USZ Universitäts Spital Zürich

# COVID-19 Quo vadis 2021?

## Therapie von COVID-19 in der hausärztlichen Praxis

**Dr. med. Johannes Nemeth; johannes.nemeth@usz.ch**

**PD Dr. med. Dominique Braun; dominique.braun@usz.ch**

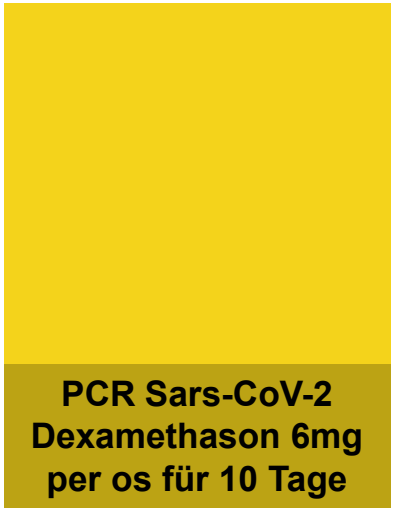
*…it's like standing out at the falls, trying to fill a glass of water. It's overwhelming and it's impossible to keep up…*

Paul E Sax

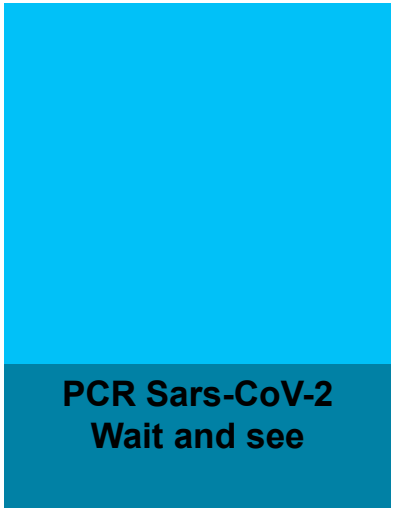
# Fallvignette: 75-jähriger männlicher Patient in der Praxis

- Kopfschmerzen, Gliederschmerzen seit 3 Tagen, seit heute zusätzlich Anosmie und Gefühl von Fieber
- Vorerkrankungen:
  - Diabetes mellitus Typ 2, unter Metformin gut eingestellt
  - Arterielle Hypertonie behandelt mit Sartan
  - Dyslipidämie behandelt mit Statin
  - COPD behandelt mit Symbicort
  - Adipositas
- Temperatur 38.3°C, BD 123/72mmHg, P 96/min, Sa02 bei Raumluft 96%, AF 14/min
- Spastische Atemgeräusche über allen Lungenfeldern

# Nächster Schritt?







## Die zwei Musketiere

I. **Dexamethason**

II. **Remdesivir**

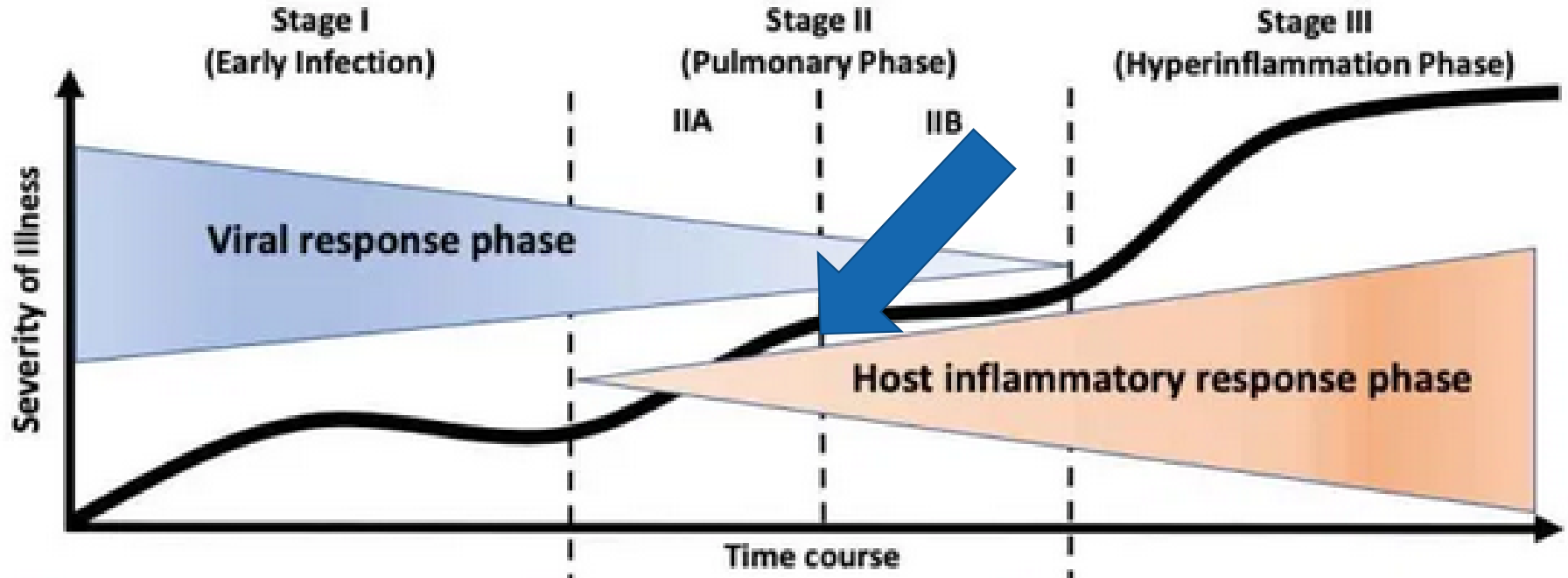
III. Convalescent plasma therapy **(CPT)**

IV. Tocilizumab (

V. L ®)

VI. Hydroxychloroquine

**Keine wirksame Therapie für COVID-19 im ambulanten setting zugelassen (noch….)**




| | | | |
|---|---|---|---|
| *Clinical Symptoms* | Mild constitutional symptoms<br>Fever >99.6°F<br>Dry Cough, diarrhea, headache | Shortness of Breath<br>Hypoxia (PaO2/FiO2≤300mmHg) | ARDS<br>SIRS/Shock<br>Cardiac Failure |
| *Clinical Signs* | Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild) | Abnormal chest imaging<br>Transaminitis<br>Low-normal procalcitonin | Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)<br>Troponin, NT-proBNP elevation |

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# Fallvignette: 75-jähriger männlicher Patient in der Praxis

- Tag 8 nach Symptombeginn:
  - Dyspnoe bei Mobilisation
  - Leichter Druck auf der Brust
  - Persistierend Gefühl von Fieber
- Temperatur 38.6°C, BD 115/65mmHg, P 104/min, Sa02 bei Raumluft 91%, AF 23/min
- Spastische Atemgeräusche über allen Lungenfeldern und abgeschwächtes Atemgeräusch über allen Lungenfeldern
- Röntgen-Thorax: angedeutete bilaterale Transparenzverminderungen

