COVID-19: TREATMENT AND GUIDELINES

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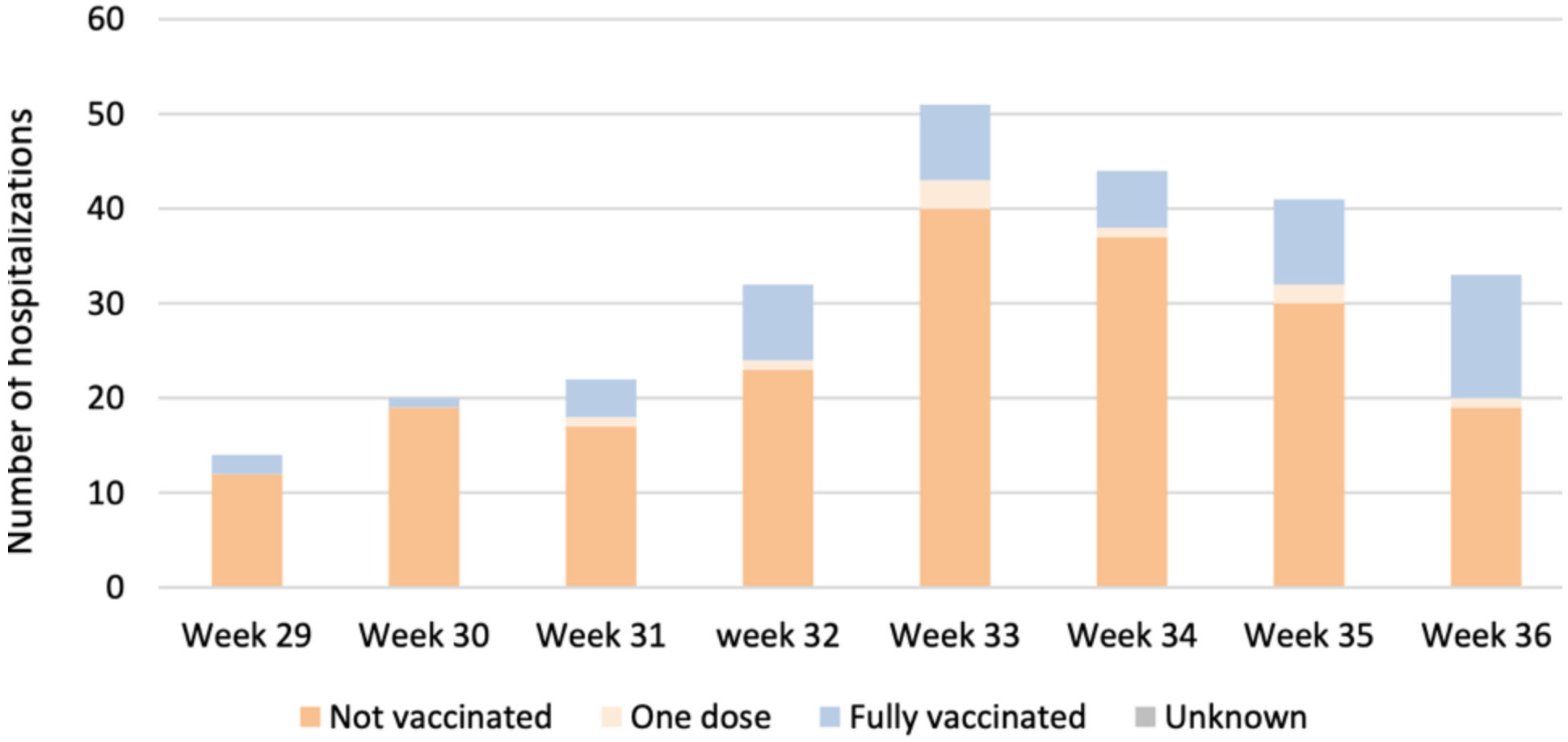
Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE

Nb hospitalisation par semaine – status vaccinal (HUG)



