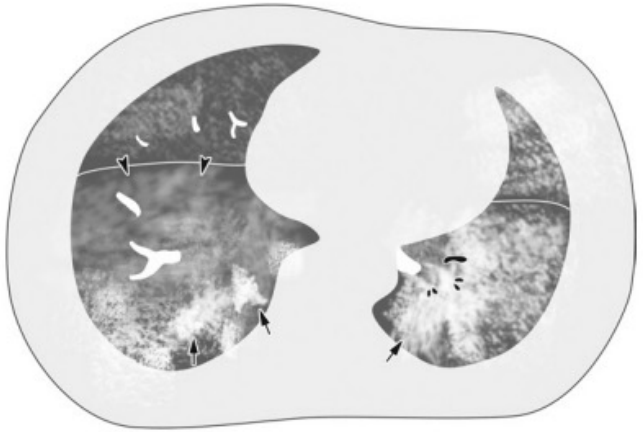
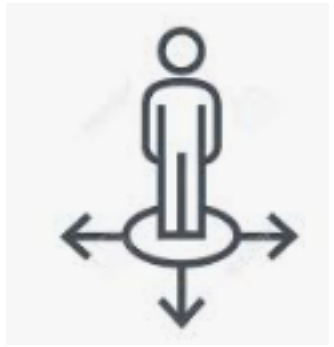
Infectología y Medicina Intensiva

1. Características de los virus
2. Epidemiologia
3. Fisiopatología
4. Características del paciente critico
5. Diagnostico
6. Manejo
7. Antivirales
8. Vacunas
9. Complicaciones

1. ¿Cómo lo estudio?
2. ¿Qué sirve?



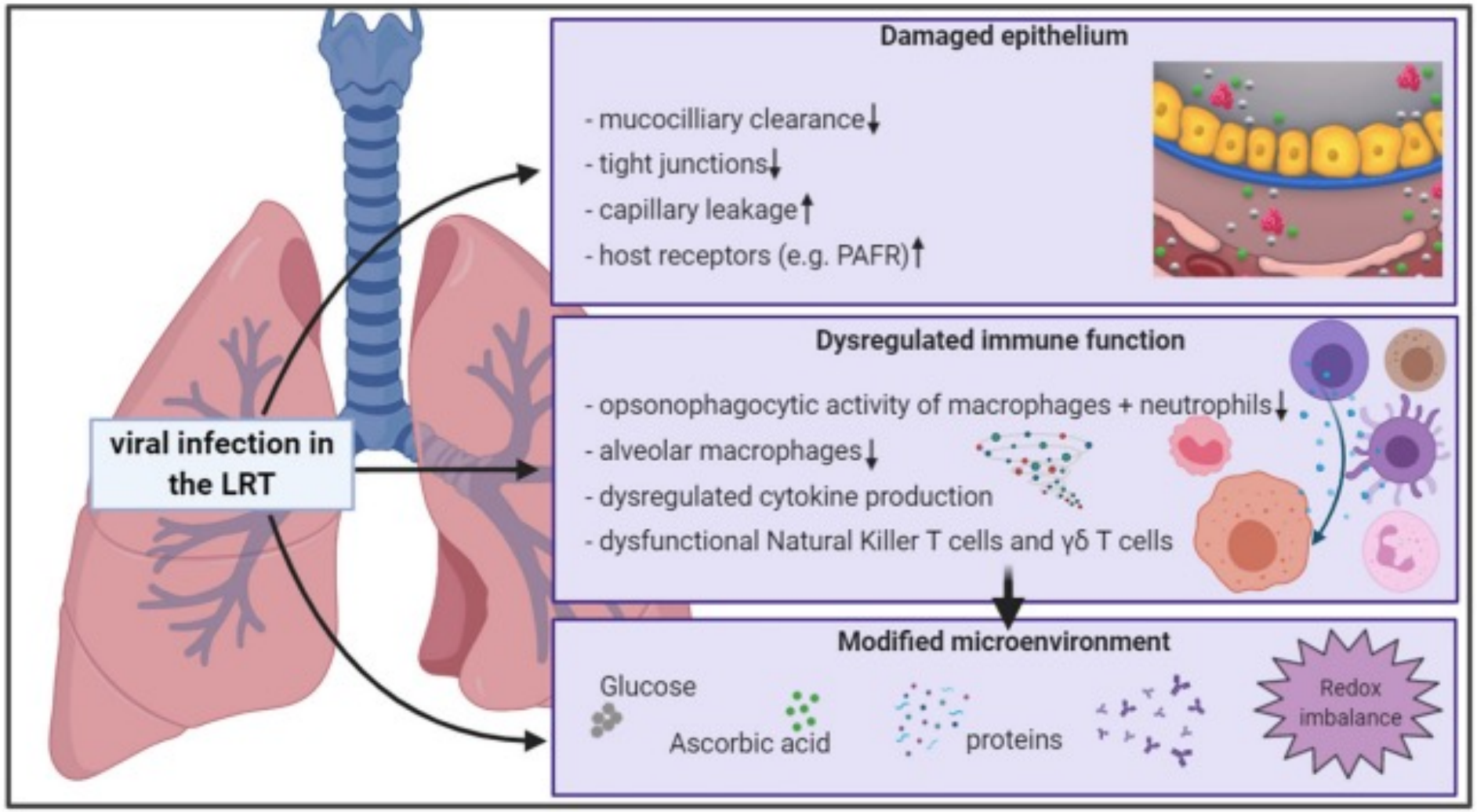


1. ¿Le pido panel viral, CCAT?
2. ¿Le dejo antibióticos?
3. ¿Le dejo antivirales?
4. ¿Le dejo corticoides?

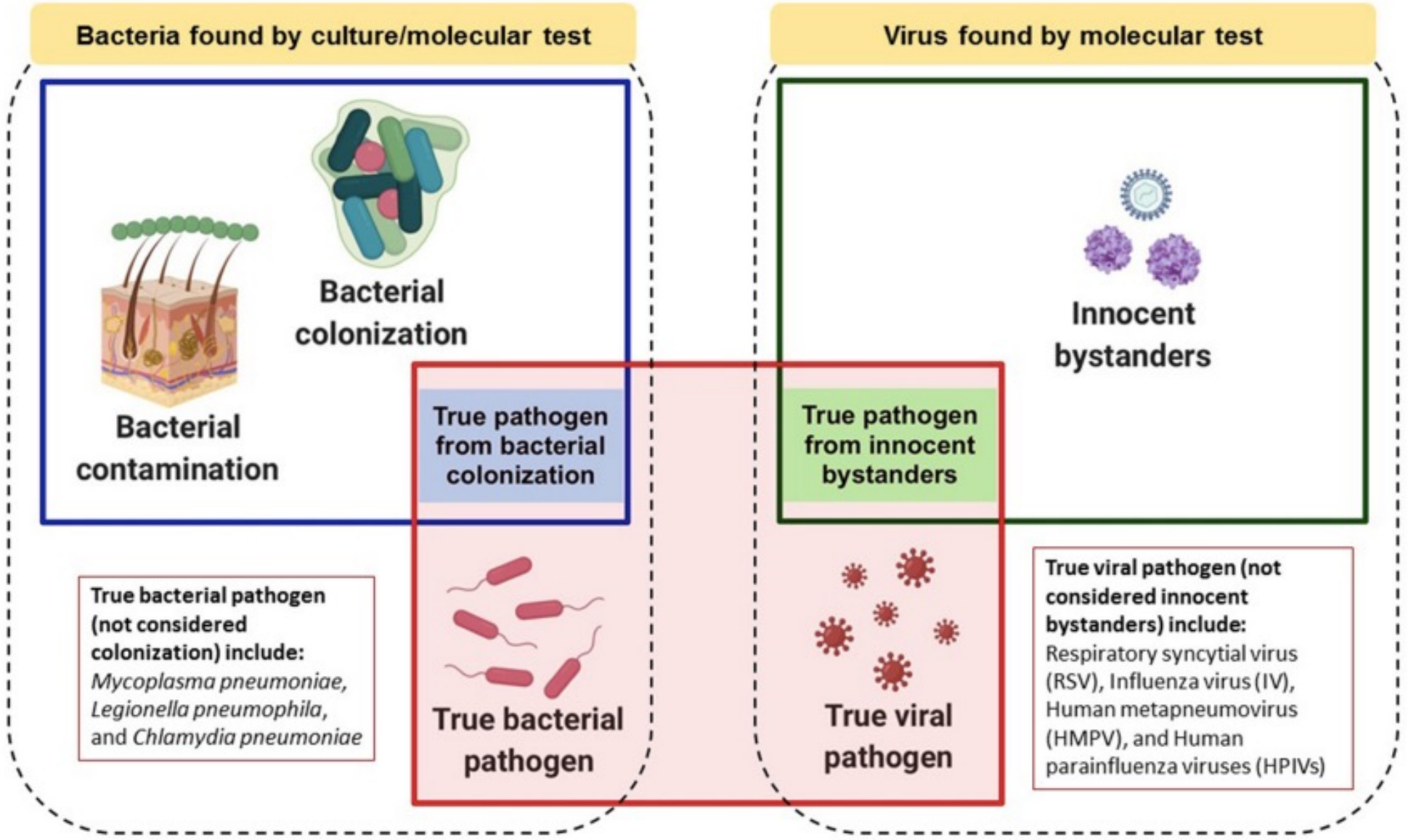
SEMANA 16 – 2024: 3337 casos: 44% (+)

1. **Influenza A: 44,2% (700 casos)**
2. Rinovirus : 38,9% (617)
3. Adenovirus: 6,4% (102)
4. Parainfluenza: 4,0% (64)
5. SARS-CoV-2: 2,9% (46)
6. Metapneumovirus: 1,3% (20)
7. Otros virus respiratorios: 1,1% (17)
8. VRS: 0,9% (14)
9. Influenza B: 0,3% (5)

Rol de infección viral previo a la infección bacteriana



Sender, V. (2021). Virus-Induced Changes of the Respiratory Tract Environment Promote Secondary Infections With Streptococcus pneumoniae. Frontiers in cellular and infection microbiology, 11, 643326.



¿Cómo lo estudio?