# Nächster Schritt?



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New York Times, Oktober 2019

# Remdesivir

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

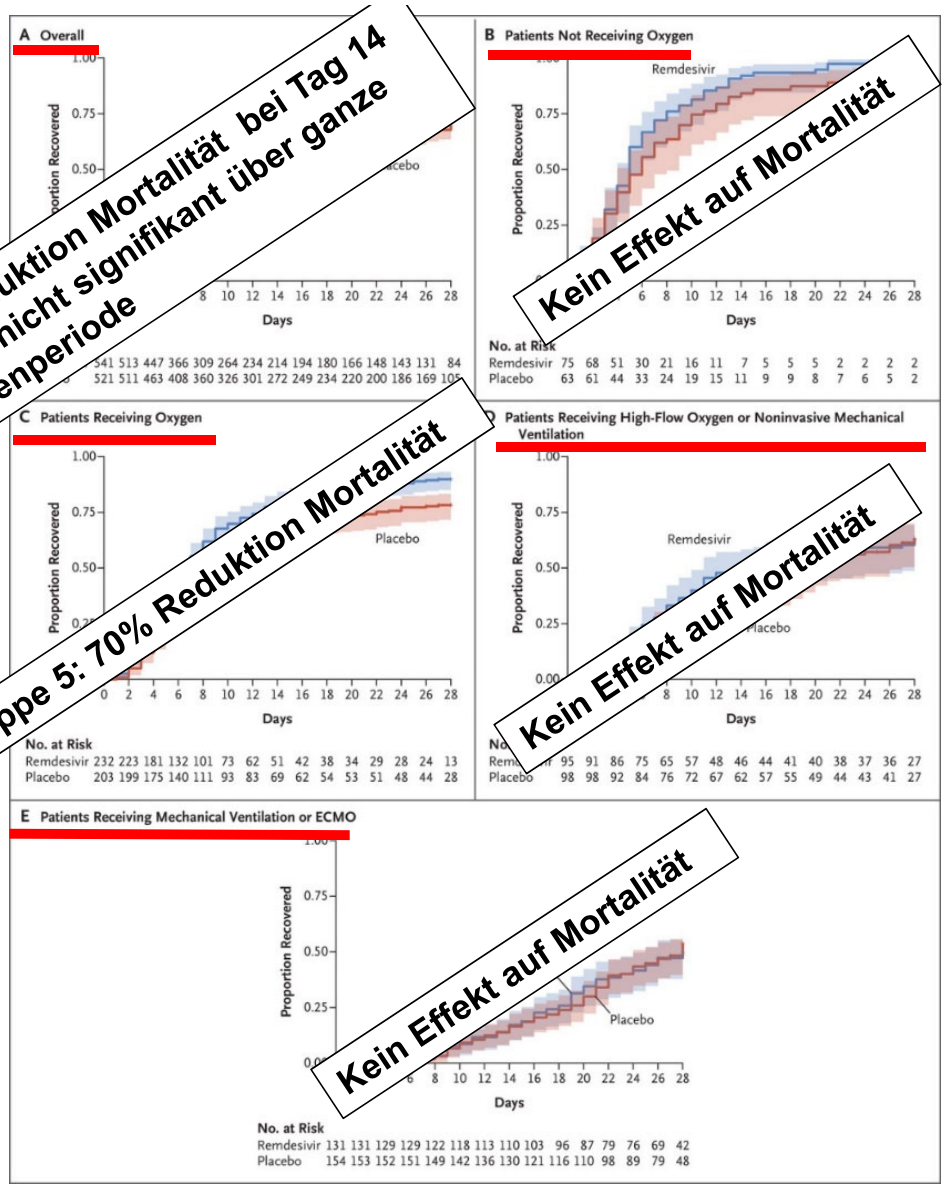
## Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

# Remdesivir


- Ursprünglich für Behandlung von Ebola entwickelt
- Langer Herstellungsprozess, hoch explosiv
- Nur intravenöse Verabreichungsform
- Vorerst befristete Zulassung für 2 Jahre durch Swissmedic
- Dosierung: 200mg als Ladedosis Tag 1, danach 100mg Tag 2-5
- Kosten: 2’207 CHF für 5 Tage Therapie

# Remdesivir




JH Beigel et al. N Engl J Med 2020.

**Table 2.** Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

| | Overall | | Ordinal Score at Baseline | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 4 | | 5 | | 6 | | | |
| | Remdesivir (N=541) | Placebo (N=521) | Remdesivir (N=75) | Placebo (N=63) | Remdesivir (N=232) | Placebo (N=203) | Remdesivir (N=95) | | | acebo 154) |
| **Recovery** | | | | | | | | | | |
| No. of recoveries | 399 | 352 | 73 | 58 | 206 | 156 | | | | |
| Median time to recovery (95% CI) — days | 10 (9–11) | 15 (13–18) | 5 (4–6) | 6 (4–7) | 7 (6–8) | 9 | | | | |
| Rate ratio (95% CI)† | 1.29 (1.12–1.49 [P<0.001]) | | 1.29 (0.91–1.83) | | | | | | | 0–1.36) |
| **Mortality through day 14‡** | | | | | | | | | | |
| Hazard ratio for data through day 15 (95% CI) | 0.55 (0.36–0.83) | | 0.42 (0.04–4.67) | | | | | | 0.76 (0.39–1.50) | |
| No. of deaths by day 15 | 35 | 61 | 1 | | | | | 17 | 14 | 21 |
| Kaplan–Meier estimate of mortality by day 15 — % (95% CI) | 6.7 (4.8–9.2) | 11.9 (9.4–15.0) | | | | | –23.2) | 17.3 (11.2–26.4) | 10.9 (6.6–17.6) | 13.8 (9.2–20.4) |
| **Mortality over entire study period‡** | | | | | | | | | | |
| Hazard ratio (95% CI) | 0.73 (0 | | | | | 4) | 1.02 (0.54–1.91) | | 1.13 (0.67–1.89) | |
| No. of deaths by day 29 | | | | | | 25 | 19 | 20 | 28 | 29 |
| Kaplan–Meier estimate of mortality by day 29 — % (95% CI) | | | | | 4.0 (2.1–7.5) | 12.7 (8.8–18.3) | 21.2 (14.0–31.2) | 20.4 (13.7–29.8) | 21.9 (15.7–30.1) | 19.3 (13.8–26.5) |
| **Ordinal score at day 15 ( no. (%)§** | | | | | | | | | | |
| 1 | | | 7 | 28 (44.4) | 90 (38.8) | 62 (30.5) | 18 (18.9) | 14 (14.3) | 11 (8.4) | 11 (7.1) |
| 2 | | | (26.7) | 15 (23.8) | 70 (30.2) | 58 (28.6) | 22 (23.2) | 19 (19.4) | 5 (3.8) | 10 (6.5) |
| 3 | | | 8 (10.7) | 4 (6.3) | 6 (2.6) | 4 (2.0) | 0 | 0 | 0 | 0 |
| 4 | | | (6.3) | 3 (4.0) | 7 (11.1) | 17 (7.3) | 13 (6.4) | 12 (12.6) | 4 (4.1) | 6 (4.6) | 9 (5.8) |
| 5 | | 60 (11.5) | 3 (4.0) | 5 (7.9) | 25 (10.8) | 18 (8.9) | 2 (2.1) | 14 (14.3) | 28 (21.4) | 23 (14.9) |
| 6 | (5.2) | 24 (4.6) | 1 (1.3) | 0 | 5 (2.2) | 7 (3.4) | 12 (12.6) | 11 (11.2) | 10 (7.6) | 6 (3.9) |
| 7 | 95 (17.6) | 121 (23.2) | 1 (1.3) | 3 (4.8) | 13 (5.6) | 21 (10.3) | 16 (16.8) | 20 (20.4) | 57 (43.5) | 74 (48.1) |
| 8 | 34 (6.3) | 58 (11.1) | 1 (1.3) | 1 (1.6) | 6 (2.6) | 20 (9.9) | 13 (13.7) | 16 (16.3) | 14 (10.7) | 21 (13.6) |
| Odds ratio (95% CI) | 1.5 (1.2–1.9) | | 1.5 (0.8–2.7) | | 1.6 (1.2–2.3) | | 1.4 (0.9–2.3) | | 1.2 (0.8–1.9) | |