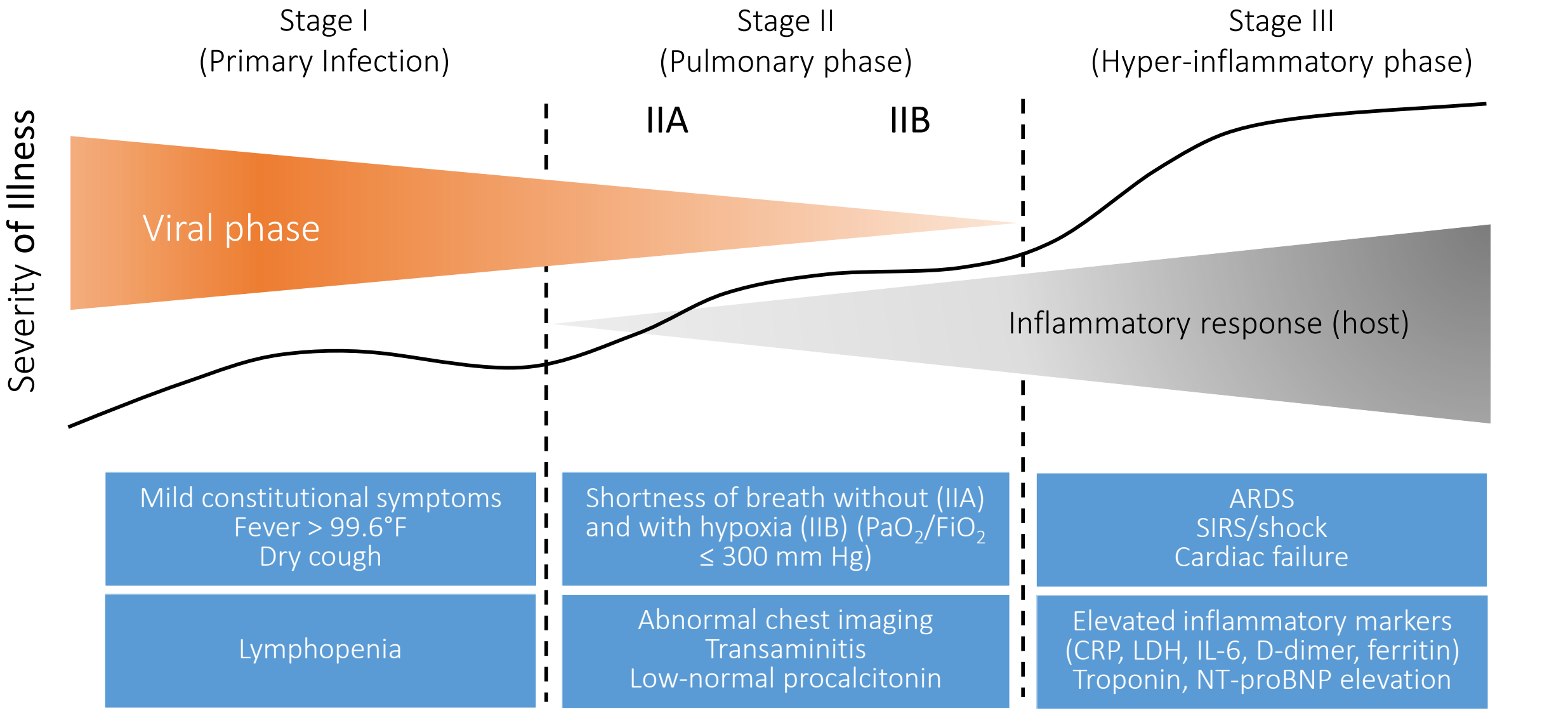
âge médian: 53 ans, hospitalisation rapide après premiers symptômes

LE VARIANT DELTA

- **Delta: Un virus plus virulent**
  - Maladie sévère chez les femmes enceintes
    - **↑ sévérité de la maladie**: 45% (OR= 1.53 (95%CI 1.07-2.17) (Delta vs Alpha) (Vousden, MedRxiv, 2021)
  - Dans la population non vaccinée
    - **↑ hospitalisations:** (adjusted hazard ratio [HR] 2·26 [95% CI 1·32–3·89]) (Twohig, Lancet, 2021)

Histoire naturelle

Siddiqi. J Heart Lung Transplant. 2020



Que recommande la SSI?