Virus patogénicos:

- ✓ VRS
- ✓ Influenza
- ✓ Metapneumovirus
- ✓ Parainfluenza

* Se ha descrito persistencia de PCR rhinovirus (+) hasta 5 semanas post cuadro sintomático

Mardian, Y., (2021). Approach to Identifying Causative Pathogens of Community-Acquired Pneumonia in Children Using Culture, Molecular, and Serology Tests. Frontiers in pediatrics, 9, 629318

Tabla 5. Resumen de los estudios chilenos de las principales etiologías de la neumonía adquirida en la comunidad

Microorganismo	Luchsinger et al.[5] (n = 356)	Saldias et al.[6] (n = 935)	Arancibia et al.[7] (n = 104)
	Hospitalizados		UCI
Bacterias	42,7%	23%	51,8%
S. pneumoniae	21%	10,7%	26%
Gérmenes atípicos	22%	2,8%	18,2%
Virus respiratorios	34,8%	14,1%	6,7%
Co-infección	16,9%	2,1%	4,8%
Desconocido	34.8%	60,8%	40%

4 UCI, 2005-2006

Estudio viral: IFI ➔ baja sensibilidad: 20% vs PCR virus

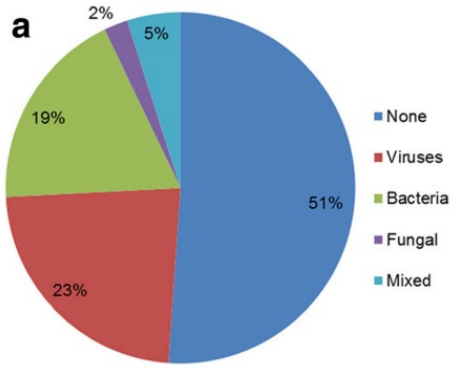
Arancibia, F., Cortes, C. P., Valdés, M., Cerda, J., Hernández, A., Soto, L., & Torres, A. (2014). Importance of Legionella pneumophila in the etiology of severe community-acquired pneumonia in Santiago, Chile. Chest, 145(2), 290–296. https://doi.org/10.1378/chest.13-0162

Prades Pérez, Y. C., Luchsinger Farías, V., & Contreras Osorio, L. (2014). Comparación de las técnicas de inmunofluorescencia, TR-RCP multiplex en tiempo real y Luminex en la detección de virus respiratorios en adultos con neumonía adquirida en la comunidad [recurso electrónico]. Tesis (bioquímica)--Universidad de Chile, 2014.

RESEARCH Open Access

Impact of viral multiplex real-time PCR on management of respiratory tract infection: a retrospective cohort study

Lena M. Mayer[1,4], Christian Kahlert[2,4], Frank Rassouli[3], Pietro Vernazza[4] and Werner C. Albrich[4*]



ADULTOS:
23% detección de virus

Suiza, 2017
254 pacientes adultos y niños:

140 (55%) se identificaron MO

¿Cambia el uso de antibióticos?

Table 5 Outcome depending on relevant detected pathogen for adult patients

	Viral (*n* = 40)	*Bacterial* (*n* = 36)	*Mixed* (*n* = 6)	*No pathogen* (*n* = 100)	*p-value*[a]		
					Viral vs. bacterial	*Viral vs. mixed*	*Viral vs. no pathogen*
LOS inpatients, median days (IQR)	8 (6–21)	21 (13–35)	11.5 (5–44.25)	15 (8–23.5)	<0.001	0.67	0.03
Complications, n (%)							
ICU admission	11 (27.5)	13 (36.1)	3 (50.0)	24 (24.0)	0.42	0.51	0.67
Mechanical ventilation	6 (15.0)	11 (30.6)	3 (50.0)	19 (19.0)	0.11	0.16	0.58
ARDS	3 (7.5)	5 (13.9)	2 (33.3)	6 (6.0)	0.60	0.24	1.00
Sepsis	24 (60.0)	24 (66.7)	5 (83.3)	6 (6.0)[b]	0.55	0.53	n/a
Mortality (all cause)	4 (10.0)	4 (11.1)	1 (16.7)	6 (6.0)	1.00	1.00	0.62
Antibiotic use (any indication)							
Any inpatient antibiotics, n (%)	30/35 (85.7)	29/32 (90.6)	4/6 (66.7)	72/89 (80.9)	0.81	0.54	0.53
Duration of inpatient use, mean days ± SD (range)	12.5 ± 14.3 (0–63)	18.1 ± 16.0 (0–72)	10.3 ± 12.1 (0–31)	10.8 ± 11.4 (0–63)	0.14	0.73	0.49
Discharged receiving oral antibiotics, n (%)	11 (30.6)[c]	17 (53.1)[d]	1 (20.0)[e]	23 (24.5)[f]	0.06	1.00	0.48

ARDS acute respiratory distress syndrome, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *n* number, *SD* standard deviation

Mayer, L. M (2017). Impact of viral multiplex real-time PCR on management of respiratory tract infection: a retrospective cohort study. Pneumonia (Nathan Qld.), 9, 4.

¿Cambia el pronóstico?

España, 2023
590 pacientes. 63,5% se identifica MO.
HC, PCR virus, cultivo expectoración, Ag urinario

Table 6
Risk factors for respiratory failure and ICU admission. Multivariate analysis.

	Respiratory failure		ICU admission	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Heart disease	1.50 (0.99–2.25)	0.056	0.94 (0.45–1.95)	0.863
History of chronic lung disease	2.16 (1.47–3.17)	<0.001	0.99 (0.85–1.16)	0.905
Age >65 years	2.14 (1.45–3.17)	<0.001	0.57 (0.30–1.07)	0.08
Viral infection	2.23 (1.44–3.45)	<0.001	2.77 (1.52–5.02)	0.001
Positive blood cultures[a]	1.97 (1.07–3.65)	0.03	1.51 (0.63–3.62)	0.352
Isolation of any bacteria	1.21 (0.85–1.74)	0.296	1.26 (0.68–2.33)	0.464

[a] Positive blood cultures: growth of a pathogen concordant with a cause of CAP.

Subanálisis en falla ventilatoria:
INFLUENZA: OR, 3.72; 95% CI, 2.06–6.73

Sellarès-Nadal, J. (2023). Impact of viral detection in patients with community-acquired pneumonia: An observational cohort study. Medicina clinica, 161(12), 523–529.

¿Cambia el pronóstico?

Japón, 2017
Pacientes >15 años, 2617 pacientes
HC, PCR múltiple, cultivo expectoración, Ag urinario
Comorbilidad respiratoria: 3,3 veces mayor riesgo de morir cuando la infección era por Influenza A o B.

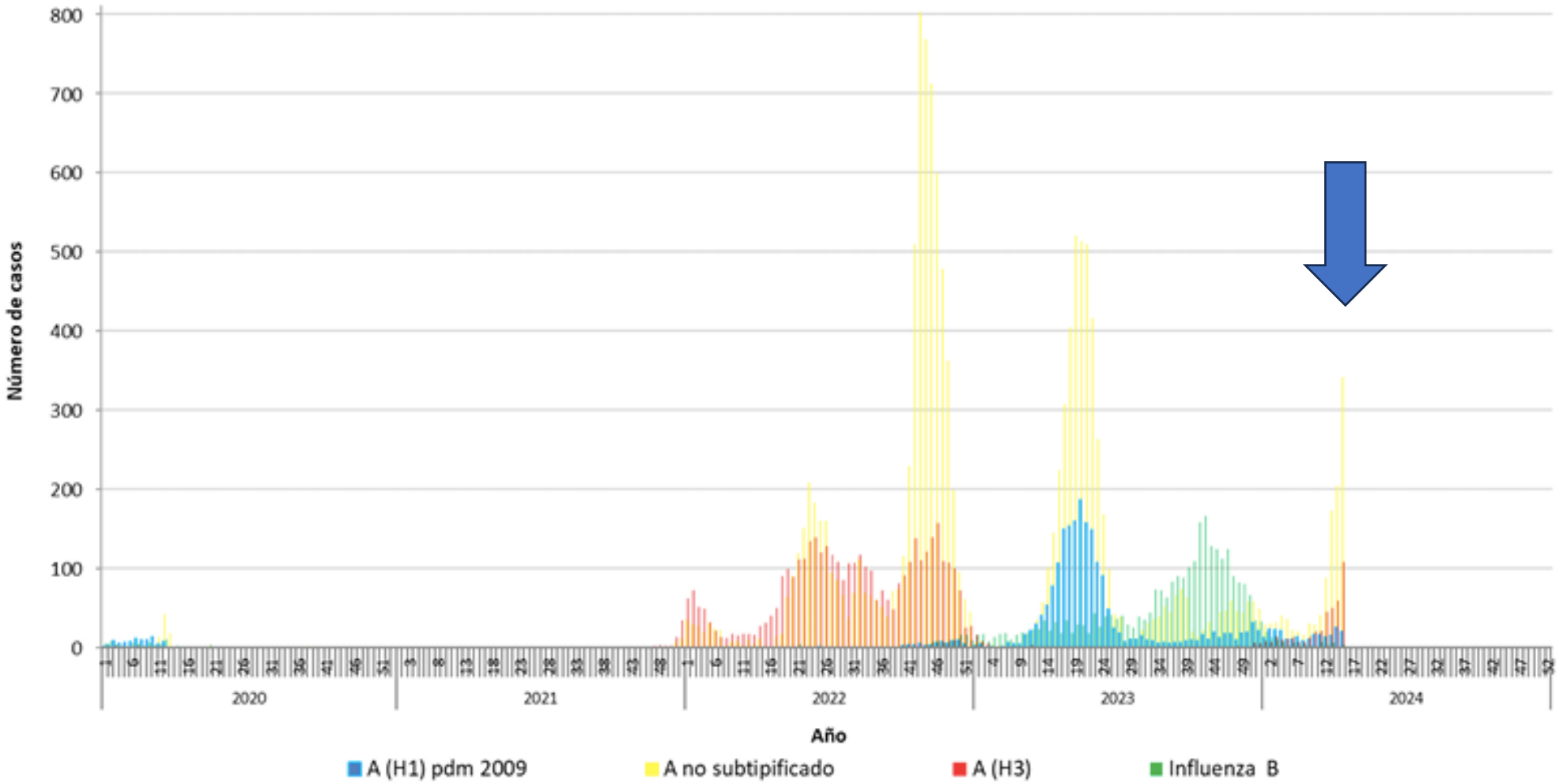
Table 5 Viral and bacterial infection status and in-hospital mortality among pneumonia patients by comorbidity status