**Patienten im Schnitt 5 Tage früher gesund**
**10 Tage versus 15 Tage**
**70 Prozent Reduktion Mortalität in Gruppe 5**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

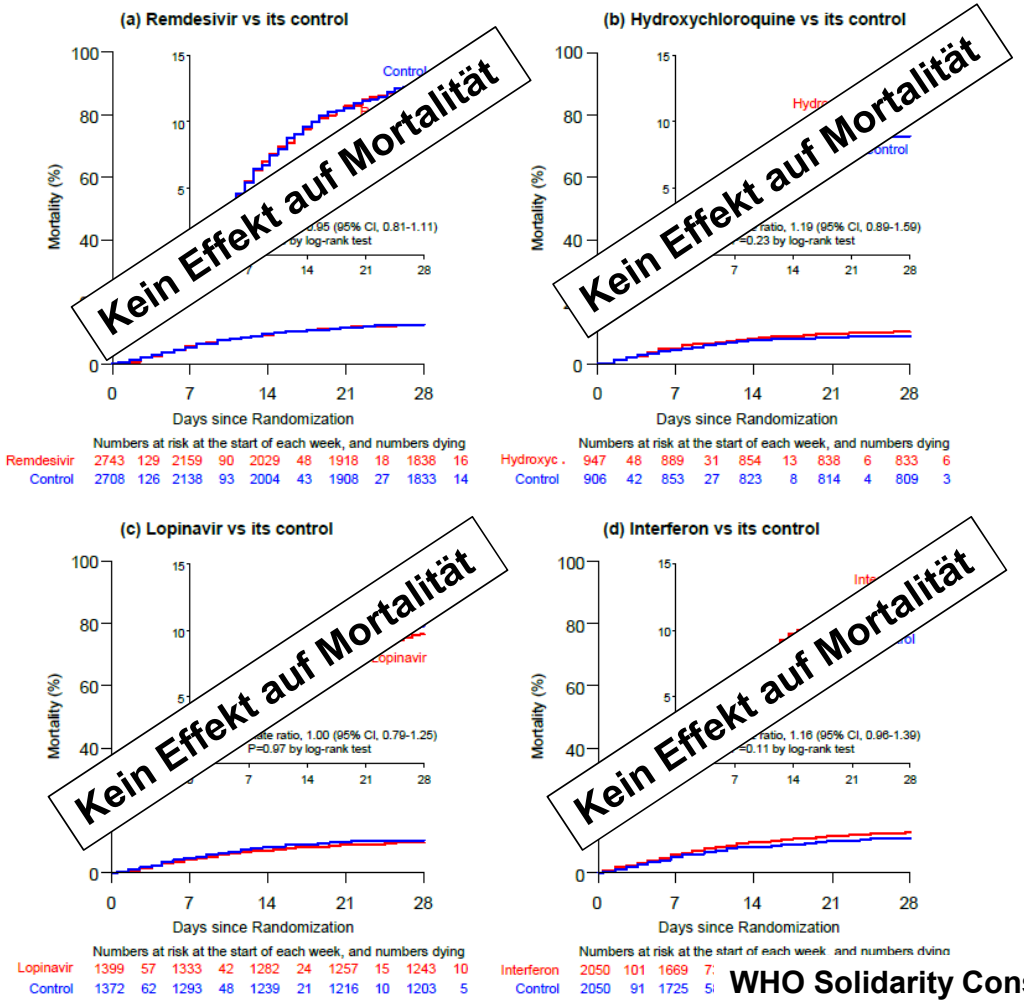
# Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

**CONCLUSIONS**

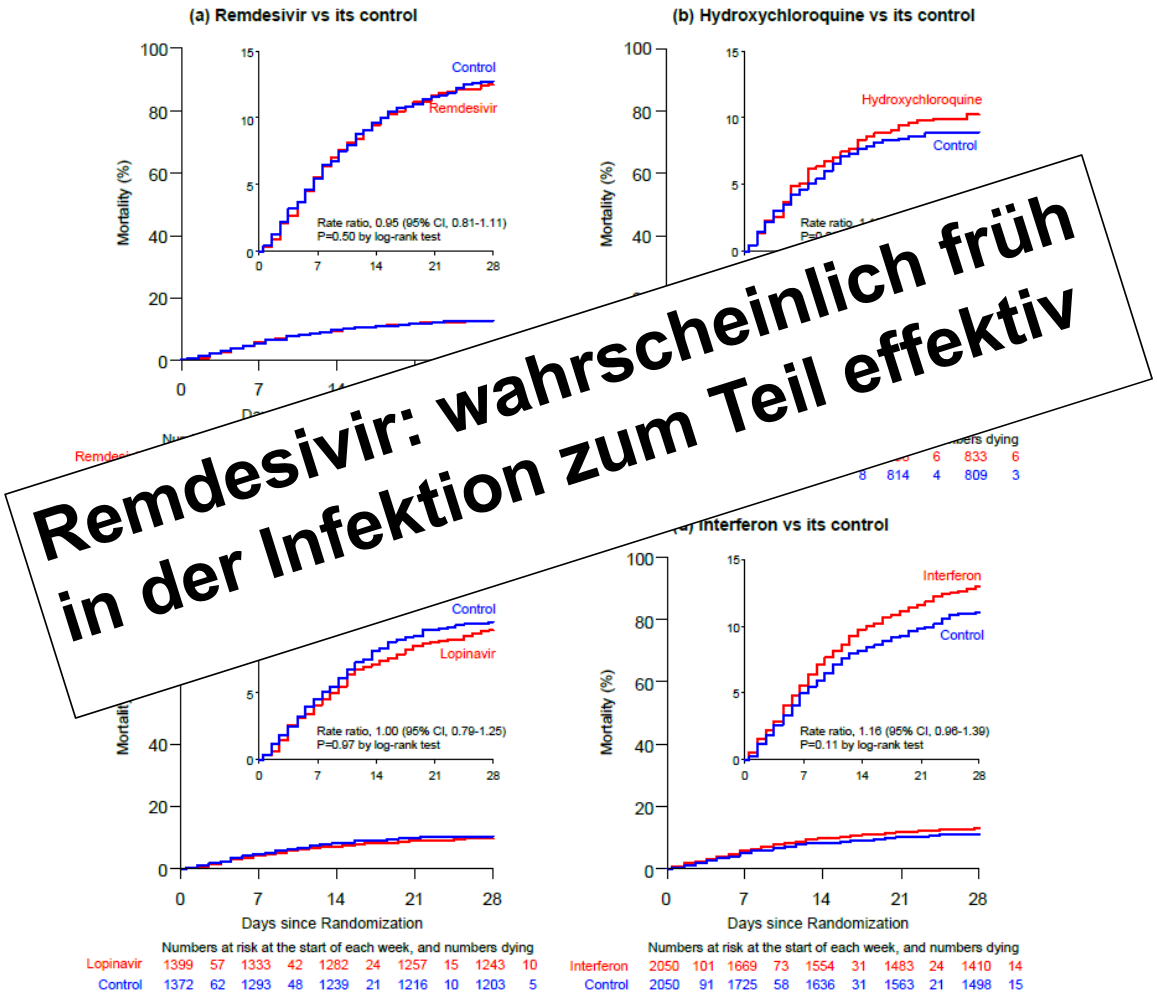
These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. (Funded by the World Health Organization; ISRCTN Registry number, ISRCTN83971151; ClinicalTrials.gov number, NCT04315948.)