Société Suisse d'infectiologie

deux types de traitements en ambulatoire

- ✓ Anticorps monoclonaux
- ✓ Budesonide inhalé

Stéroïdes inhalés

- Efficacité claire, mais établie seulement dans une petite étude , potentiel de dommages faible
- Hospitalisation ou traitement d'urgence réduit de 14 % à 1 % (NNT : 8)
- Utilisation recommandée:
  - En cas de toux sèche, au début du cours
  - Budésonide (par exemple Pulmicort® 400µg) 2x2 coups par jour
  - Délai de soulagement des symptômes (5-7 jours)

AK monoclonale

- Efficacité ("hard endpoints") pas encore montrée, pas d'approbation officielle par Swissmedic
- Des études de phase 2 suggèrent une efficacité avec une utilisation précoce (réduction du taux d'hospitalisation, NST : 28)
- L'indication doit être vérifiée et approuvée par le bureau cantonal de l'indication
- Sans approbation de Swissmedic, utiliser uniquement après une évaluation détaillée des risques avec les patients
- Déploiement réglementé par le canton

https://ssi.guidelines.ch/guideline/3934

Les stéroïdes et les maladies virales…

Ce que nous savions des études antérieures…

Uncontrolled data

- Less patients treated for asthma or COPD are being hospitalized
- Recovery (dexamethasone): patients with no need for oxygen do not seem to benefit from dexamethasone.

Does inhaled budésonide given twice daily during 14 days in ambulant patients improve recovery and reduce hospitalization/death at Day 28?

How useful it is to prescribe budesonide in non hospitalized patients?

Yu et al

Research consortium
PRINCIPLE

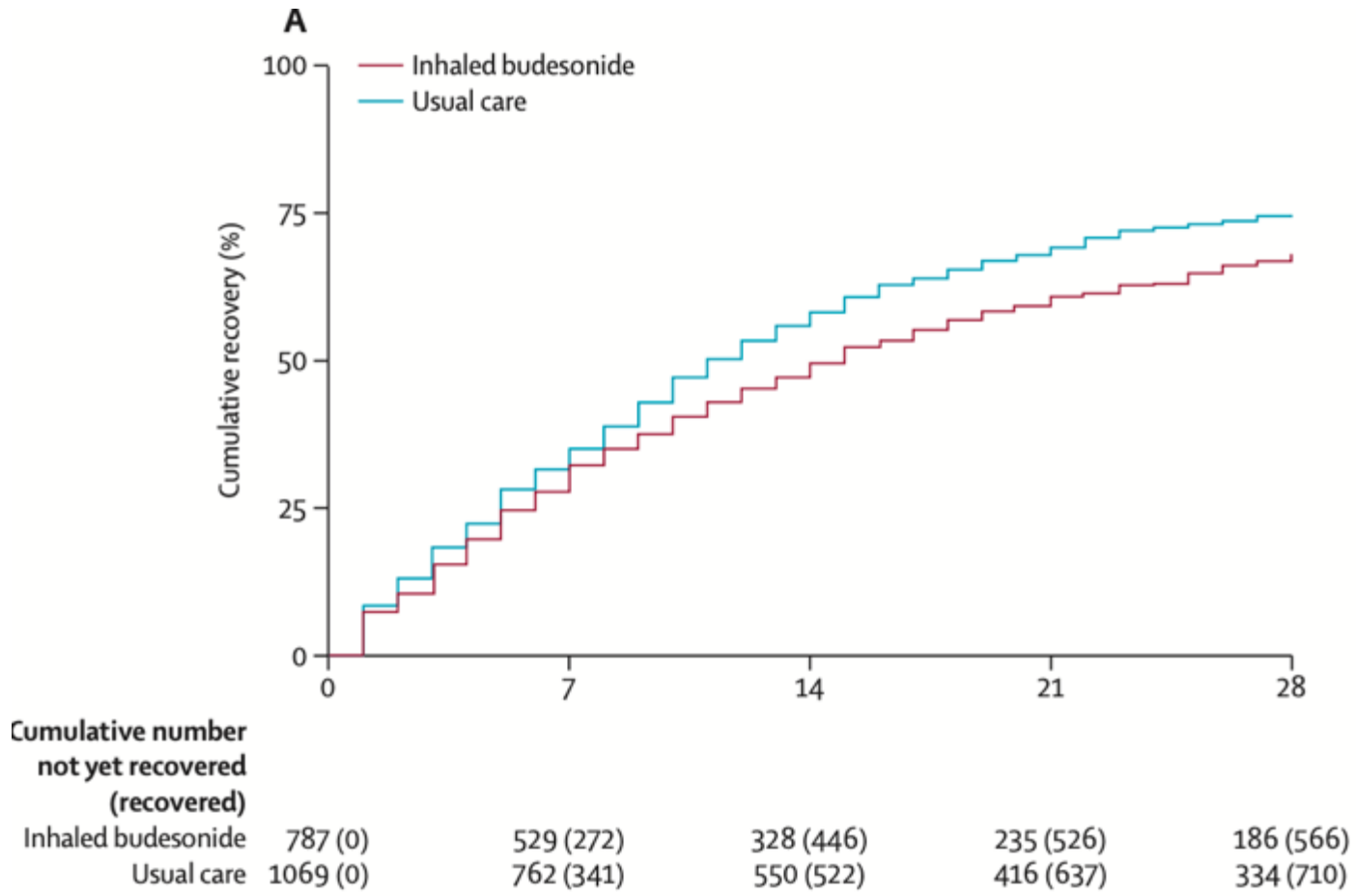
Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