	Without comorbidities, $n = 574$		With chronic respiratory disease, $n = 790$		With other comorbidities[a], $n = 1253$	
	No. death/no. cases (% mortality)	ARR[b] (95% CI)	No. death/no. cases (% mortality)	ARR[b] (95% CI)	No. death/no. cases (% mortality)	ARR[b] (95% CI)
HRV	2/53 (3.8)	0.73 (0.18–2.96)	4/83 (4.8)	0.78 (0.28–2.14)	8/98 (8.2)	0.97 (0.48–1.96)
Inf A/B	0/22 (0.0)	0.00 (0.00–0.00)	6/31 (19.4)	3.38 (1.54–7.42)	4/57 (7.0)	0.73 (0.26–2.02)
Paramyxovirus (RSV/hMPV/PIV1–4)	1/32 (3.1)	0.47 (0.07–3.26)	3/71 (4.2)	0.66 (0.20–2.13)	1/109 (0.9)	0.10 (0.01–0.70)
Other viruses (HAdV/HBoV/HCoV)	0/4 (0.0)	0.00 (0.00–0.00)	1/5 (20.0)	4.55 (0.58–35.5)	1/9 (11.1)	1.33 (0.21–8.66)
Multiple viruses	0/7 (0.0)	0.00 (0.00–0.00)	1/6 (16.7)	3.98 (0.68–23.24)	3/18 (16.7)	1.68 (0.56–5.03)
No virus	26/456 (5.7)	Reference	44/594 (7.4)	Reference	88/962 (9.2)	Reference
		ARR[c](95% CI)		ARR[c](95% CI)		ARR[c](95% CI)
Only viruses	1/64 (1.6)	0.24 (0.03–1.78)	9/108 (8.3)	1.28 (0.59–2.81)	9/187 (4.8)	0.51 (0.26–1.01)
Only bacterial pathogens	8/179 (4.5)	0.83 (0.36–1.93)	16/227 (7.1)	1.13 (0.61–2.09)	27/340 (7.9)	0.84 (0.54–1.31)
Viral-bacterial co-infection	2/54 (3.7)	0.58 (0.14–2.38)	6/88 (6.8)	1.29 (0.55–3.06)	8/104 (7.7)	0.77 (0.38–1.59)
No viral or bacterial pathogens	18/277 (6.5)	Reference	28/367 (7.6)	Reference	61/622 (9.8)	Reference
		ARR[b] (95% CI)		ARR[b] (95% CI)		ARR[b] (95% CI)
Multiple viruses	0/7 (0.0)	0.00 (0.00–0.00)	1/6 (16.7)	3.22 (0.52–19.81)	3/18 (16.7)	2.98 (0.91–9.78)
Single virus	3/111 (2.7)	Reference	14/190 (7.4)	Reference	14/273 (5.1)	Reference

ARR adjusted risk ratio, *CI* confidence interval, *HRV* human rhinovirus, *InfA* influenza A virus, *RSV* respiratory syncytial virus, *PIV1–4* human parainfluenza virus type 1–4, *HMPV* human metapneumovirus, *InfB* influenza B virus, *HCoV* human coronavirus (229E/OC43), *HAdV* human adenovirus, *HBoV* human bocavirus
[a] Other comorbidities include diabetes mellitus, cerebrovascular disease, dementia, neuromuscular disease, cardiac failure, ischaemic heart disease, collagen disease, malignancy, renal disease, and liver disease
[b] Adjusted for age, study site, duration of symptoms, month of diagnosis, antibiotic use and presence of bacteria
[c] Adjusted for age, study site, duration of symptoms, month of diagnosis, and antibiotic use

Katsurada, (2017). The impact of virus infections on pneumonia mortality is complex in adults: a prospective multicentre observational study. BMC infectious diseases, 17(1), 755.

Figura N°5. Distribución del número de casos de Influenza por tipos y subtipos por semana epidemiológica, Chile 2020-2024*.



*Información hasta la SE N°15 del 2024.

Fuente: Sección Virus Respiratorios y Exantemáticos. Departamento de Laboratorio Biomédico. Instituto de Salud Pública de Chile.

Influenza: ¿qué sirve? (en el paciente crítico)

OMS, 2022

Estudio con PCR: hisopado nasal, faríngeo, ambos (sin falla ventilatoria) o aspirado traqueal/LBA si sospecha y estudio inicial negativo

3.1 Oseltamivir (oral)

RECOMMENDATION 1

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest administering oseltamivir as soon as possible (vs not administering oseltamivir)** (conditional recommendation, low-quality evidence).

Marzo 2018

IDSA
Infectious Diseases Society of America

IDSA, 2018

Estudio con PCR a todo hospitalizado por falla ventilatoria (en temporada)

Inicio precoz de inhibidores de neuraminidasa: oseltamivir vo (absorción adecuada). Dosis habitual, se podría aumentar duración de tratamiento

Influenza: ¿qué sirve? (en el paciente crítico)

Public Health England

Reino Unido, 2019
Oseltamivir: ideal <48 hrs pero en pacientes críticos ”incluso el tratamiento más tardío se asocia con una reducción de la mortalidad vs no tratamiento”

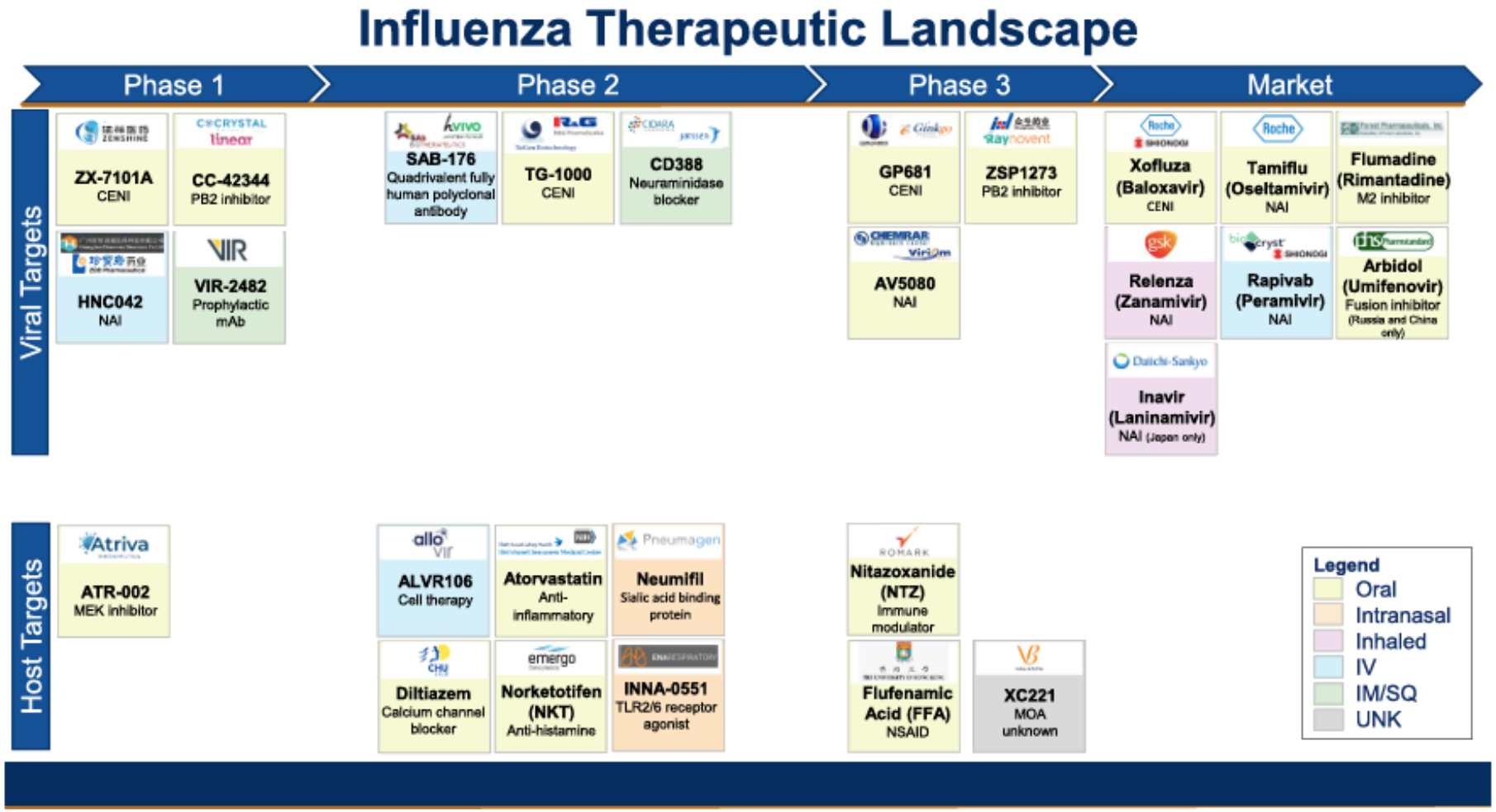
ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

CDD europeo: 2023
Recomienda oseltamivir y zanamivir EV (Dectova®) en pacientes graves
*Resistencia a oseltamivir es <1% y si es resistente, es sensible a zanamivir