# Remdesivir: Solidarity WHO trial

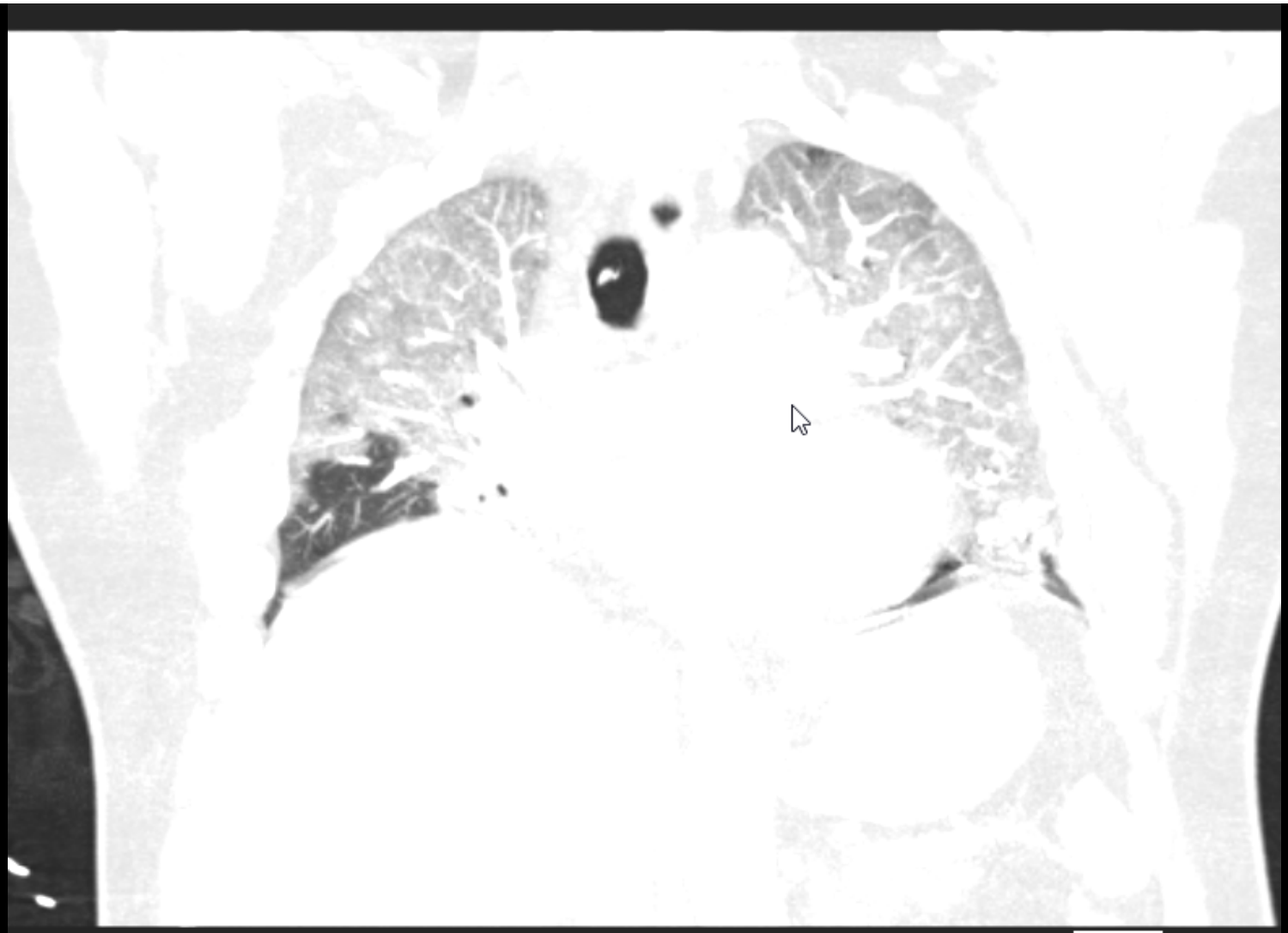



WHO Solidarity Consortium, October 2020, preprint

# Remdesivir: Solidarity WHO Studie




**Remdesivir: wahrscheinlich früh in der Infektion zum Teil effektiv**



# Dexamethasone

ORIGINAL ARTICLE

## Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

ABSTRACT

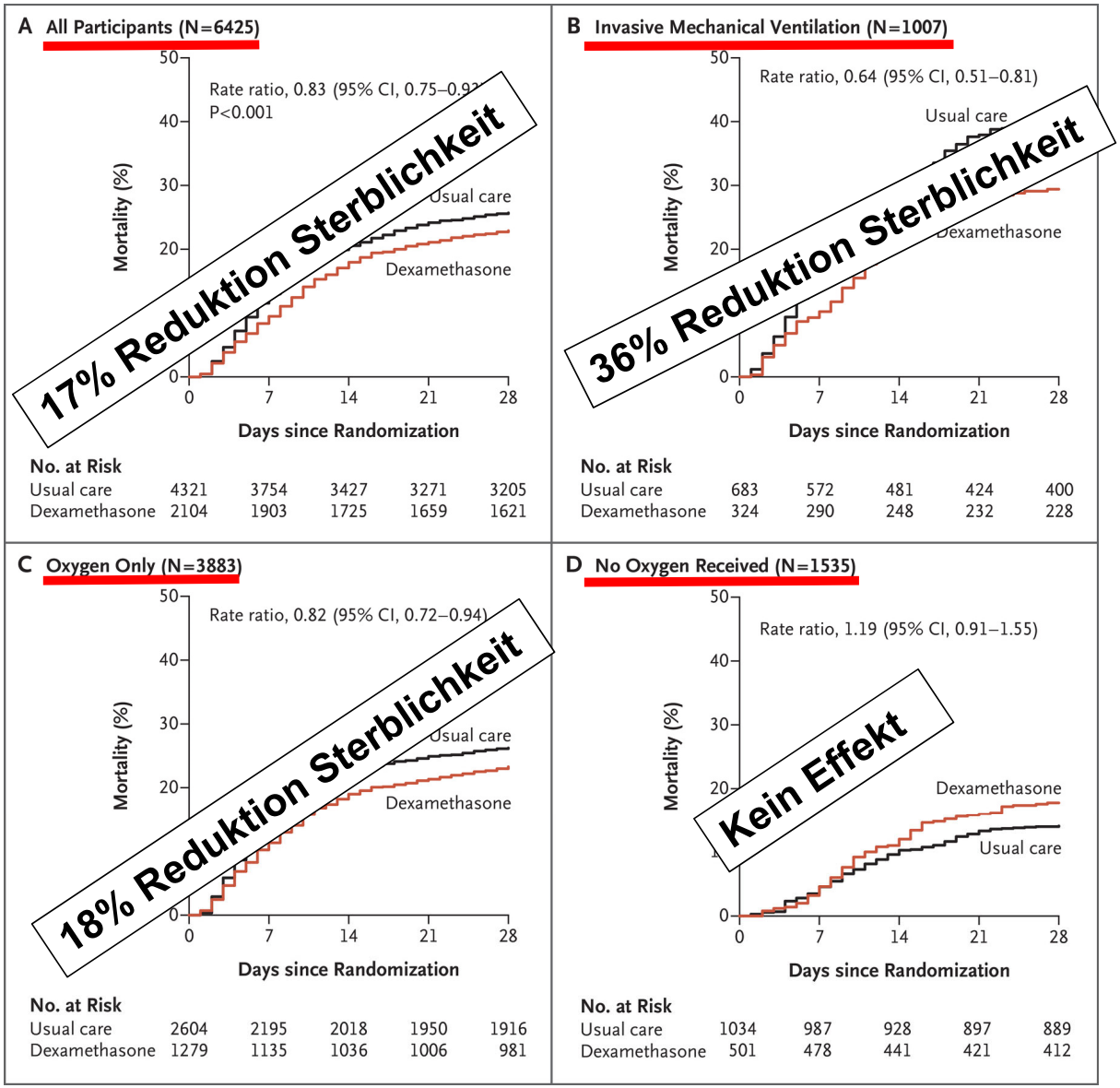
**BACKGROUND**

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

The members of the writing committee (Peter Horby, F.R.C.P., Wei Shen Lim, F.R.C.P., Jonathan R. Emberson, Ph.D., Marion Mafham, M.D., Jennifer L. Bell,

# Dexamethason


- Dosierung: 6mg per os oder intravenös für 7-10 Tage
- Kosten der Therapie: ca. 20 CHF
- Weltweit verfügbar


A All Participants (N=6425)
Rate ratio, 0.83 (95% CI, 0.75–0.9
P<0.001
17% Reduktion Sterblichkeit
Mortality (%)
Usual care
Dexamethasone
Days since Randomization
No. at Risk
Usual care 4321 3754 3427 3271 3205
Dexamethasone 2104 1903 1725 1659 1621
B Invasive Mechanical Ventilation (N=1007)
Rate ratio, 0.64 (95% CI, 0.51–0.81)
36% Reduktion Sterblichkeit
Usual care
Dexamethasone
Mortality (%)
Days since Randomization
No. at Risk
Usual care 683 572 481 424 400
Dexamethasone 324 290 248 232 228
C Oxygen Only (N=3883)
Rate ratio, 0.82 (95% CI, 0.72–0.94)
18% Reduktion Sterblichkeit
Usual care
Dexamethasone
Mortality (%)
Days since Randomization
No. at Risk
Usual care 2604 2195 2018 1950 1916
Dexamethasone 1279 1135 1036 1006 981
D No Oxygen Received (N=1535)
Rate ratio, 1.19 (95% CI, 0.91–1.55)
Kein Effekt
Dexamethasone
Usual care
Mortality (%)
Days since Randomization
No. at Risk
Usual care 1034 987 928 897 889