Ly-Mee Yu, Mona Bafadhel*, Jienchi Dorward*, Gail Hayward, Benjamin R Saville, Oghenekome Gbinigie, Oliver Van Hecke, Emma Ogburn, Philip H Evans, Nicholas P B Thomas, Mahendra G Patel, Duncan Richards, Nicholas Berry, Michelle A Detry, Christina Saunders, Mark Fitzgerald, Victoria Harris, Milensu Shanyinde, Simon de Lusignan, Monique I Andersson, Peter J Barnes, Richard E K Russell, Dan V Nicolau Jr, Sanjay Ramakrishnan, F D Richard Hobbs†, Christopher C Butler†, on behalf of the PRINCIPLE Trial Collaborative Group‡*

Main Results

Yu et al

- **>65 years** ou >50 years with comorbidities (maladies cardiaques, **HTA**, asthme ou maladie pulmonaire, diabète, maladie hépatique, AVC ou trouble neurologique, immunosuppression, BMI >35)
- No need for hospitalization
- COVID-19 symptoms (<14 days) + (pos) PCR SARS-CoV-2



Main results (bis)

Yu et al

Consortium étude clinique
PRINCIPLE

	Inhaled budesonide (95% BCI)	Usual care (95% BCI)
Primary analysis—SARS-CoV-2-positive participants		
Number of participants	787	1069
Time to first reported recovery, days*	11·8 (10·0 to 14·1)	14·7 (12·3 to 18·0)
Hospital admission or death at 28 days†	6·8% (4·1 to 10·2)	8·8% (5·5 to 12·7)

Sensitivity analyses: seems to have more benefits in patients aged 65 or more, or with symptoms lasting since more than 7 days.

- Does inhaled budesonide accelerate recovery in ambulant patients with risks factors?

Yes

- Does inhaled budesonide reduce hospitalization or death at Day 28?

Yes, but not very convincing data

Budesonide vs Fluvoxamine vs REGN-COV2 in outpatients (pre-print)

REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients

David M. Weinreich, M.D.[¶,1], Sumathi Sivapalasingam, M.D.[1], Thomas Norton, M.D.[1], Shazia Ali, Pharm.D.[1], Haitao Gao, Ph.D.[1], Rafia Bhore, Ph.D.[1], Jing Xiao, Ph.D.[1], Andrea T. Hooper, Ph.D.[1], Jennifer D. Hamilton, Ph.D.[1], Bret J. Musser, Ph.D.[1], Diana Rofail, Ph.D.[1], Mohamed Hussein, Ph.D.[1], Joseph Im, B.S.[1], Dominique Y. Atmodjo, B.A.[1], Christina Perry, M.B.A.[1], Cynthia Pan, B.Pharm.[1], Adnan Mahmood, M.D.[1], Romana Hosain, M.D., M.P.H.[1], John D. Davis, Ph.D.[1], Kenneth C. Turner, Ph.D.[1], Alina Baum, Ph.D.[1], Christos A. Kyratsous, Ph.D.[1], Yunji Kim, Pharm.D.[1], Amanda Cook, B.S., Dip.Reg.Aff.[1], Wendy Kampman, M.D.[1], Lilia Roque-Guerrero, M.D.[2], Gerard Acloque, M.D.[3], Hessam Aazami, M.D.[4], Kevin Cannon, M.D.[5], J. Abraham Simón-Campos, M.D., M.S.[6], Joseph A. Bocchini, M.D.[7], Bari Kowal, M.S.[1], Thomas DiCioccio, Ph.D.[1], Yuhwen Soo, Ph.D.[1], Neil Stahl, Ph.D.[1], Leah Lipsich, Ph.D.[1], Ned Braunstein, M.D.[1], Gary Herman, M.D.[1], and George D. Yancopoulos, M.D., Ph.D.[1], for the Trial Investigators

