

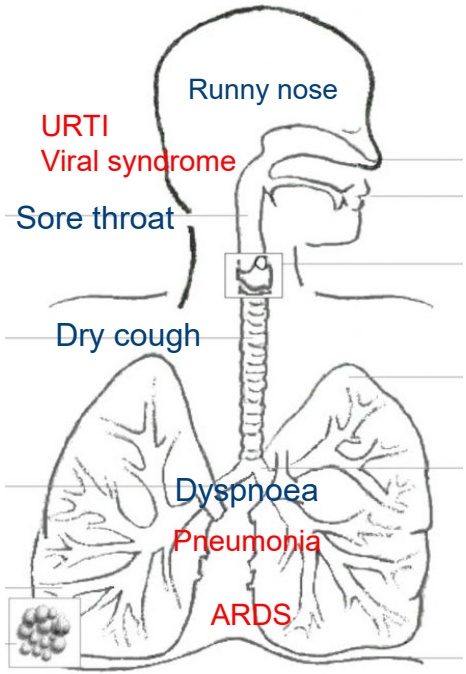
COVID-19

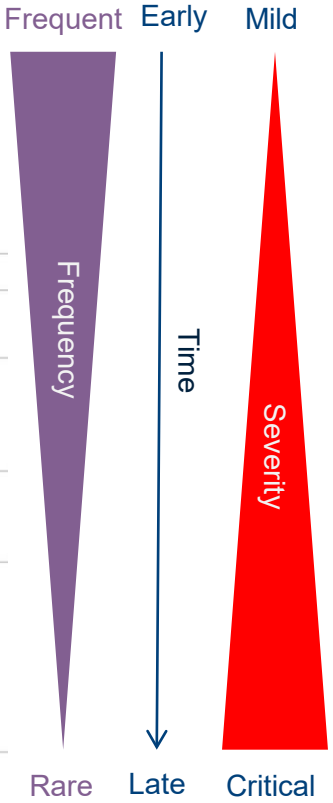
crash course

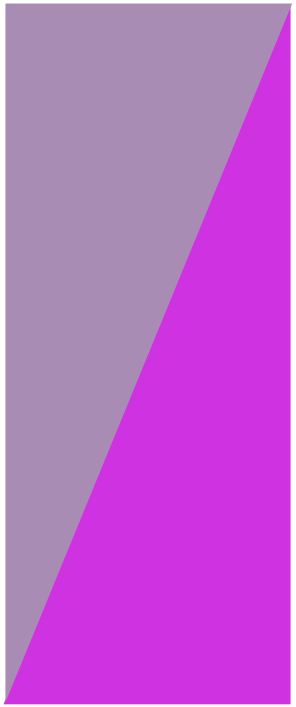
Antiviral treatment for COVID 19

prof.dr. Paul De Munter
Algemene Interne Geneeskunde

COVID 19









Pre-exposure prophylaxis

Post-exposure prophylaxis

Early treatment of mild disease

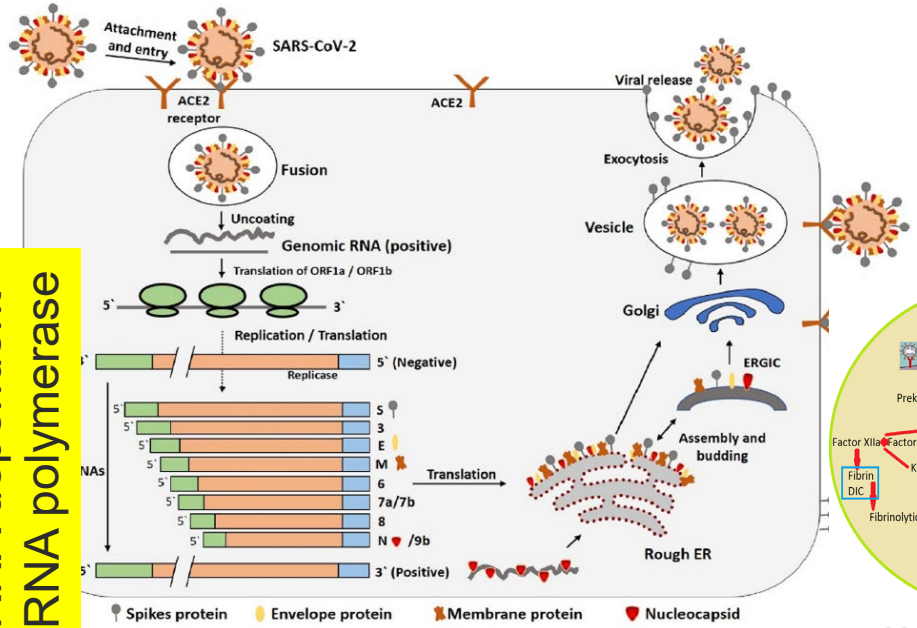
?