Dexamethasone 501 478 441 421 412

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
## A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

**IMPORTANCE** Effective therapies for patients with coronavirus disease 2019 (COVID-19) are needed, and clinical trial data have demonstrated that low-dose dexamethasone reduced mortality in hospitalized patients with COVID-19 who required respiratory support.

**OBJECTIVE** To estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality.

Editorial page 1292

Related articles pages 1298, 1307, and 1317

Supplemental content

| Drug and trial | ClinicalTrials.gov identifier | Initial dose and administration | No. of deaths/total No. of patients | | Odds ratio (95% CI) | Weight, % |
|---|---|---|---|---|---|---|
| | | | Steroids | No steroids | | |
| Dexamethasone | | | | | | |
| DEXA-COVID 19 | NCT04325061 | High: 20 mg/d intravenously | 2/7 | 2/12 | 2.00 (0.21-18.69) | 0.92 |
| CoDEX | NCT04327401 | High: 20 mg/d intravenously | 69/128 | 76/128 | 0.80 (0.49 | 18.69 |
| RECOVERY | NCT04381936 | Low: 6 mg/d orally or intravenously | 95/324 | 283/683 | | 7.00 |
| Subgroup fixed effect | | | 166/459 | | | 60 |
| Hydrocortisone | | | | | | |
| CAPE COVID | NCT02517489 | Low: 200 mg/d intraven | | | | |
| COVID STEROID | NCT04348305 | Low: 200 m | | | | 2.39 |
| REMAP-CAP | NCT02735707 | | | | | 11.75 |
| Subgroup fixed effect | | | | | | 19.94 |
| Methylpredni | | | | | | |
| Ster | | | | | | 3.46 |
| Overall | | | | | (0.53-0.82) | 100.0 |
| *P* = .31 fo | | | | | | |
| Overall (r | | | 678 | 425/1025 | 0.70 (0.48-1.01) | |

Favors steroids

Favors no ster

0.2

1

4

Odds ratio (95% CI)