EFFECT OF EARLY TREATMENT WITH FLUVOXAMINE ON RISK OF EMERGENCY CARE AND HOSPITALIZATION AMONG PATIENTS WITH COVID-19: THE TOGETHER RANDOMIZED PLATFORM CLINICAL TRIAL

Authors: Gilmar Reis, MD[1,2]; Eduardo Augusto dos Santos Moreira Silva, MD[1,2]; Daniela Carla Medeiros Silva, MD[1,2]; Professor Lehana Thabane, PhD[3]; Aline Cruz Milagres, RN[4,5]; Thiago Santiago Ferreira, MD[1]; Castilho Vitor Quirino dos Santos[1,2]; Adhemar Dias de Figueiredo Neto, MD[6]; Eduardo Diniz Callegari, MD[7]; Leonardo Cançado Monteiro Savassi, MD[2]; Vitoria Helena de Souza Campos,[1,2] Maria Izabel Campos Simplicio, BScPharm[1]; Luciene Barra Ribeiro, RN[1]; Rosemary Oliveira[1]; Ofir Harari, PhD[4]; Jamie I Forrest, MPH[4]; Hinda Ruton, MSc[4]; Sheila Sprague, PhD[3]; Paula McKay, MSc[3]; Alla V Glushchenko, MD,[3] PhD, Craig R. Rayner, PharmD, FRCP *Edin*[10,11]; Professor Eric J. Lenze, MD;[12] Angela M. Reiersen, MD[12]; Professor Gordon H. Guyatt, MD[3]; Professor Edward J. Mills, PhD, FRCP[3]; for the TOGETHER Investigators*

JAMA Network

QUESTION Does fluvoxamine, a selective serotonin reuptake inhibitor and σ-1 receptor agonist, prevent clinical deterioration in outpatients with acute coronavirus disease 2019 (COVID-19)?

CONCLUSION In this preliminary trial, outpatients with symptomatic COVID-19 treated with fluvoxamine, vs placebo, had a lower likelihood of clinical deterioration over 15 days; however, determination of clinical efficacy requires larger trials with more definitive outcome measures.

POPULATION

109 Women
43 Men

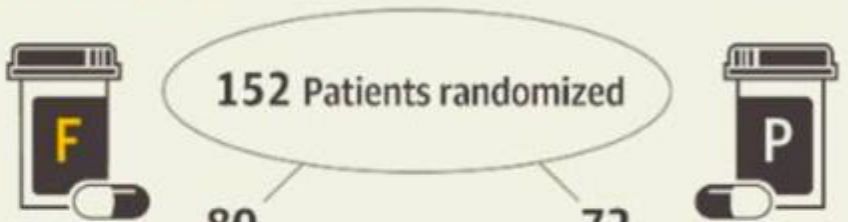
Adults with symptomatic, confirmed SARS-CoV-2 infection and O_2 ≥92%

Mean age: **46** years

LOCATIONS

Remote contactless trial in St Louis metropolitan area (Missouri and Illinois)

INTERVENTION



80
Fluvoxamine
50 mg, day 1
100 mg, 2 times daily for 2 days
100 mg, 3 times daily through day 15

72
Placebo
Equivalent dosing

(Study materials left at quarantined patients' homes)

PRIMARY OUTCOME

Clinical deterioration within 15 days: shortness of breath or pneumonia and O_2 <92% or supplemental oxygen

FINDINGS

© AMA

Patients with clinical detorioration within 15 days

Fluvoxamine
0 of 80 patients

Placebo
6 of 72 patients

The between-group difference was significant:

8.7% (95% CI, 1.8% to 16.4%); *P* = .009

However, small sample size and short follow-up limit determination of efficacy

Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. Published online November 12, 2020. doi:10.1001/jama.2020.22760