SER

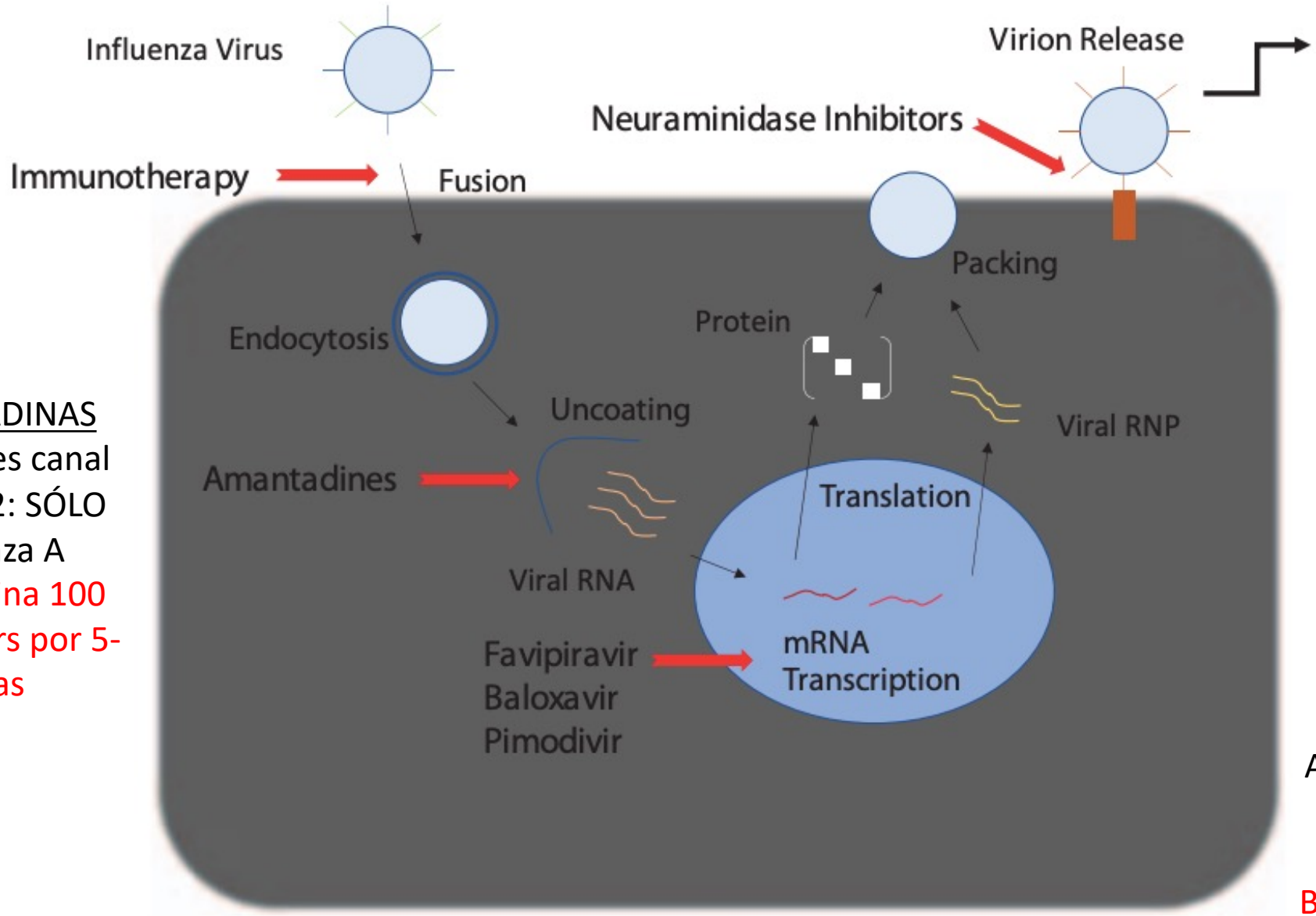
Sociedad Chilena de Enfermedades Respiratorias, 2023
MINSAL: inicio precoz de oseltamivir si PCR influenza (+)
Pacientes críticos: el tratamiento precoz con oseltamivir es una variable independiente asociada a una reducción de la mortalidad en la UCI (OR: 0,44; IC95% 0,21-0,87)

Influenza: ¿algo nuevo?



1. Fusión: inmunoterapia, umifenovir
2. Liberación DNA "uncoating": amantadina, rimantadina
3. Transcripción RNAm:
   - Favipiravir
   - Baloxavir
   - Pimodivir
4. Inhibidores NA:
   - Oseltamivir
   - Zanamivir
   - Laninamivir
   - Peramivir

O'Sullivan, S; Influenza management with new therapies. Current Opinion in Pulmonary Medicine 26(3):p 215-221, May 2020.



<u>AMANTADINAS</u>

Inhibidores canal iónico M2: SÓLO influenza A

Amantadina 100 mg c/12 hrs por 5-7 días

<u>INHIBIDORES DE LA NEUROAMINIDASA</u>

NA: permite salida de viriones de la célula infectada

Oseltamivir 75 mg bid

Zanamivir inh 5 mg bid por 5 días

<u>INHIBIDORES DE LA TRANSCRIPCION VIRAL</u>

Acción en polimerasa viral (inhibidor de la endonucleasa)

Baloxavir 40 -80 mg x 1 vez

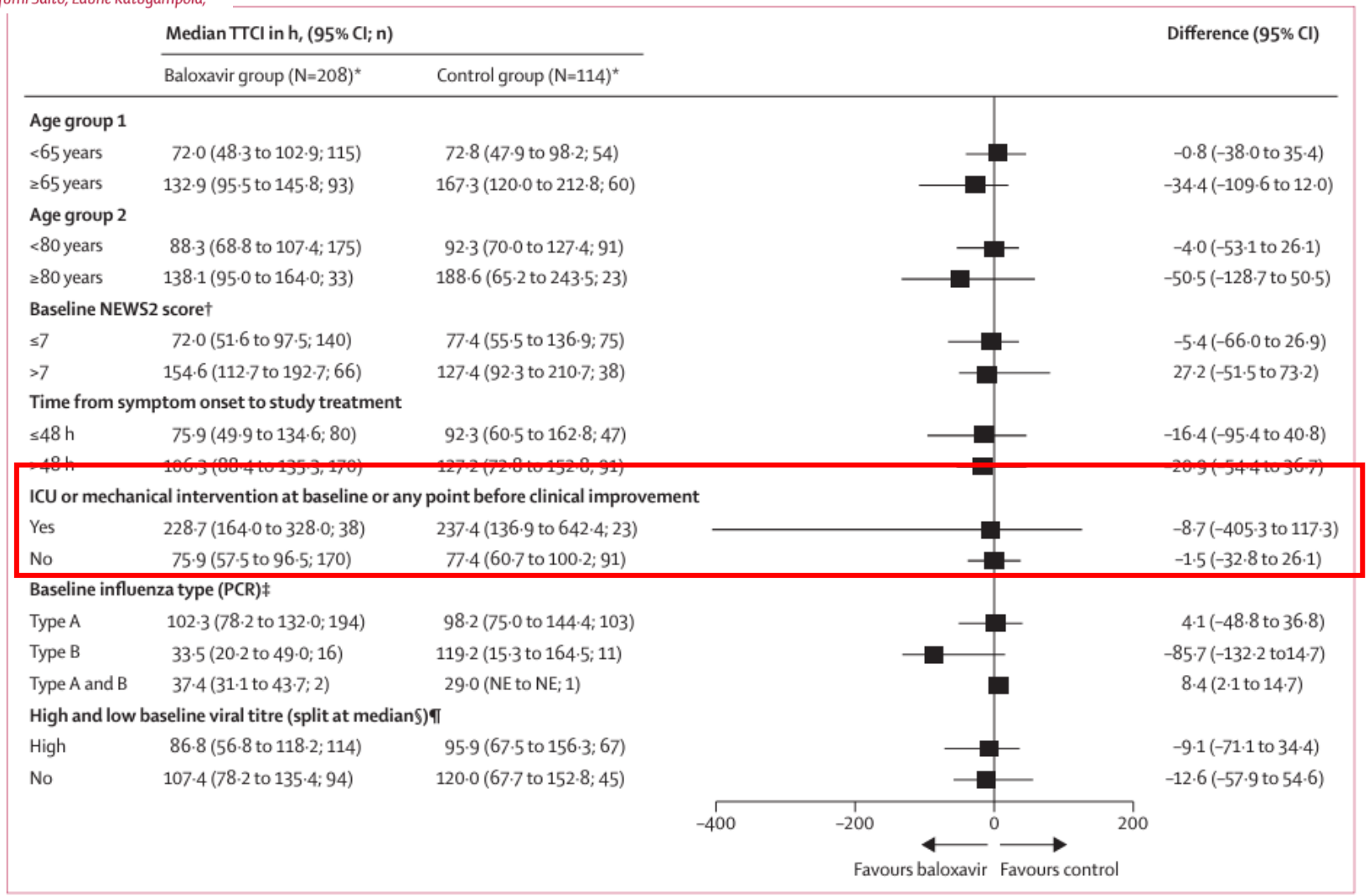
Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial

Deepali Kumar, Michael G Ison, Jean-Paul Mira, Tobias Welte, Jick Hwan Ha, David S Hui, Nanshan Zhong, Takefumi Saito, Laurie Katugampola,

RCT, multicéntrico, 2022
366 pacientes: 241 baloxavir + oseltamivir
215 oseltamivir + placebo

Baloxavir: aprobado para influenza no complicada

UCI o VMI: <u>sin</u> significancia estadística en tiempo de mejoría clínica: alta médica o NEWS2<2



	Median TTCI in h, (95% CI; n)		Difference (95% CI)
	Baloxavir group (N=208)*	Control group (N=114)*	
Age group 1			
<65 years	72·0 (48·3 to 102·9; 115)	72·8 (47·9 to 98·2; 54)	−0·8 (−38·0 to 35·4)
≥65 years	132·9 (95·5 to 145·8; 93)	167·3 (120·0 to 212·8; 60)	−34·4 (−109·6 to 12·0)
Age group 2			
<80 years	88·3 (68·8 to 107·4; 175)	92·3 (70·0 to 127·4; 91)	−4·0 (−53·1 to 26·1)
≥80 years	138·1 (95·0 to 164·0; 33)	188·6 (65·2 to 243·5; 23)	−50·5 (−128·7 to 50·5)
Baseline NEWS2 score†			
≤7	72·0 (51·6 to 97·5; 140)	77·4 (55·5 to 136·9; 75)	−5·4 (−66·0 to 26·9)
>7	154·6 (112·7 to 192·7; 66)	127·4 (92·3 to 210·7; 38)	27·2 (−51·5 to 73·2)
Time from symptom onset to study treatment			
≤48 h	75·9 (49·9 to 134·6; 80)	92·3 (60·5 to 162·8; 47)	−16·4 (−95·4 to 40·8)
>48 h	186·3 (88·4 to 135·3; 170)	127·2 (72·8 to 152·8; 91)	20·3 (−54·4 to 36·7)
ICU or mechanical intervention at baseline or any point before clinical improvement			
Yes	228·7 (164·0 to 328·0; 38)	237·4 (136·9 to 642·4; 23)	−8·7 (−405·3 to 117·3)
No	75·9 (57·5 to 96·5; 170)	77·4 (60·7 to 100·2; 91)	−1·5 (−32·8 to 26·1)
Baseline influenza type (PCR)‡			
Type A	102·3 (78·2 to 132·0; 194)	98·2 (75·0 to 144·4; 103)	4·1 (−48·8 to 36·8)
Type B	33·5 (20·2 to 49·0; 16)	119·2 (15·3 to 164·5; 11)	−85·7 (−132·2 to14·7)
Type A and B	37·4 (31·1 to 43·7; 2)	29·0 (NE to NE; 1)	8·4 (2·1 to 14·7)
High and low baseline viral titre (split at median§)¶			
High	86·8 (56·8 to 118·2; 114)	95·9 (67·5 to 156·3; 67)	−9·1 (−71·1 to 34·4)
No	107·4 (78·2 to 135·4; 94)	120·0 (67·7 to 152·8; 45)	−12·6 (−57·9 to 54·6)

Figure 3: Subgroup analyses showing median TTCI by treatment group and difference between groups

Kumar, D. (2022). Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial. The Lancet. Infectious diseases, 22(5), 718–730.