**36% Reduktion Sterblichkeits-Inzidenz bei schwerkranken, intubierten COVID-19 Patient*innen**

**20% Reduktion der Sterblichkeit bei O2-bedürftigen, schwerkranken, aber nicht intubierten Patient*innen**

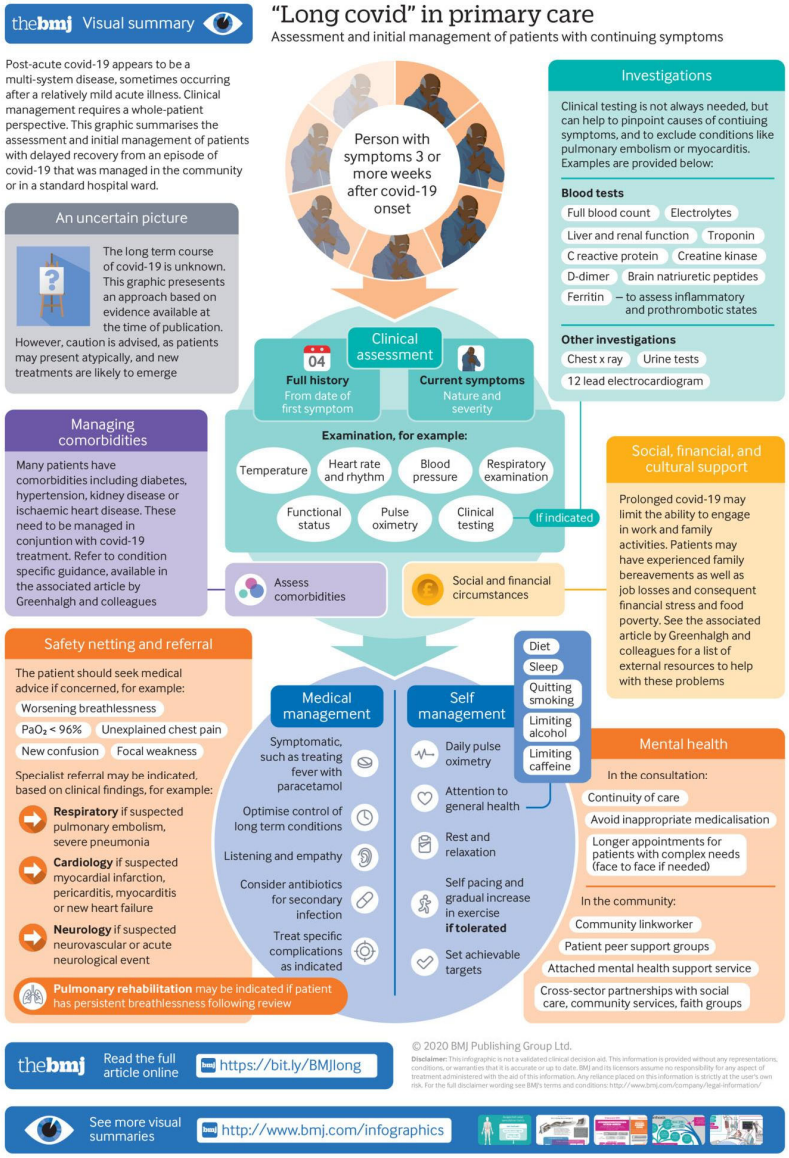
# Rekonvaleszentes Plasma


**Möglicherweise Effekt bei früher Gabe bei Patienten auf Normalstation mit Sauerstoffbedarf**
**Schnellere Negativierung der Sars-CoV-2 Viruslast**

# Fallvignette: 75-jähriger männlicher Patient zurück in der Praxis nach 2 Wochen Spital und 4 Wochen Reha

- Hospitalisation für 14 Tage auf Normalstation
  - Subsegmentale Lungenembolien
  - Therapeutisch niedermolekulares Heparin, aktuell für 3 Monate NOAK
  - Gabe von Remdesivir für 5 Tage
  - Gabe von Dexamethason für 10 Tage
- Aktuelle Beschwerden:
  - Ausgeprägte Müdigkeit mit Leistungsintoleranz
  - Vermehrtes Schwitzen
  - Anstrengungsdyspnoe
  - Mentale Verlangsamung, depressive Verstimmung, Angstattacken

# Post COVID






Trisha Greenhalgh et al. BMJ 2020;370:bmj.m3026

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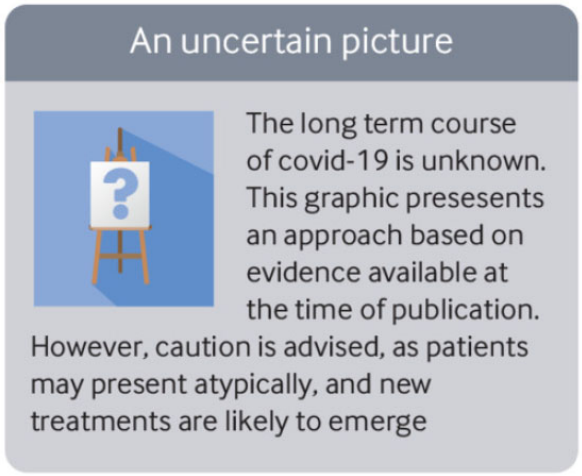