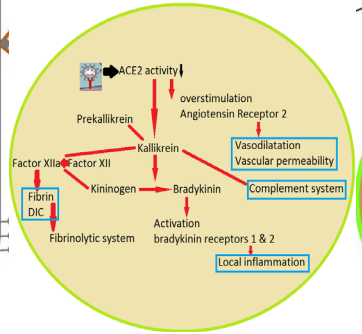
?

Treatment of severe disease

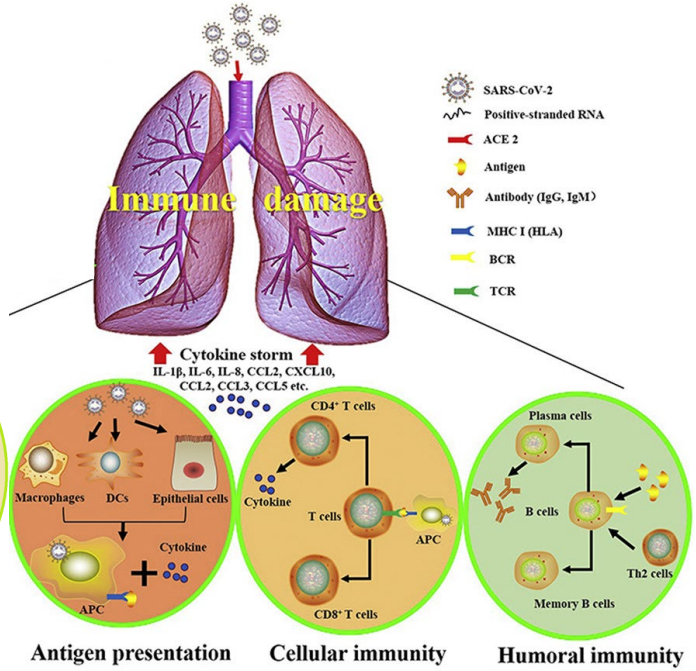
Pathophysiology of COVID 19

RNA dependent RNA polymerase





Link ACE2 receptor inflammation-coagulation



Viral replication

Immune pathology

MA Shereen et al. J of Advanced Research 2020. 24:91–98

(Hydroxy)chloroquine

- Chloroquine
  - old antimalarial
  - no longer available in Belgium
- Hydroxychloroquine (HCQ)
  - used in reumatic diseases
- known anti-inflammatory effects, in vitro antiviral effects
- Higher dose in COVID 19
- Only drug in Sciensano treatment guideline for mild, moderate and severe disease

Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial

Zhaowei Chen[1,†], Jijia Hu[1,†], Zongwei Zhang[1], Shan Jiang[2], Shoumeng Han[3], Dandan Yan[4], Ruhong Zhuang[5], Ben Hu[6] and Zhan Zhang[7,*]

Covid-19: US gives emergency approval to hydroxychloroquine despite lack of evidence

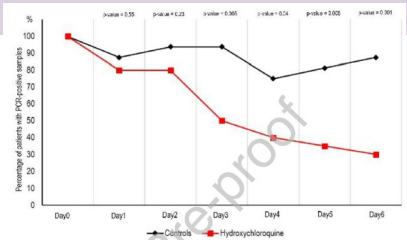
Jeanne Lenzer

One small Chinese RCT *(preprint)*:

- 62 patients randomized 1:1 to:
  - HCQ sulfate (200mg bid 5 days)
  - standard of care (SOC)
- Outcomes:
  - Clinical recovery 1 day faster HCQ vs SOC
  - Progression to severe disease: 0% (HCQ) vs 13% (SOC)
  - Improved chest CT: 81% (HCQ) vs 55% (SOC)

One open label controled trial *(preproof)*:

- 36 patients:
  - 26 patients: hydroxychloroquine sulfate (200 mg tid for ten days) - 6 also azithromycin
  - 16 controls (CTR) (no treatment)
- Virological clearance day 6: 70% (HCQ) vs 12.5% (CTR) ($p<0.05$).