Clinical Infectious Diseases

MAJOR ARTICLE

Effect of Early Oseltamivir Treatment on Mortality in Critically Ill Patients With Different Types of Influenza: A Multiseason Cohort Study

Theodore Lytras,[1] Elisavet Mouratidou,[1,2] Anastasia Andreopoulou,[1] Stefanos Bonovas,[3,4] and Sotirios Tsiodras[1,5]

Grecia, 2019
1330 pacientes graves con influenza confirmada
46,8% fallecidos

87% recibió oseltamivir
Sin diferencias en mortalidad entre inicio precoz vs tardío
EXCEPTO en influenza A/H3N2

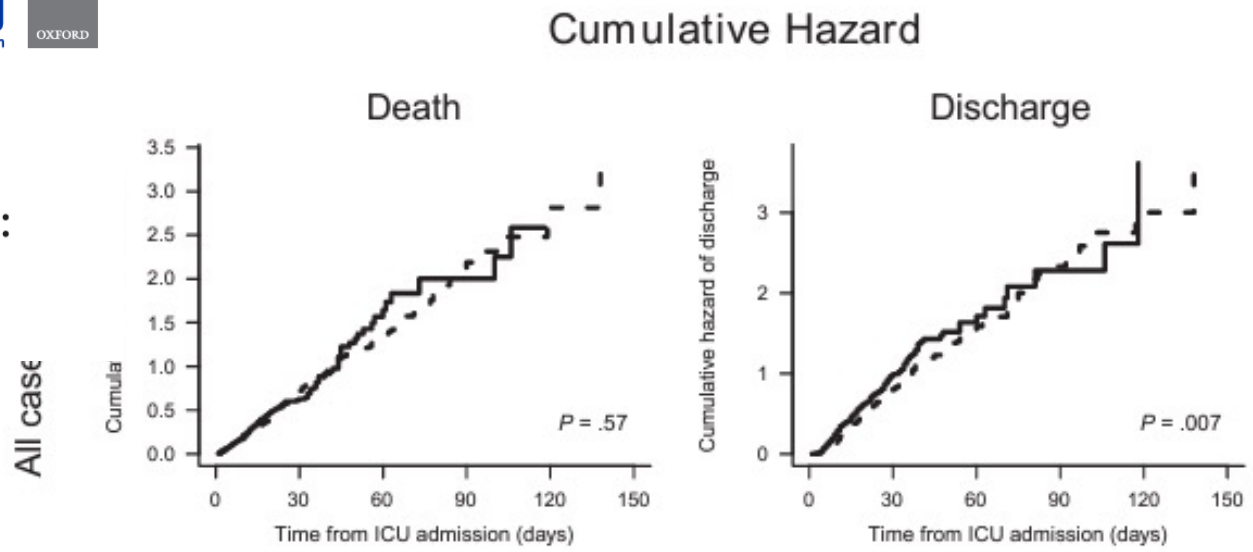


Table 2. Adjusted Effects of Early Versus Late Oseltamivir Treatment on Mortality Risk, Mortality, and Discharge Cause-specific Hazards and Subdistribution Hazards, and on Median Length of Stay Among Survivors

	Unadjusted	Log-binomial Model	Proportional Hazards Model		Proportional Subdistribution Hazards Model		Difference in Predicted Median Length of Stay Among Survivors, d
Type	RR of Death	RR of Death	csHR of Death	csHR of Discharge	sHR of Death	sHR of Discharge	
Overall	0.89 (.75–1.06)	0.94 (.78–1.14)	1.03 (.79–1.34)	1.20 (.94–1.51)	0.88 (.65–1.18)	1.10 (.85–1.42)	–0.3 (–1.2 to .5)
Stratified by influenza type							
A/H1N1	1.12 (.87–1.45)	1.04 (.85–1.28)	1.09 (.81–1.47)	0.98 (.74–1.32)	1.05 (.77–1.44)	0.88 (.65–1.18)	0.3 (–.5 to 1.2)
A/H3N2	**0.66 (.46–.95)**	**0.69 (.49–.94)**	0.87 (.57–1.32)	**1.89 (1.33–2.70)**	**0.58 (.37–.88)**	**1.66 (1.18–2.37)**	**–1.8 (–3.5 to –.5)**
B	0.92 (.60–1.41)	0.94 (.64–1.35)	1.01 (.60–1.69)	1.08 (.66–1.73)	0.92 (.54–1.57)	0.98 (.59–1.60)	0.1 (–1.7 to 1.6)

Data are presented as posterior median (95% credible interval). Significant results are indicated in bold text.

Abbreviations: csHR, cause-specific hazard ratio; RR, relative risk; sHR, subdistribution hazard ratio.

Lytras, T., (2019). Effect of Early Oseltamivir Treatment on Mortality in Critically Ill Patients With Different Types of Influenza: A Multiseason Cohort Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 69(11), 1896–1902.

REVIEW ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Comparison of double-dose vs standard-dose oseltamivir in the treatment of influenza: A systematic review and meta-analysis

Lei Li MPharm | Jing Liu MPharm | Kan Qin MPharm

MORTALIDAD: Doble dosis vs estándar

Stratification	No. of patients	Studies	OR (95% CI)	*P*-value	I^2 (%)
All studies	20 501	5	1.50 [0.95, 2.37]	.19	35
Study design					
RCTs	294	1	1.29 [0.52, 3.15]	.58	/
Observational studies	20 207	4	1.59 [0.79, 3.19]	.20	51
ICU patients					
ICU	20 052	3	1.52 [0.68, 3.40]	.31	66
Non-ICU	449	2	1.38 [0.59, 3.25]	.46	0

*Pocos estudios disponibles

No hubo diferencia significativa en mortalidad entre dosis estándar (75 mg c/12 hrs) vs doble dosis (150 mg c/12 hrs)

Tampoco hubo diferencias en:

- ✓ Outcome virológico: 5-d clearance rate (PCR)
- ✓ Efectos adversos

Li, L., (2020). Comparison of double-dose vs standard-dose oseltamivir in the treatment of influenza: A systematic review and meta-analysis. Journal of clinical pharmacy and therapeutics, 45(5), 918–926.

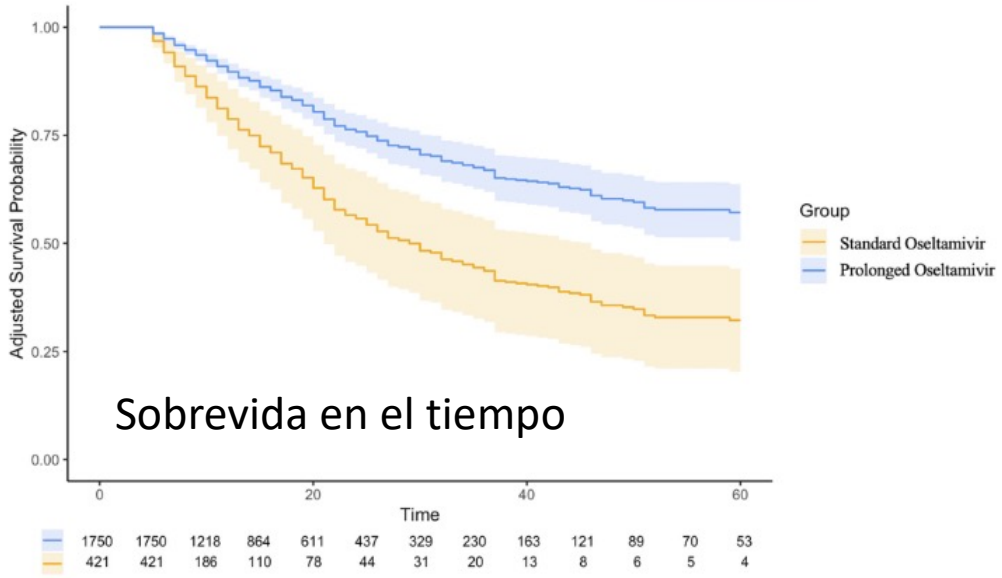
RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Effectiveness of prolonged versus standard-course of oseltamivir in critically ill patients with severe influenza infection: A multicentre cohort study

Gerard Moreno[1] | Raquel Carbonell[1] | Emili Díaz[2] | Ignacio M

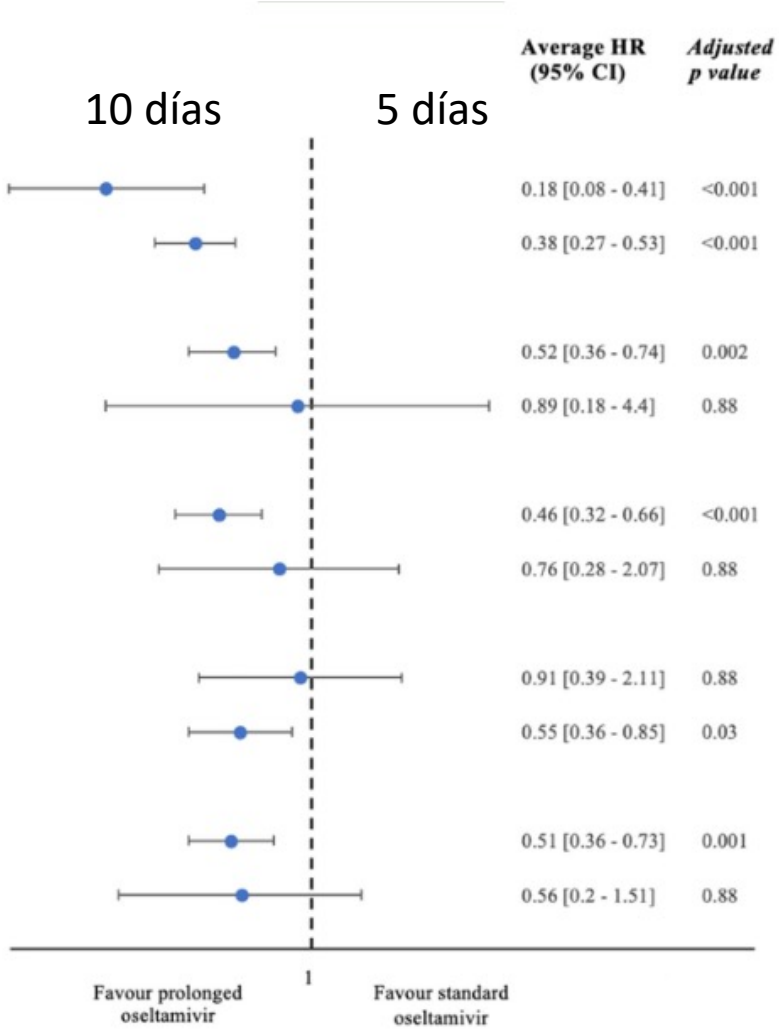
España, 2023
2397 pacientes críticos con influenza
5 días vs 10 días: beneficio en paciente critico