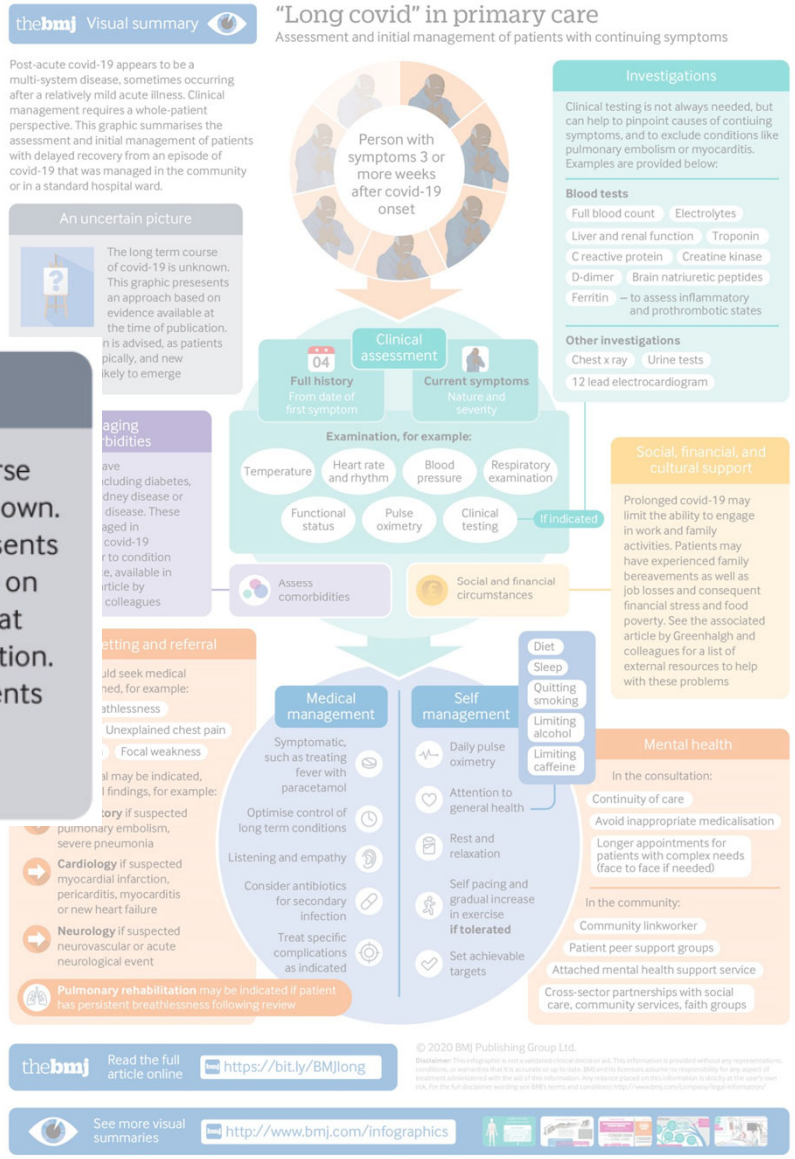


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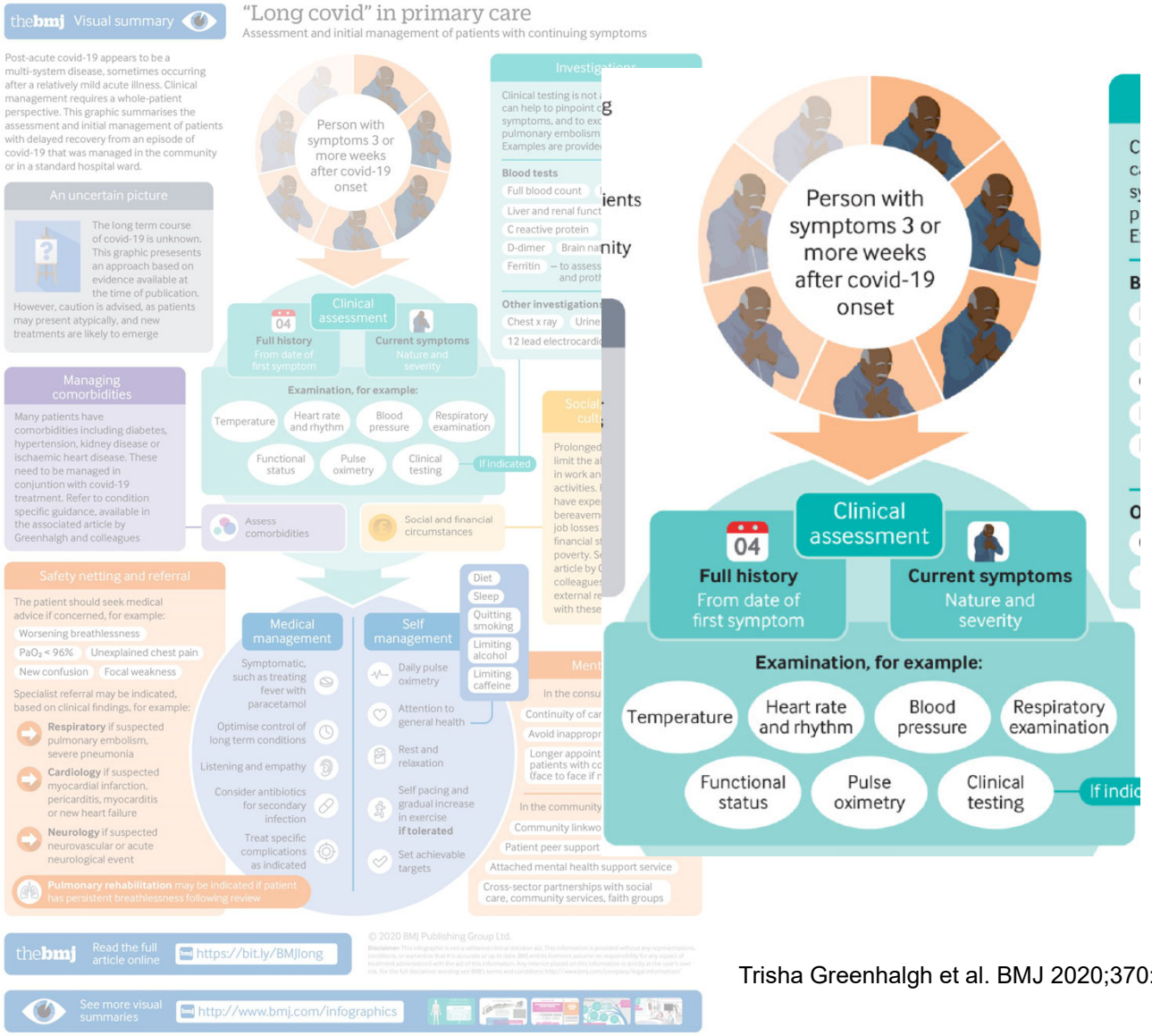


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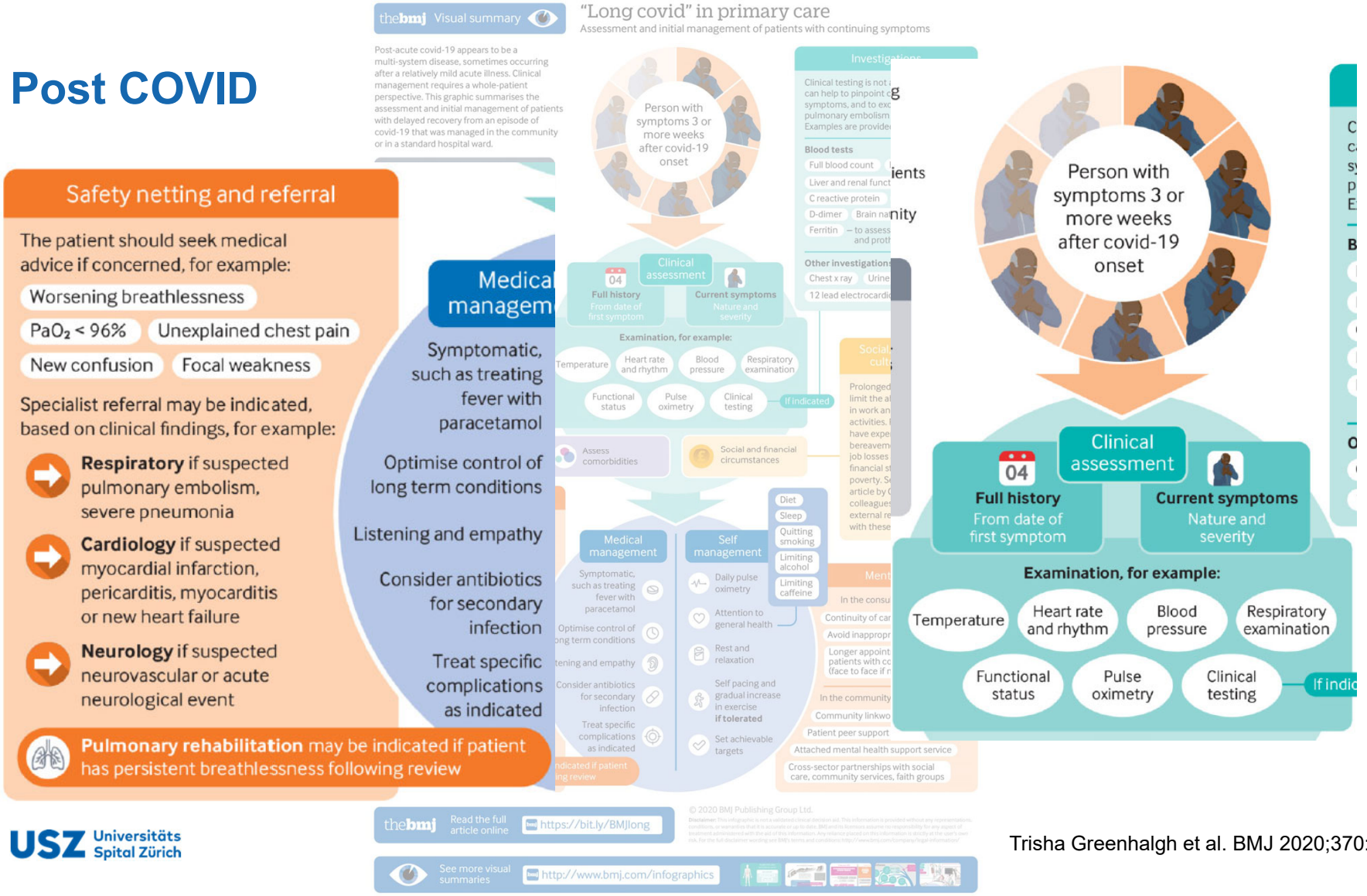