Preproof

medRxiv preprint doi: https://doi.org/10.1101/2020.03.22.20040758
Gautret P et al. Int J Antimicrob Agents. 2020

Remdesivir

- Drug developed for ebola, failed in ebola RCT
- Direct antiviral, targets viral RNA-dependent RNA polymerase
- In vitro active against SARS-CoV-2, potent
- Only IV formulation, not yet commercialised, initial compassionate use access, now limited availability through expanded access programs
- Very limited data on side effects suggest good tolerance
- Use mentioned in Sciensano treatment guideline


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Search

Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

EMA provides recommendations on compassionate use of remdesivir for COVID-19 Share

Press release 03/04/2020

During an extraordinary virtual meeting held on 2 April 2020, EMA's human medicines committee (CHMP) gave recommendations on how the investigational antiviral medicine remdesivir should be used for treating coronavirus disease (COVID-19) in compassionate use programmes in the European Union.

Cases published reporting succesful treatment

Currently no evidence of clinical benefit (yet?)

Covid 19 clinical trial results awaited in april 2020:

- Effect?
- Side effects?
- Effect if used early? Also if used late?

Favipiravir

- Direct antiviral, targets viral RNA-dependent RNA polymerase
- Registered in Japan for influenza
- Theoretically potent against SARS CoV-2
- Relatively low toxicity

Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial

Chang Chen, MD[1,2,#], Jianying Huang, MD[1,3,#], Zhenshun Cheng, MD[4], Jianyuan Wu, PhD[1,3], Song Chen, MD[5], Yongxi Zhang, MD[6], Bo Chen, PhD[1,3], Mengxin Lu, MD[5], Yongwen Luo, MD[5], Jingyi Zhang, MD[7], Ping Yin, PhD[8], Xinghuan Wang, MD[1,3,5,9,*]

One open label RCT *(preprint)*:

- 240 patients randomized 1:1 to
  - favipiravir (1600mg bid d1, 600mg bid d2-7)
  - arbidol (200 mg tid, 7 days)
- clinical recovery:
  - overall: 61.2% vs 51.7% (p=0.14)
  - subgroup non-critical patients without comorbidity: 71.43% vs 55.9% (*p=0.02*)
- Only significant difference in side effects, increased uric acid in favipiravir group

medRxiv preprint doi:
https://doi.org/10.1101/2020.03.17.20037432

Other repurposed drugs

- Lopinavir/ritonavir
  - no evidence of effect in *'best'* RCT*
- Azithromycin: see DAWN azithro
- Reconvalescent plasma

- Immunological treatments
  - Corticosteroids:
    - no evidence for use in Covid
    - evidence against use in MERS and SARS
    - in ARDS?
  - Specific drugs targeting cytokines:
    - Anakinra: anti-IL1
    - Toculizimab: anti-IL6

=> Cases, no evidence



** Cao B et al. N Engl J Med. 2020*

Conclusion

- Currently no *convincing* evidence of beneficial effects of any drug on outcome of COVID-19; but science rapidly evolving
- Rare or expensive drugs may not be accessible if proven effective
- Question may not only be ‘which drug’ but ‘which drugs at which stage’
- National guidelines: www.sciensano.be

INSTITUTE OF TROPICAL MEDICINE ANTWERP | Universiteit Antwerpen | CHU Saint-Pierre UMC Sint-Pieter | sciensano | afmps fagg

INTERIM CLINICAL GUIDANCE FOR ADULTS WITH SUSPECTED OR CONFIRMED COVID-19 IN BELGIUM

07 Avril 2020; Version 7

=> For now, do not feel guilty not prescribing a drug: benefit/harm not settled



Studies in Belgium *(maybe far from complete)*

SARPAC = randomized, inhaled recombinant granulocyte macrophage-CSF (5d) vs standard of care (1:1, n=80)

COVID19⁺ "Progressie risico" → **Inclusie**

- Acute hypoxie:
  - PF ratio < 350 (= PaO2 73,5 kamerlucht)
  - OF SpO2 < 93% onder 2L O2

Exclusie

- > 80j
- DNR > 0
- Zwangerschap
- Hematologische (myeloide) maligniteit
- **Ferritine > 2000**

Prof Bart Lambrecht : bart.lambrecht@ugent.be

COV-AID = randomized Anti-IL6(R) EN/OF Anti-IL1 vs standard of care (5:1, n=342)