Sobrevida en el tiempo

FIGURE 3 Adjusted survival curves plotted based on the Cox regression stratified by Prolonged versus Standard Oseltamivir treatment. The model was adjusted for age, immunosuppression, APACHE II and SOFA scores, ICU gap, gender, number of pulmonary infiltrates, acute kidney injury, viral pneumonia, septic shock, invasive mechanical ventilation, prone positioning, hematological disease, bacterial co-infection, ventilator-associated pneumonia, and corticosteroids. The ICU gap was the time between hospital and ICU admission. APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Subgroup	Prolonged oseltamivir	Standard oseltamivir	Average HR (95% CI)	*Adjusted p value*
	no. of patients with primary outcome/total no.(%)			
Inmunosupresión				
Inmunosupression	113/291 (38.8%)	35/79 (44.3%)	0.18 [0.08 - 0.41]	<0.001
No inmunosupression	315/1652 (19.1%)	89/375 (23.7%)	0.38 [0.27 - 0.53]	<0.001
Neumonía				
Pneumonia	398/1742 (22.8%)	108/366 (29.5%)	0.52 [0.36 - 0.74]	0.002
No pneumonia	30/201 (14.9%)	16/88 (18.2%)	0.89 [0.18 - 4.4]	0.88
VMI				
IMV	369/1362 (27.1%)	98/257 (38.1%)	0.46 [0.32 - 0.66]	<0.001
No IMV	59/581 (10.2%)	26/197 (13.2%)	0.76 [0.28 - 2.07]	0.88
Early oseltamivir	78/389 (20.1%)	32/127 (25.2%)	0.91 [0.39 - 2.11]	0.88
Late oseltamivir	350/1554 (22.5%)	92/327 (28.1%)	0.55 [0.36 - 0.85]	0.03
FOM				
Multiorgan failure	371/1400 (26.5%)	105/295 (35.6%)	0.51 [0.36 - 0.73]	0.001
No multiorgan failure	57/543 (10.5%)	19/159 (11.9%)	0.56 [0.2 - 1.51]	0.88

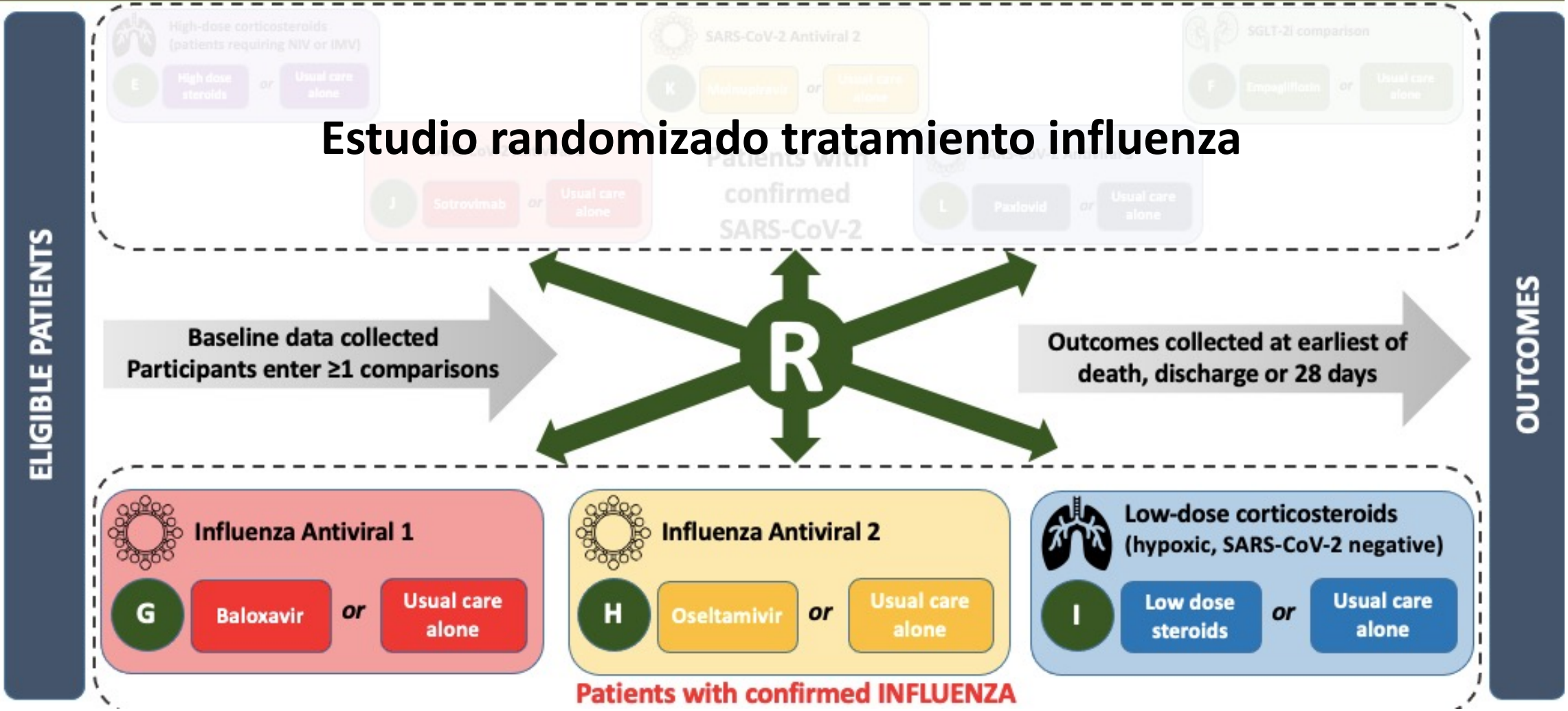


Moreno, G., (2023). Effectiveness of prolonged versus standard-course of oseltamivir in critically ill patients with severe influenza infection: A multicentre cohort study. Journal of medical virology, 95(8), e29010.

Current design (adults)

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Estudio randomizado tratamiento influenza



Paramyxoviridae: VRS, parainfluenza, metapneumovirus

- Presencia de proteína de fusión

	Live-attenuated	Subunit	Vector-based	Particle-based	Monoclonal antibody	mRNA
Phase 3	None	1. RSVpreF3 2. RSVpre-F	1. MVA-BN-RSV 2. Ad26.RSV.preF	None	1. Nirsevimab 2. Clesrovimab	mRNA-1345
Phase 2	RSV/ΔNS2/Δ1313/I1314L	MEDI7510	None	None	Narsyn	None
Phase 1	1. LID ΔM2-2 2. LIDcpΔM2-2 3. LID/ΔM2-2/10 4. D46/NS2/N/ΔM2-2-HindIII30s 5. RSVΔG 6. rA2cp248/404ΔSH 7. rA2cp248/404/1030ΔSH 8. MEDI-599	1. DS-Cav1 2. RSV F vaccine 3. DPX-RSV	1. MVA-RSV 2. PanAd3-RSV 3. ChAd155-RSV	IVX-121 V306-VLP	RSM01	mRNA-1777

Fig. 3. Overview of the RSV vaccine candidates and monoclonal antibodies in clinical trials.

Rol en vacunas

- ✓ Nirsevimab: Ac monoclonal IgG1κ humano recombinante de larga duración, neutralizante de la conformación de prefusión de la proteína F del VRS
- ✓ FDA-EMA 2023: Vacunas aprobadas para >60 años y embarazadas:
  - Subunidad proteína F prefusión
  - ABRYSVO: menor riesgo de infección respiratoria por VRS vs placebo: riesgo de incidencia: 0.156, IC 95%: 0.048- 0.40
  - Evidencia moderada
  - Eficacia vaccinal 84,4% (incidencia)

Qiu, X., (2022). Development of mRNA vaccines against respiratory syncytial virus (RSV). Cytokine & growth factor reviews, 68, 37–53.
CDC (2023) Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer RSVpreF Vaccine (ABRYSVO)

SARS-COV2: ¿algo nuevo?

Treating COVID-19: 32 recommendations from the Infectious Diseases Society of America

Recommended	Not recommended
Dexamethasone for hospitalized critically ill patients	**Hydroxychloroquine**
Dexamethasone for hospitalized patients with severe but noncritical COVID-19	**Hydroxychloroquine plus azithromycin** for hospitalized patients with COVID-19
Tocilizumab for hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation	**Hydroxychloroquine** for patients exposed to COVID-19
Sarilumab for patients who would qualify for tocilizumab, if tocilizumab is not available	**Lopinavir-ritonavir** for patients exposed to COVID-19
Convalescent plasma for ambulatory patients with mild to moderate COVID-19 at high risk of progressing to severe disease who have no other treatment options, within 8 days of symptom onset	**Lopinavir-ritonavir** for ambulatory patients with mild to moderate COVID-19
Remdesivir for patients with mild to moderate COVID-19 within 7 days of symptom onset at high risk of progressing to severe disease	**Lopinavir-ritonavir** for hospitalized patients
Remdesivir for 5 days rather than 10 days for patients on supplemental oxygen but not on mechanical ventilation or extracorporeal mechanical ventilation	**Glucocorticoids** for hospitalized patients with mild to moderate COVID-19 without hypoxemia requiring supplemental oxygen
Remdesivir for hospitalized patients with severe COVID-19	**Inhaled corticosteroids** for ambulatory patients with mild to moderate COVID-19
Baricitinib with corticosteroids for hospitalized adults with severe COVID-19	**Convalescent plasma** for hospitalized immunocompetent patients
Baricitinib with remdesivir for hospitalized patients with severe COVID-19 who cannot receive a corticosteroid	**Routine use of convalescent plasma** for hospitalized immunocompromised patients
Tofacitinib for hospitalized adults with severe COVID-19 but not on noninvasive or invasive mechanical ventilation	**Remdesivir** for those on mechanical ventilation, extracorporeal membrane oxygenation, or both
Fluvoxamine (but only in a clinical trial)	**Famotidine** for ambulatory patients with mild to moderate COVID-19
Nirmatrelvir-ritonavir within 5 days of symptom onset in ambulatory patients with mild to moderate COVID-19 at high risk of progressing to severe disease	**Famotidine** for hospitalized patients with severe COVID-19
Molnupiravir within 5 days of symptom onset in ambulatory adults with mild to moderate COVID-19 at high risk of progressing	**Ivermectin** for hospitalized patients
	Ivermectin for ambulatory patients
	Colchicine for hospitalized patients
	Colchicine for ambulatory patients
	Anakinra for hospitalized patients with severe COVID-19

Bash, K., Sacha, G., & Latifi, M. (2023). COVID-19: A management update. Cleveland Clinic journal of medicine, 90(11), 677–683.