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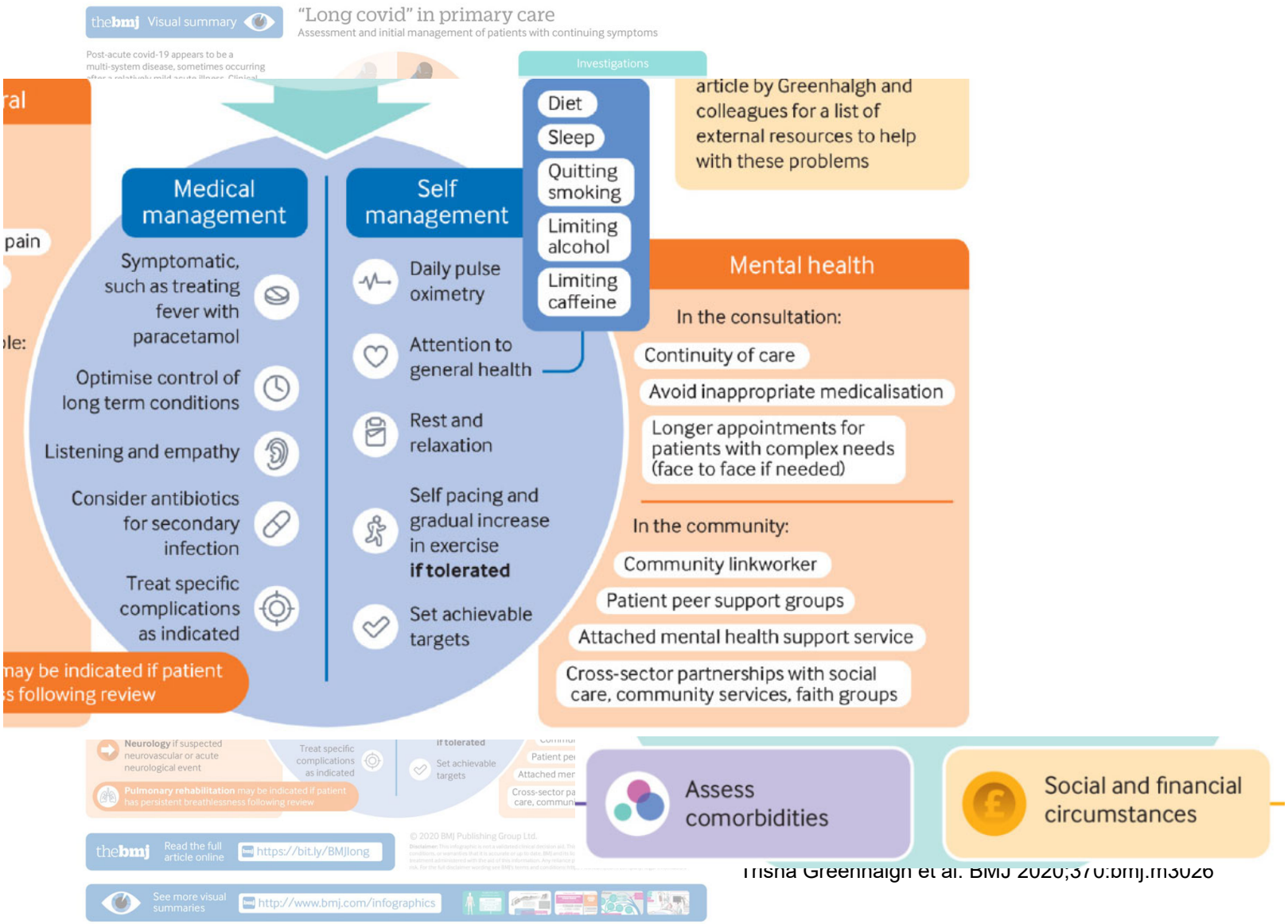


Trisha Greenhalgh et al. BMJ 2020;370:bmj.m3026

# Konklusion

- Aktuell keine spezifische Therapie für COVID-19 Infektion im ambulanten Rahmen zugelassen oder empfohlen
- Eine bakterielle Super-Infektion bei COVID-19 ist selten und Antibiotika meistens nicht indiziert
- Die Indikation zur Hospitalisation basiert auf klinischen Kriterien:
  - Progrediente Dyspnoe
  - Sa02 bei Raumluft <92% bzw. Sauerstoffbedarf
- Thrombo-embolische Ereignisse sind häufig und sollten niederschwellig gesucht werden
- Aktuell 2 Therapeutika *standard of care* bei hospitalisierten Patienten mit Sauerstoffbedarf:
  - Remdesivir für 5 Tage im frühen Stadium der Behandlung
  - Dexamethason 6mg per os für 7-10 Tage inkl. intubierte Patienten
- Post-akutes COVID-19 Syndrom in ca. 10-30%
  - Hohe Rate an Spontanheilung
  - Angepasstes, graduelles sportliches Training
  - Symptom-basierte Abklärungen (z.B. EKG Ausschluss Perimyokarditis, CT Thorax Ausschluss LE)