COVID19⁺ "Actieve cytokinestorm" → **Inclusie**

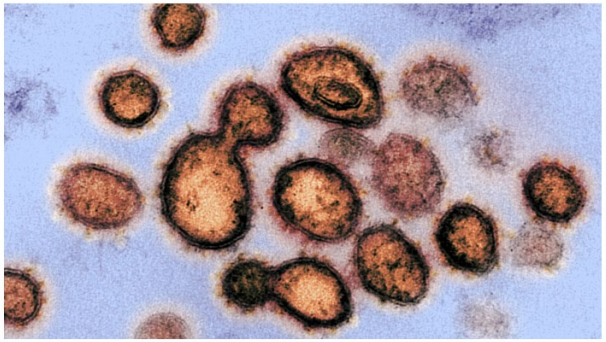
- Acute hypoxie:
  - PF ratio < 350 (= PaO2 73,5 kamerlucht)
  - OF SpO2 < 93% onder 2L O2
- Bilaterale infiltraten Rx of CT thorax
- COVID dag 6 – 16
- Cytokine storm syndroom:
  - Ferritine > 1000 en stijgend laatste 24h
  - OF Ferritine > 2000 onder high flow O2 of mechanische ventilatie
  - OF lymfopenie (<800/µl, met aantal andere stijgende parameters zoals LDH, CRP, ferritine, D-dimeren)

Exclusie

- Frailty score > 3
- Actieve bacteriële/fungale (sur)infectie
- Zwangerschap
- Mechanische ventilatie > 24h
- Hoge dosis corticosteroïden voor begin studie

Studies in Belgium *(maybe far from complete)*

- Multicenter
  - Solidarity *(contact prof.dr.H.Goossens – UZ Antwerpen)*
    - standard of care
    - standard of care plus remsedivir,
    - standard of care plus lopinavir and ritonavir,
    - standard of care plus lopinavir, ritonavir and interferon beta 1a
    - standard of care plus hydroxy-chloroquine



Transmission electron microscope image of severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019, isolated from a patient in the United States NATIONAL INSTITUTES OF HEALTH

WHO launches global megatrial of the four most promising coronavirus treatments

By Kai Kupferschmidt, Jon Cohen | Mar. 22, 2020 , 3:28 PM

  - DAWN trial – from lab (Rega institute – prof.J. Neyts) to clinic
    - DAWN itraco: itraco versus standard of care, currently monocentric *(contact prof.dr.E.Van Wijngaerden – UZ Leuven)*
    - DAWN azithro: see next slides

    - More to come…



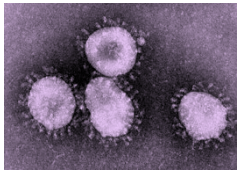
COVID-19 crash course

Azithromycin in COVID-19

Robin Vos, UZ Leuven

Azithromycin: what's the fuss about?







Thailand Medical News®
A Collaborative Platform of Medical Information, Resources and News

ABOUT CONTRIBUTE

News | Trending Topics | Meds | Medical Devices | Local Medical Scene | Resources | Events

BREAKING NEWS Incapable Of Transporting Oxygen. Current Medical Protocols Could All Be Wrong!

Source: COVID-19 Drug Research Apr 04, 2020 5 days ago

BREAKING! COVID-19 Drug Research: Study Shows That Hydroxychloroquine And Azithromycin Has No Effect On COVID-19 Patients, No Better Than A Dangerous Placebo

NEWS / CORONAVIRUS

BCFi

zoeken naar merknaam, stofnaam of trefwoord

GOED OM TE WETEN

COVID-19: geen azithromycine voorschrijven voor thuisbehandeling van COVID-19-patiënten 20 maart 2020

laatste update: 25 maart 2020

De Belgische Gezondheidsinstanties en experten (o.a. BAPCOC) roepen op om azithromycine niet voor te schrijven voor thuis behandelde patiënten met COVID-19. Er is geen bewezen werkzaamheid van azithromycine bij COVID-19 (ondanks circulerende berichten daarover!) en er zijn risico's aan verbonden.

HEALTH EUROPA

THE LATEST **EU POLICY** UPDATES
CLICK HERE TO SUBSCRIBE

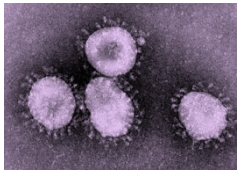
Home › News › Pharma News › Could azithromycin prevent NHS workers from developing COVID-19?

News | Pharma News

Could azithromycin prevent NHS workers from developing COVID-19?

By **Shakera Halim** - 8th April 2020

Azithromycin: why?



