

A composite image featuring a Star Wars battle scene. The top half shows a space battle with various ships like TIE fighters, X-wings, and a Star Destroyer against a backdrop of a planet. The bottom half shows a ground battle with AT-AT walkers and soldiers on a rocky, hilly terrain. The text is overlaid on the center of the image.

# RSV Strikes Back

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“The COVID-19 pandemic has drastically changed the epidemiology of other viral respiratory infections in both children and adults. Worldwide, the autumn and winter RSV epidemics have virtually disappeared....”

Hernández-Rivas, Lucía, Teresa Pedraz, Cristina Calvo, Isabel San Juan, M<sup>a</sup> José Mellado, and Ana Robustillo. Dec 2021. RSV outbreak during COVID-19 pandemic. How has it changed? *Enfermedades infecciosas y microbiología clínica*.

(CNN) — The measures that helped keep us safe from Covid-19 over the past 2½ years – lockdowns, physical distancing, wearing masks, washing hands – also helped limit the spread of other viruses. As people return to school and work and take off their masks, those viruses, including respiratory syncytial virus and flu, are back in full force.

That “immunity gap” from the last few years is probably behind the “unprecedented” early surge in RSV infections this year, scientists say – and it has thrown other seasonal respiratory viruses out of whack around the world.

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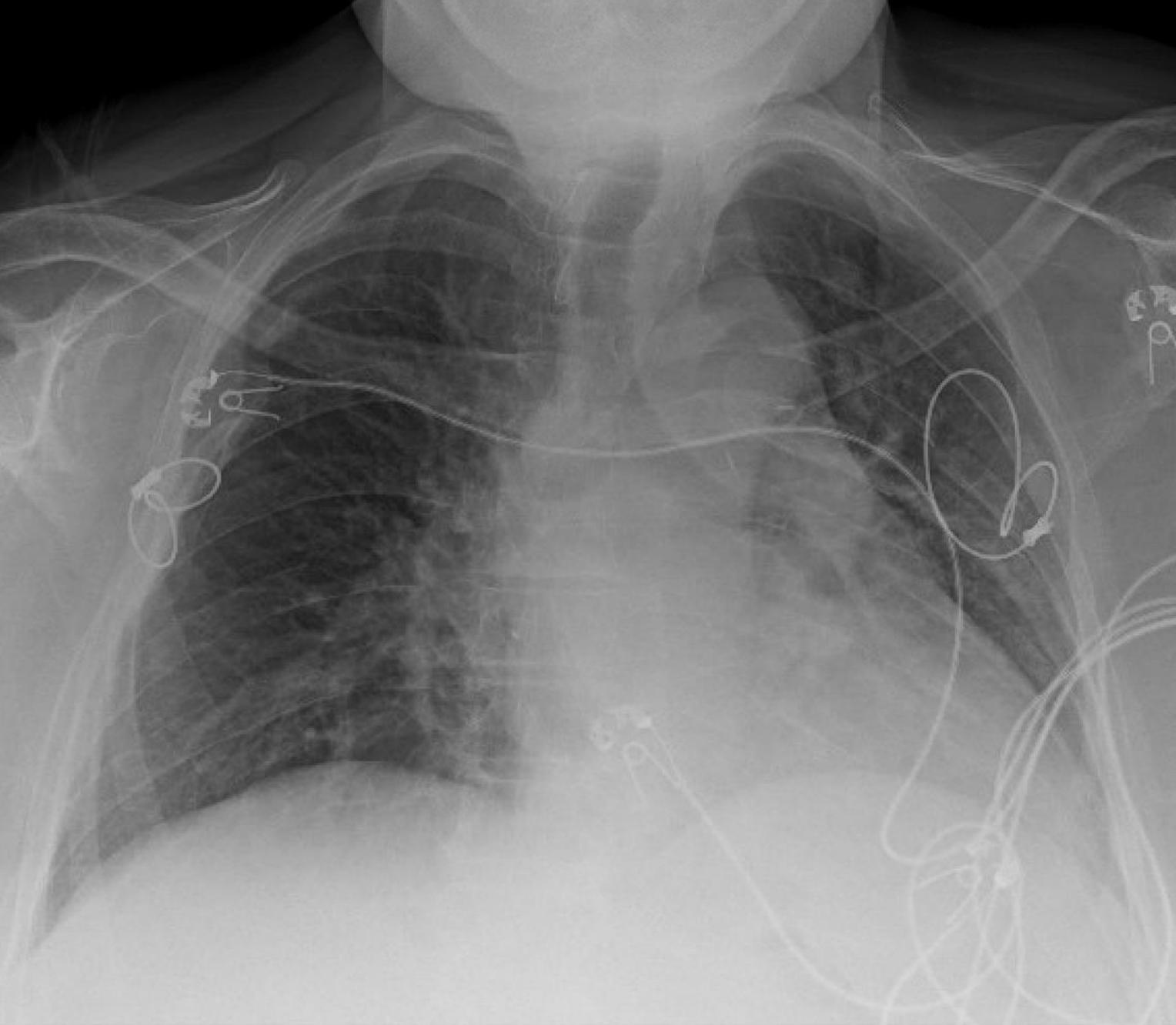
— Temperatures are dropping and the risk of COVID-19 and influenza are up. And for the last few months, patients with a different malady — respiratory syncytial virus, known as RSV — have been overwhelming hospitals. Public health officials warn that come winter there could be a **"tripledeemic."**

# Case Presentation

- ■ yo ■ with PMH of ILD s/p single R lung transplant on ■ (CMV R+) c/b chronic lung allograft dysfunction and s/p single L lung transplant on ■/22, who presented with complaints of severe sore throat x 3 days
- Productive cough with white phlegm and fever
- Outpatient provider prescribed doxycycline and monitor for 72 hours
- Felt worse → ER

# Case Presentation

- Vitals on arrival:
  - Febrile (38.6), HR (113), RR (15), BP (125/59), and O2 92% on room air
- Initial labs
  - WBC 1.63, Hgb 8.9, Hct 27.3, Plt 206
  - Diff: Neutrophils (0.7), lymphocytes (0.6)
  - CMP WNL
  - COVID, Flu - negative
  - **Respiratory panel + RSV**



## Question 1

What additional diagnostics would you ask for (if any)?