Recomendaciones para manejo del paciente crítico con covid19

IDSA, 2023
Disponible en Chile:

- ✓ Corticoides: dexametasona 6 mg día = prednisona 40 mg = metilprednisolona 32 mg por 10 días

- ✓ Tocilizumab
- ✓ Baricitinib
- ✓ Tofacitinib

Hospitalized for critically ill COVID-19, needing non-invasive ventilation or Hi flow oxygen	Corticosteroids (dexamethasone 6 mg/d x 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone). • Tocilizumab or Sarilumab in patients with elevated inflammatory makers • Baricitinib or tofacitinib in patients with elevated inflammatory markers • No benefit demonstrated in RCTs for remdesivir, convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin.
Hospitalized for critically ill COVID-19, needing invasive mechanical ventilation or ECMO	• Corticosteroids (dexamethasone 6 mg/d x 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone). • Tocilizumab or sarilumab in patients with elevated inflammatory makers • Baricitinib or tofacitinib in patients with elevated inflammatory markers • No benefit demonstrated in RCTs for remdesivir, convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin.

Bhimraj A et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2023; Version 11.0.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 28/04/2024.

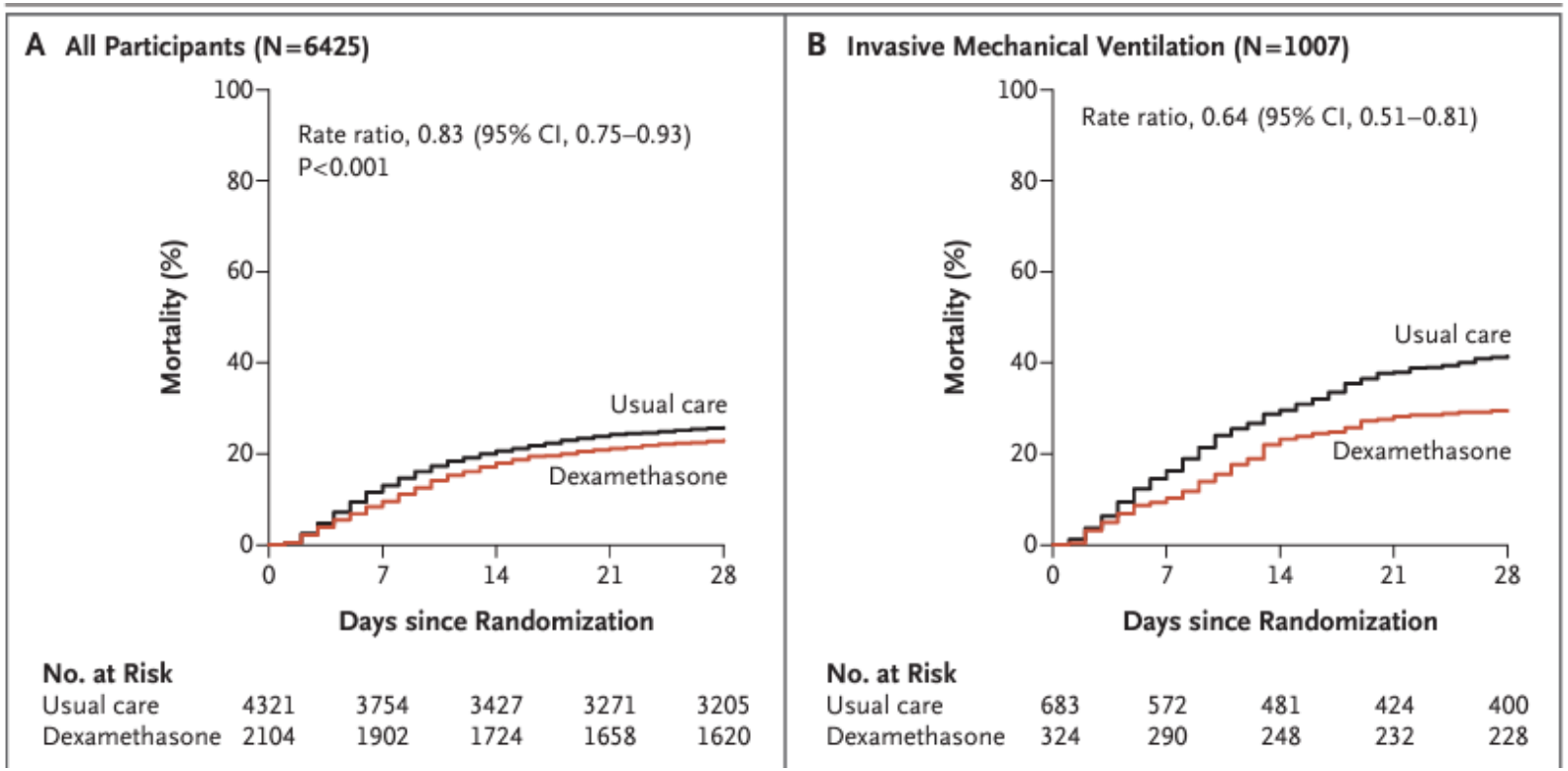
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 25, 2021 VOL. 384 NO. 8

Dexametasona 6 mg por 10 días vs manejo habitual
Outcome: mortalidad a 28 días

Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

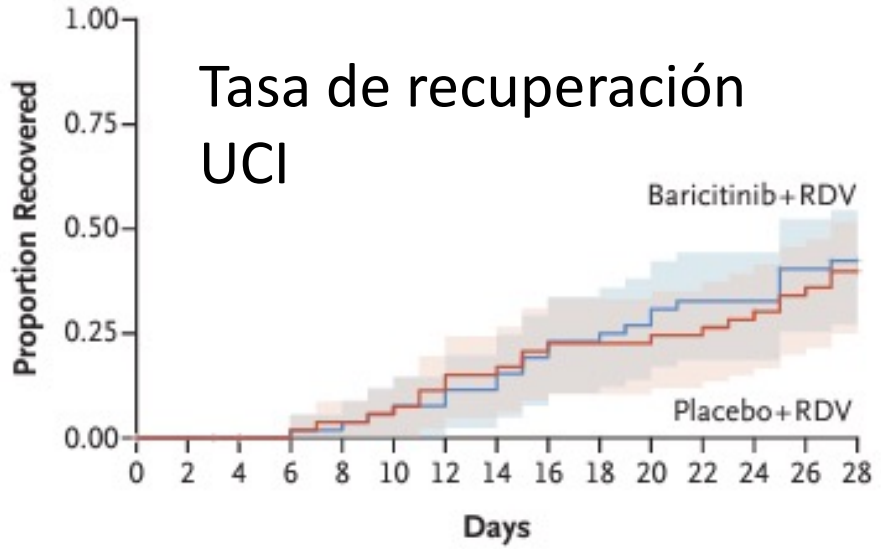


- Pacientes críticos con covid19: 34% menor mortalidad a 28 días en el grupo que recibió corticoides (OR: 0.66; 95% CI: 0.54; 0.82; ALTA certeza de la evidencia).

RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021; 384(8):693–704.

SARS-COV2: ¿y si no puedo usar corticoides?

- IDSA: baricitinib 4 mg/día por 14 días + remdesevir 200 mg día EV luego 100 mg día por 10 días



No. at Risk

Baricitinib+RDV	54	53	52	52	51	49	48	46	42	40	38	35	35	30	15
Placebo+RDV	57	54	54	53	51	50	47	45	42	41	41	40	38	34	16

Kalil, A. C., ACTT-2 Study Group Members (2021). Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. The New England journal of medicine, 384(9), 795–807.