	Inhaled budesonide **800 ug 2x/j pendant 14 j**	**Fluvoxamine** **100 mg 2x/j pendant 10 j**	**REGN-COV2** **1.2 mg ou 2.4 mg iv (une seule prise)**
Population	- Patients SARS-CoV-2 + - Non hospitalisés - Haut risque de développer un COVID-19 sévère: • >65 ans • >50 ans avec facteur de risque: maladies cardiaques, HTA, asthme ou maladie pulmonaire, diabète, maladie hépatique, AVC ou trouble neurologique, immunosuppression, BMI >35 2530 patients (multi-arm) – sponsor académique UK	- Patients SARS-CoV-2 + - Non hospitalisés - Haut risque de développer un COVID-19 sévère: • Diabète, HTA, maladie cardiaque, asthme ou maladie pulmonaire, tabac, BMI >30, patient transplanté, IRC stade IV, immunosuppression, cancer dans les 6 derniers mois, > 50 ans; et non vacciné 3228 patients (multi-arm) (sponsor acadéimique, CA)	- Patients SARS-CoV-2 + - Non hospitalisés - Haut risque de développer un COVID-19 sévère: • >50 ans, obésité, maladie cardiaque, maladie chronique des poumons, maladie métabolique, IRC, maladie hépatique, immunosupprimé 4057 patients (sponsor industriel, Roche, Regeneron)
Outcome primaire	- Temps avant rétablissement (co-primary) - Hospitalisation ou décès	- Observation dans un service d'urgence >6h ou hospitalisation dans les 28 jours	- Proportion d'hospitalisations ou décès dans les 28 jours
Résultats Principaux	- Rétablissement: **11.8 j (budésonide) vs 14.7 j** (HR 1.21 (95% BCI 1.08 to 1.36)) - Hospitalisations et décès: **6.8% (budésonide) vs 8.8%** (OR 0.75 (95% BCI 0.55 to 1.03))	Risque d'hospitalisation et surveillance >6h dans un service d'urgence : - **77/739 vs 108/733**; **RR 0.71**, (95BIC 0.53-0.93) avec une probabilité du supériorité à 99.4%	- 71.3% réduction des hospitalisations [1.3% vs 4.6%; p<0.0001]
Conclusions	Diminution de la durée des symptômes et réduction non significative des hospitalisations et décès chez les patients à risque	Réduction des visites aux urgences>6h et hospitalisations (?) chez les patients à risque	Réduction des hospitalisations et des décès (?), avec une résolution rapide des symptômes et diminution des charges virales (phase 2)

Les enjeux des traitements précoces

La stratégie test and treat

Vaccines are preventive

- **Durée de la protection? Impact des variants? Populations les plus fragiles?**

Traitements ambulatoires COVID-19

- Peu de molécules avec un effet convaincant
- Le cahier des charges des molécules à utiliser en ambulatoire est exigent
- Colchicine, budesonide, fluvoxamine, fluoxetine, protuxamide, nitazoxanide, ivermectine*, hydroxychloroquine, etc.
- Il faut des essais de très large ampleur, car le nb d'événement est très faible (e.g. COLCORONA 104/2235)
- Pas encore d'antiviral commercialisé (DAA)

- Marion et al, Annals of Internal Medicine, May 25th, 2021; *Ramakrishnan et al* Lancet Resp Med 9 April, 2021; C Perez-Casas, UNITAID, * TOGETHER trial, COLCORONA trial, Tardif et al, Lancet Respir Med May 26th

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COLCORONA – THE LARGEST COLCHICINE TRIAL SO FAR (BUT NOT THE LAST)

Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial

*Jean-Claude Tardif, Nadia Bouabdallaoui, Philippe L L'Allier, Daniel Gaudet, Binita Shah, Michael H Pillinger, Jose Lopez-Sendon, Protasio da Luz, Lucie Verret, Sylvia Audet, Jocelyn Dupuis, André Denault, Martin Pelletier, Philippe A Tessier, Sarah Samson, Denis Fortin, Jean-Daniel Tardif, David Busseuil, Elisabeth Goulet, Chantal Lacoste, Anick Dubois, Avni Y Joshi, David D Waters, Priscilla Hsue, Norman E Lepor, Frédéric Lesage, Nicolas Sainturet, Eve Roy-Clavel, Zohar Bassevitch, Andreas Orfanos, Gabriela Stamatescu, Jean C Grégoire, Lambert Busque, Christian Lavallée, Pierre-Olivier Hétu, Jean-Sébastien Paquette, Spyridon G Deftereos, Sylvie Levesque, Marième Cossette, Anna Nozza, Malorie Chabot-Blanchet, Marie-Pierre Dubé, Marie-Claude Guertin, Guy Boivin, for the COLCORONA Investigators**

- ✓ 104/2235 (colchicine)
- ✓ 131/2253 (placebo)

We performed a randomized, double-blind trial involving non-hospitalized patients with COVID-19 diagnosed by polymerase chain reaction (PCR) testing or clinical criteria. The patients were randomly assigned to receive colchicine (0.5 mg twice daily for 3 days and once daily thereafter) or placebo for 30 days. The primary efficacy endpoint was the composite of death or hospitalization for COVID-19.

Can you talk a little more on ivermectine?