If so, how would it influence your management?

# Case Presentation

- Sputum culture – negative
- Blood cultures – negative
- IgG – 595 (normal 700-1600 mg/dl)
- CMV DNA PCR – negative
- CT chest – next slide



## CT chest w/o contrast

- Focal centrilobular and tree-in-bud nodularity with groundglass opacification is noted within the left lower lobe and lingula, appearance is consistent with an active infectious/inflammatory process

## Question 2

Would you start an anti-viral?

- A. PO ribavirin
- B. Inhaled ribavirin
- C. No antiviral

# To treat or not to treat?

- Lung: Increased risk for RSV-related mortality and morbidity compared to other organ transplants
  - Progression URTI --> LRTI
  - Development of bronchiolitis obliterans syndrome/chronic lung allograft dysfunction, drastic changes in forced expiratory volume (FEV1)
- HSCT: reports of up to 80% mortality if untreated; decreased to 6-25% with treatment
- Boeckh et al. 2007: Randomized controlled trial of 14 HSCT patients → aerosolized ribavirin decreased RSV viral load
- Inhaled ribavirin has risk of bronchospasm, staff issues, and \$\$\$; PO/IV has risk of hemolysis, anemia, leukopenia, hyperbilirubinemia, rash

## Question 3

Would you add any adjunctive immunomodulators?

A. IVIG

B. Palivizumab

C. Steroids

D. A and C

E. No additional immunomodulators

F. Other (and what? Please share with us!)

## Question 4

Would your approach change if this was a non-lung SOT? BMT?

Would you recommend antiviral +/- immunomodulator therapy to a non-lung SOT patient with RSV LRTI? What if they were a BMT patient?

# Palivizumab

- Humanized monoclonal antibody targeting the F glycoprotein of RSV to prevent membrane fusion
- No studies have been conducted to evaluate use in SOT/adults as prophylaxis
- Indicated for high-risk infants or children <2 yo who are immunocompromised

## Steroids? IVIG?

- Lee et al. 2011: investigated effects of short-term high dose steroid treatment on viral load and adaptive immunity to RSV in lung transplant patients
  - Did not affect viral load or shedding, and mildly diminished humoral immunity
- Chemaly et al. 2011 & 2014: conducted a review and found that any form of ribavirin-based therapy (alone or in combo with immunomodulators) was effective in preventing URTI progressing to LRTI in HSCT patients
  - Animal models showed benefit of IVIG and RSV-IVIG
  - Lower rate of progression to LRTI; decreased mortality
  - vs. RSV IVIG as prophylaxis in high-risk HSCT patients failed to show efficacy; off market since 2004

# To treat or not to treat?

- No clear consensus on approach to treatment
  - Beaird et al 2016: survey showed wide variety in approaches to management of RSV
- Retrospective and prospective studies with improved outcomes using:
  - IV ribavirin + steroids
  - PO ribavirin + steroids
  - IV/PO ribavirin alone
  - Inhaled ribavirin + steroids + IVIG +/- palivizumab
- Li et al. 2012: retrospective study of 21 lung transplant patients compared inhaled to PO ribavirin and saw no significant differences in outcomes

# To treat or not to treat?

The bottom line:

Ribavirin PO/IV\*/aerosolized with or without immunomodulator therapy can decrease the risk of progression of disease and is recommended for lung transplant recipients

Steroids and IVIG can be considered

Need more studies – limited by sample size, lack of randomized controlled trials, most studies have been in HSCT, lack of standardized regimens/durations, selection bias (treated the most sick)

## Question 5

Is there any utility to using Remdesivir for RSV?

# Remdesivir against COVID-19 and Other Viral Diseases

## Oral remdesivir derivative VV116 is a potent inhibitor of respiratory syncytial virus with efficacy in mouse model

monophosphate prodrug version of GS-47124, as the most promising lead against EBOV. GS-5734, later renamed remdesivir, had a broad antiviral spectrum, including EBOV, Marburg virus, respiratory syncytial virus (RSV), HCV, and several paramyxoviruses (20, 21, 24), *in vitro*. In addition, it demonstrated activity against MERS-CoV

with intact exonuclease proofreading activity.<sup>45</sup> Biochemical data from recombinant respiratory syncytial virus (RSV) RdRp suggested the primary mechanism of action was through delayed chain termination.<sup>73-75</sup> Importantly, remdesivir inhibits viral replication (demonstrated with both Ebola and RSV) in cell-based assays with IC<sub>50</sub> values of approximately 100 nM, whereas human RNA Polymerase (RNAP) II and human mitochondrial RNAP are not inhibited in the presence of compound,<sup>75</sup> providing approximately 500-fold selectivity.

# Case Presentation Wrap-up

- Empiric cefepime → If no evidence of bacterial infection and negative cultures, DC antibiotics in 48hrs
- 500mg/kg IVIG x 1
- Ribavirin 600mg PO Q12hrs x 5 days
- Pulmonology recommended solumedrol 40mg IV x 5 days and Neupogen prn
- Continued prophylaxis: valganciclovir 450mg PO Q12hrs, TMP-SMX DS PO MWF

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