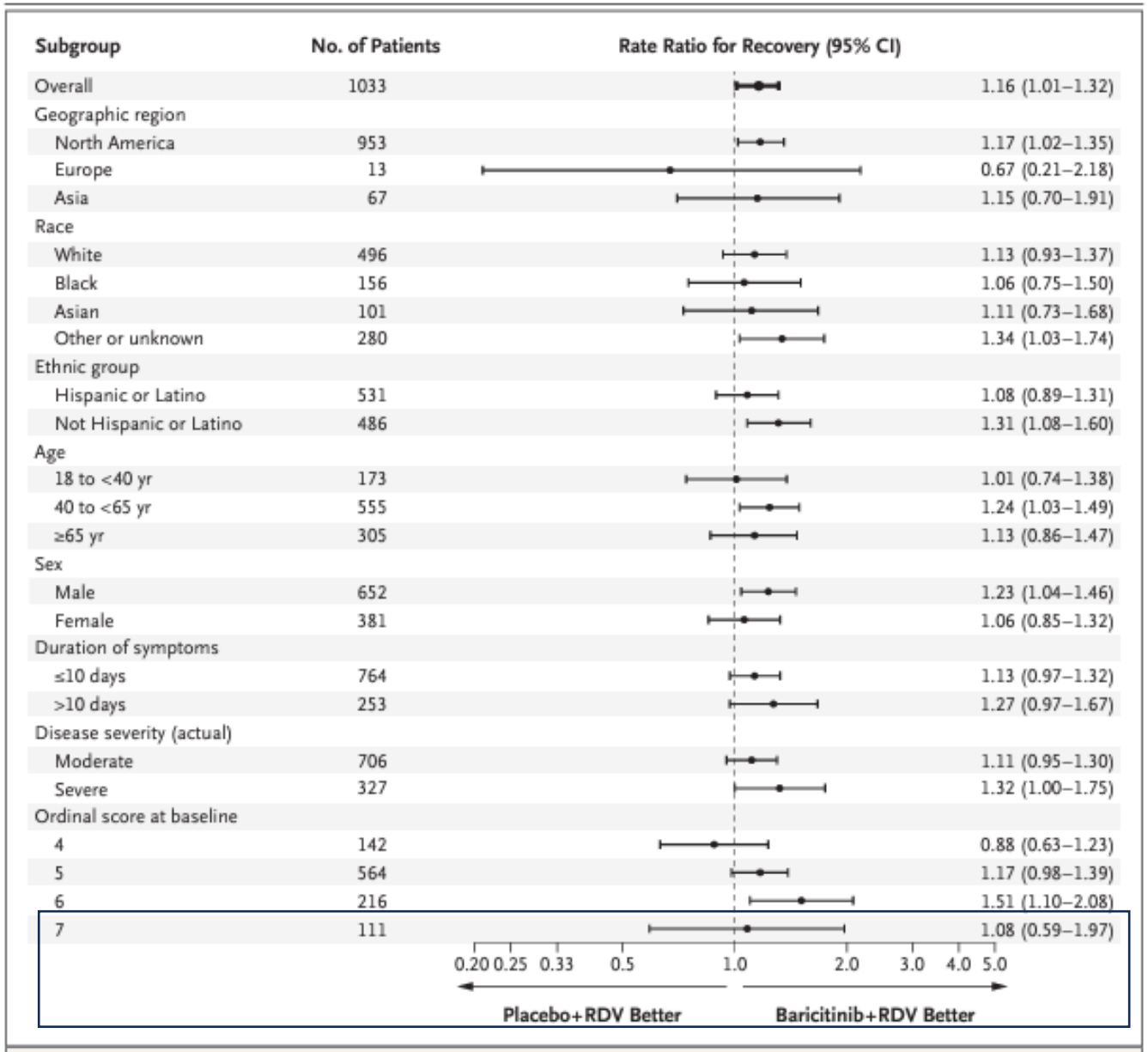


Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients. With respect to "other" race, the categories that were used when data on race were reported included American Indian or Alaska Native and Native Hawaiian or other Pacific Islander.

Question: Baricitinib with remdesivir compared to remdesivir for hospitalized patients with COVID-19

Last updated 5/16/2021; last reviewed 10/11/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib + RDV	RDV	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	24/515 (4.7%)	37/518 (7.1%)	**HR 0.65** (0.39 to 1.09)	**24 fewer per 1,000** (from 43 fewer to 6 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Clinical recovery - hospitalized requiring supplemental O_2/receiving noninvasive ventilation or high-flow O_2 (ordinal 5+6) (assessed with: Ordinal scale <4)												
1 [1]	randomized trials	serious [b]	not serious	not serious	serious [c]	none	344/391 (88.0%)	316/389 (81.2%)	**RR 1.08** (1.02 to 1.15)	**65 more per 1,000** (from 16 more to 122 more)	⨁⨁◯◯ LOW	CRITICAL
Clinical recovery - receiving noninvasive ventilation or high-flow O_2, invasive mechanical ventilation or ECMO (ordinal 6+7; stratified) (assessed with: Ordinal scale <4)												
1 [1]	randomized trials	not serious [d]	not serious	not serious	serious [e]	none	122/176 (69.3%)	114/191 (59.7%)	**HR 1.29** (1.00 to 1.66) [d]	**93 more per 1,000** (from 0 fewer to 182 more)	⨁⨁⨁◯ MODERATE	CRITICAL
New use of mechanical ventilation or ECMO (follow-up: 29 days)												
1 [1]	randomized trials	serious [f]	not serious	not serious	serious [g]	none	46/461 (10.0%)	70/461 (15.2%)	**RR 0.66** (0.46 to 0.93)	**52 fewer per 1,000** (from 82 fewer to 11 fewer)	⨁⨁◯◯ LOW	CRITICAL

Clinical Infectious Diseases
MAJOR ARTICLE

Remdesivir en paciente crítico

Deconstructing the Treatment Effect of Remdesivir in the Adaptive Coronavirus Disease 2019 (COVID-19) Treatment Trial-1: Implications for Critical Care Resource Utilization

Jonathan Fintzi,[1,©] Tyler Bonnett,[2] Daniel A. Sweeney,[3] Nikhil A. Huprikar,[4] Anuradha Ganesan,[5] Maria G. Frank,[6] Susan L. F. McLellan,[7] Lori E. Dodd,[1] Pablo Tebas,[8] and Aneesh K. Mehta[9]

	Overall		Invasive Ventilation [7]	
	Remdesivir	Placebo	Remdesivir	Placebo
	(N = 533)	(N = 518)	(N = 131)	(N = 154)
Recovery				
No. recovered (%)	395 (74.1%)	349 (67.4%)	62 (47.3%)	75 (48.7%)
HR (95% CI)	1.26 (1.10, 1.45)		1.00 (.73, 1.38)	
Any improvement relative to baseline				
No. ever improved (%)	444 (83.3%)	404 (78.0%)	91 (69.5%)	103 (66.9%)
HR (95% CI)	1.22 (1.08, 1.39)		1.05 (.81, 1.35)	
Any deterioration relative to baseline				
No. ever worsened (%)	143 (26.8%)	176 (34.0%)	Equivalent to death	
HR (95% CI)	0.73 (.59, .91)			
Death				
No. died (%)	56 (10.5%)	71 (13.7%)	27 (20.6%)	29 (18.8%)
HR (95% CI)	0.82 (.58, 1.16)		1.09 (.66, 1.83)	

ACTT-1
1051 pacientes
Remdesivir: mayor impacto en pacientes en etapas iniciales

Daño pulmonar establecido: poco beneficio de remdesivir

Fintzi, J., (2022). Deconstructing the Treatment Effect of Remdesivir in the Adaptive Coronavirus Disease 2019 (COVID-19) Treatment Trial-1: Implications for Critical Care Resource Utilization. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 74(12), 2209–2217.

Paxlovid en paciente crítico

Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study

[a,r] Sheng Zhang,[a,r] Ming Li,[b,r] Ke Ma,[c,r] Cunyi Fan,[d,r] Ying Lv,[e,r] Xiangdong Guan,[f,r] Yi Yang,[g,r] Xiaofei Ye,[h] Xingqi Deng,[i]

	Patient No.	Paxlovid plus standard treatment	Standard treatment	OR(95% CI)	adjusted OR (95% CI)
Vaccination					
equal to or more than two doses	66	0/28(0.00%)	1/38(2.63%)	0.44(0.02,11.79)	0.44(0.003,62.67)
none or only one dose	198	5/104(4.81%)	7/94(7.45%)	0.63(0.19,2.05)	0.63(0.11,3.74)
Centers					
enrolled patients less than or equal to 50	123	3/62(4.84%)	4/61(6.56%)	0.73(0.16,3.38)	0.73(0.07,7.39)
enrolled patients more than 50	141	2/70(2.86%)	4/71(5.63%)	0.49(0.09,2.78)	0.49(0.04,6.70)
Gender					
male	142	4/72(5.56%)	4/70(5.71%)	0.97(0.23,4.04)	0.97(0.11,8.34)
female	122	1/60(1.67%)	4/62(6.45%)	0.25(0.03,2.27)	0.25(0.01,7.00)
Age					
≤65 years	84	1/38(2.63%)	2/46(4.35%)	0.60(0.05,6.82)	0.60(0.02,23.55)
>65 years	180	4/94(4.26%)	6/86(6.98%)	0.59(0.16,2.18)	0.59(0.08,4.21)
Charlson scores					
<2	50	1/26(3.85%)	1/24(4.17%)	0.92(0.05,15.58)	0.92(0.01,65.51)
≥2	214	4/106(3.77%)	7/108(6.48%)	0.57(0.16,1.99)	0.57(0.09,3.78)
SOFA scores					
<2	168	0/87(0.00%)	2/81(2.47%)	0.18(0.01,3.91)	0.18(0.002,18.59)
≥2	96	5/45(11.11%)	6/51(11.76%)	0.94(0.27,3.31)	0.94(0.14,6.28)
Charlson+SOFA scores					
<5	132	1/66(1.52%)	2/66(3.03%)	0.49(0.04,5.57)	0.49(0.01,19.07)
≥5	132	4/66(6.06%)	6/66(9.09%)	0.65(0.17,2.40)	0.65(0.09,4.68)
Severity of illness					
mild	132	2/66(3.03%)	2/66(3.03%)	1.00(0.14,7.32)	1.00(0.05,20.11)
moderate	132	3/66(4.55%)	6/66(9.09%)	0.48(0.11,1.99)	0.48(0.06,4.12)

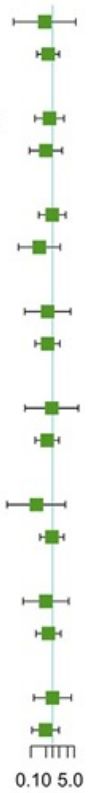


***Fig.* 3: Efficacy of Nirmatrelvir plus Ritonavir (NMV-r) on 28-day mortality from any cause in severe adult patients with COVID-19 infection, according to subgroup.** Shown are data for the primary end point in key subgroups of each group. It showed subgroup analysis of the differences in patients treated with Paxlovid plus standard treatment or only standard treatment who had COVID-19–related death from any cause through day 28, Odds ratios are plotted as squares, the horizontal lines represent 95% confidence intervals.

Shangai, 2023
264 pacientes
Tratamiento estándar
Vs
Tratamiento estándar + paxlovid
Mortalidad global: 5%

SIN diferencias en mortalidad a 28 días en pacientes graves

Liu, J., (2023). Efficacy and safety of Paxlovid in severe adult patients with SARS-Cov-2 infection: a multicenter randomized controlled study. The Lancet regional health. Western Pacific, 33, 100694.

Mensajes claves

- ❖PREVENCIÓN: vacunación contra influenza y covid19
  - ¿Rol protector contra neumonía bacteriana?
  - No olvidar vacunación de *S. pneumoniae*… futuro: vacuna VRS
- ❖Campaña de invierno: estudiar virus ➔ PCR: influenza, SARS-COV2
- ❖Inmunosuprimidos: mayor susceptibilidad para neumonía grave viral
- ❖Tratamiento: individualizar terapia
  - Evidencia de calidad moderada a favor de oseltamivir para Influenza A/B en dosis estándar, pero por mayor tiempo (10 días): estudios randomizados en curso
  - Uso de corticoides benéficos en SARS-COV2

Infecciones Respiratorias Virales en UCI

Dra Francisca Morales J

Infectología – Hospital Barros Luco

Universidad de Santiago