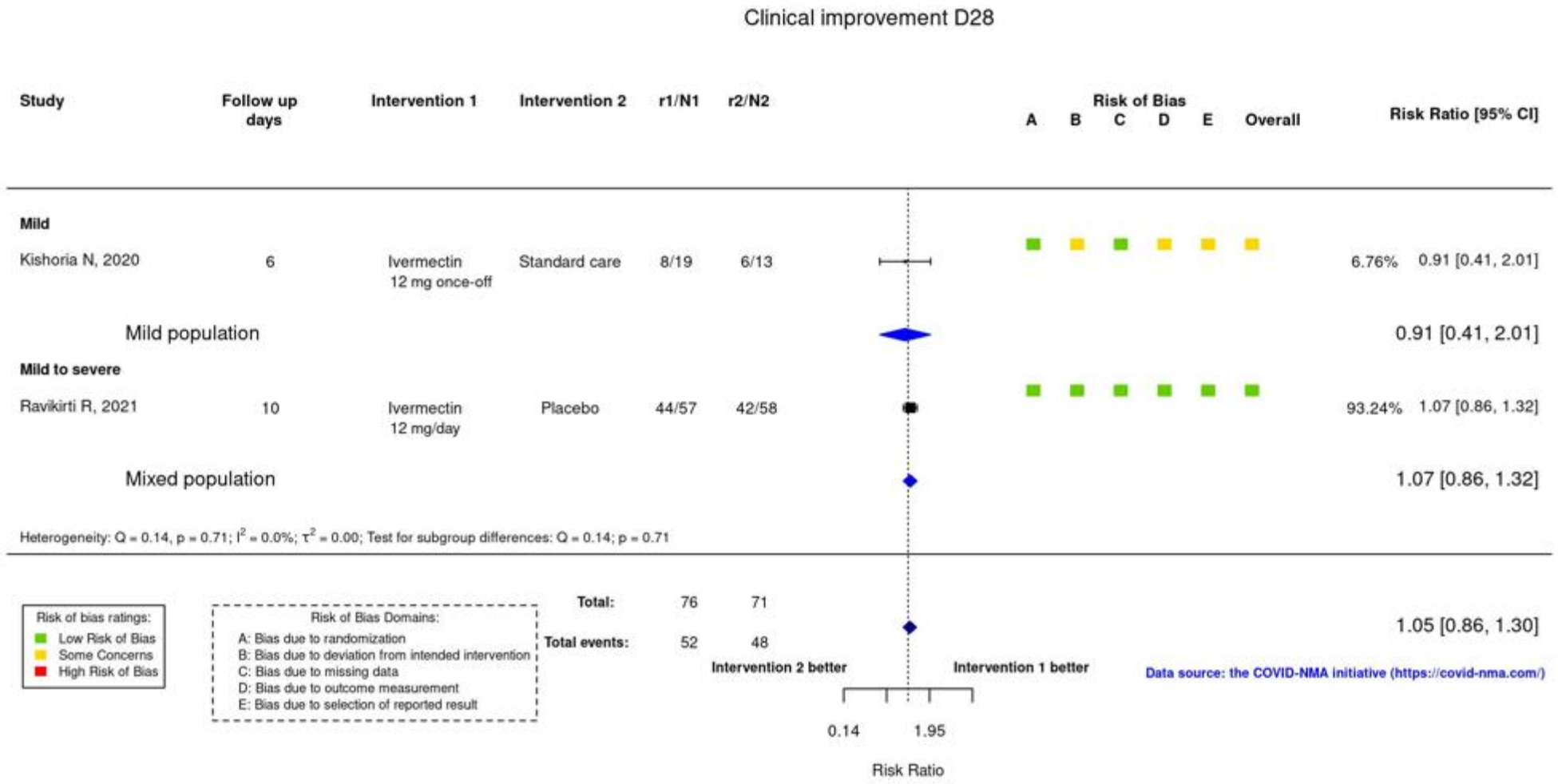
IVERMECTINE

A new hydroxychloroquine?

HOW TO INTERPRET THE MANY CLINICAL DATA AVAILABLE?

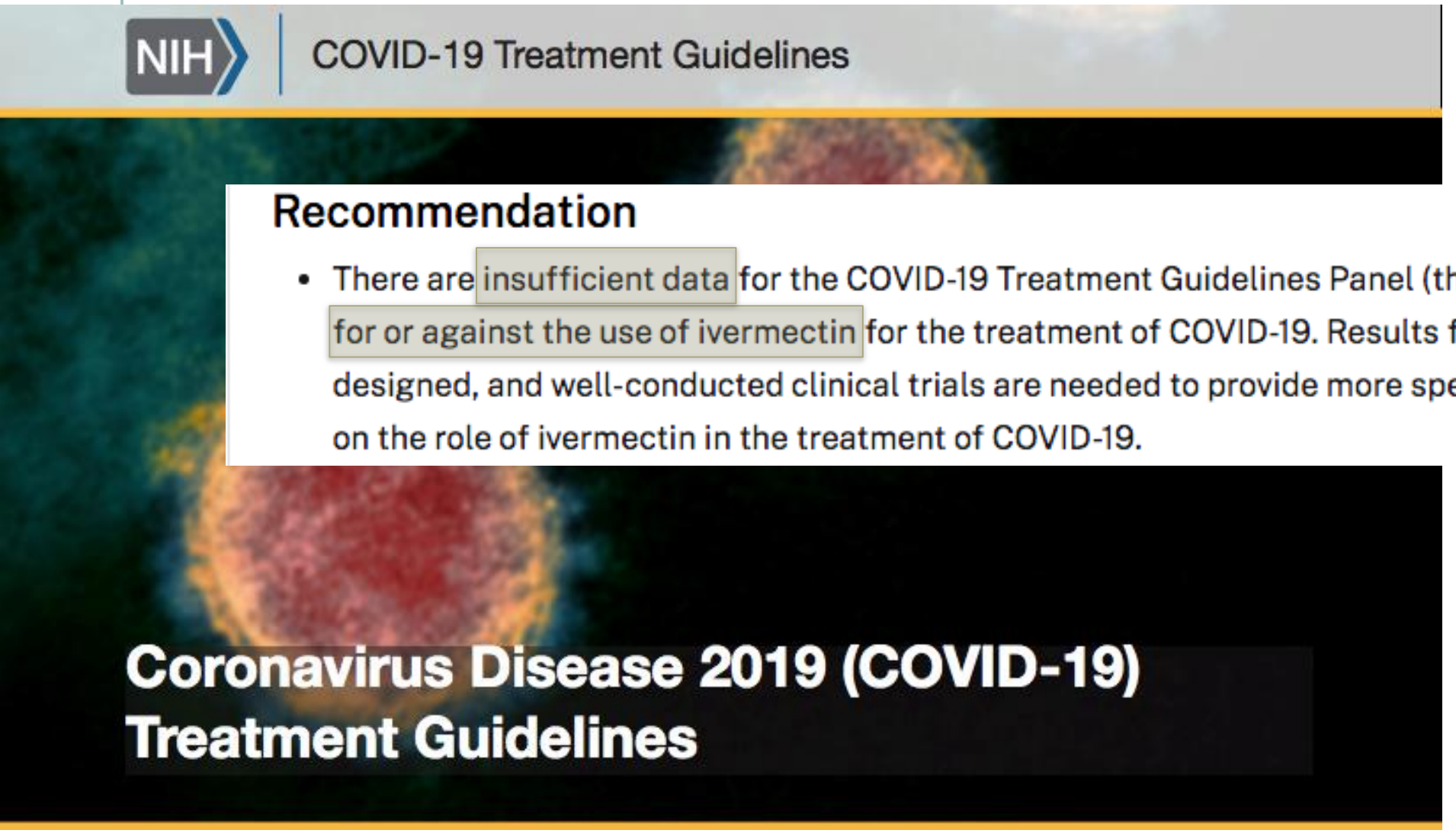
- Various study design (OBS/RCT open label, v/s placebo, SOC…)
- Small sample size
- COVID-19 disease severity often not even described
- Various doses and therapeutic strategies
- Various co-medications (HCQ, AZIT, DOXY, CS)
- SOC not described – no placebo
- Outcomes : composites, or multiples, or sometimes not even described

LIVING META ANALYSIS - COCHRANE



https://covid-nma.com/metacovid/

NIH GUIDELINES



Last Update February 11, 2021

What do you think about colchicine?

COLCHICINE

The new life of an old compound?

A FEW MESSAGES

- Extraordinary dynamism in research
- Innovative design of clinical trials (SOLIDARITY, RECOVERY, ANTICOV)
- Access and at-risk populations are key issues - as for AIDS, but with an obligation of means and results to reach our objectives quickly.
- The success of vaccination has not diminished the need to seek early therapeutic options, and in hospitalized patients.

Thank you !