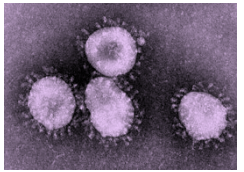
- **Anti-inflammatory/Immuno-modulatory***
  - Inhibitor of **protein synthesis**: cytokines (IL-1, IL-6, IL-8, IL-17,…), growth factors (FGF, VEGF), acute phase proteins (CRP), viral proteins,…
  - Altered intra-cellular **signal transduction** from cell surface->nucleus (MAPK pathway)
  - Inhibition of **transcription** factors (NFκ-B, AP-1) and altered **gene expression**
  - Neutrophil **degranulation**, ↑**phagocytosis**, **apoptosis**, ↓**Th1**/ ↑**Th2**, …

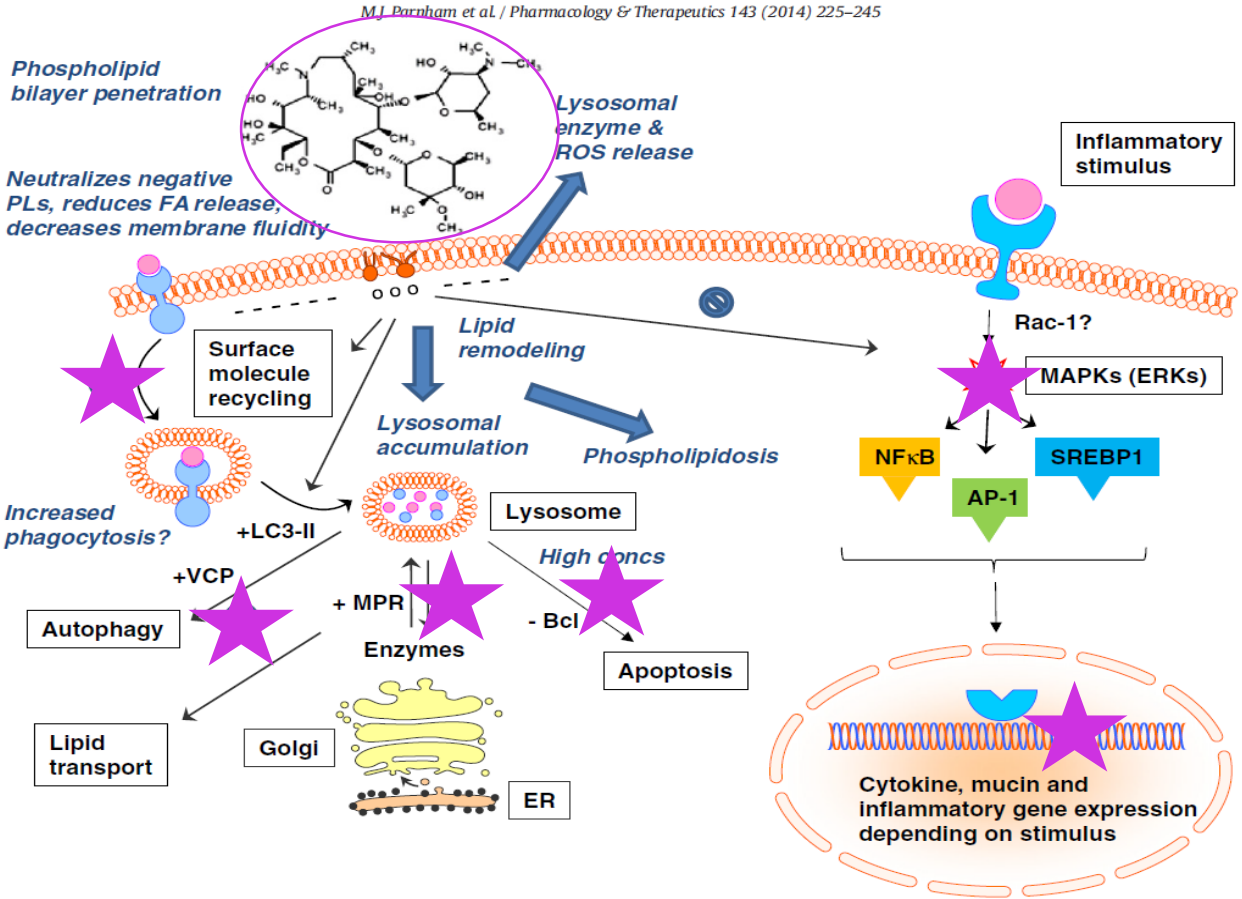
- **Viral replication***
  - **Direct**: lysosomotropic action (↑pH, ↓trafficking), ↓protein synthesis
  - **Indirect**: ↑host cell IFN-production and IFN-stimulated gene expression (activation of immune cells, ↑anti-viral defences of neighbouring structural host cells)

- **Anti-bacterial**
  - inhibits bacterial ribosomal **protein synthesis** (50S large subunit)
  - Inhibits generation of **quorum-sensing molecules**, alginate (polysaccharide) **biofilm** formation

* In structural cells (epi-/endothelial), smooth muscle cells, fibroblasts, leukocytes

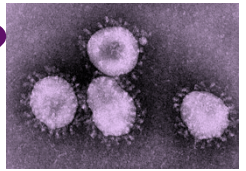
Azithromycin: why?

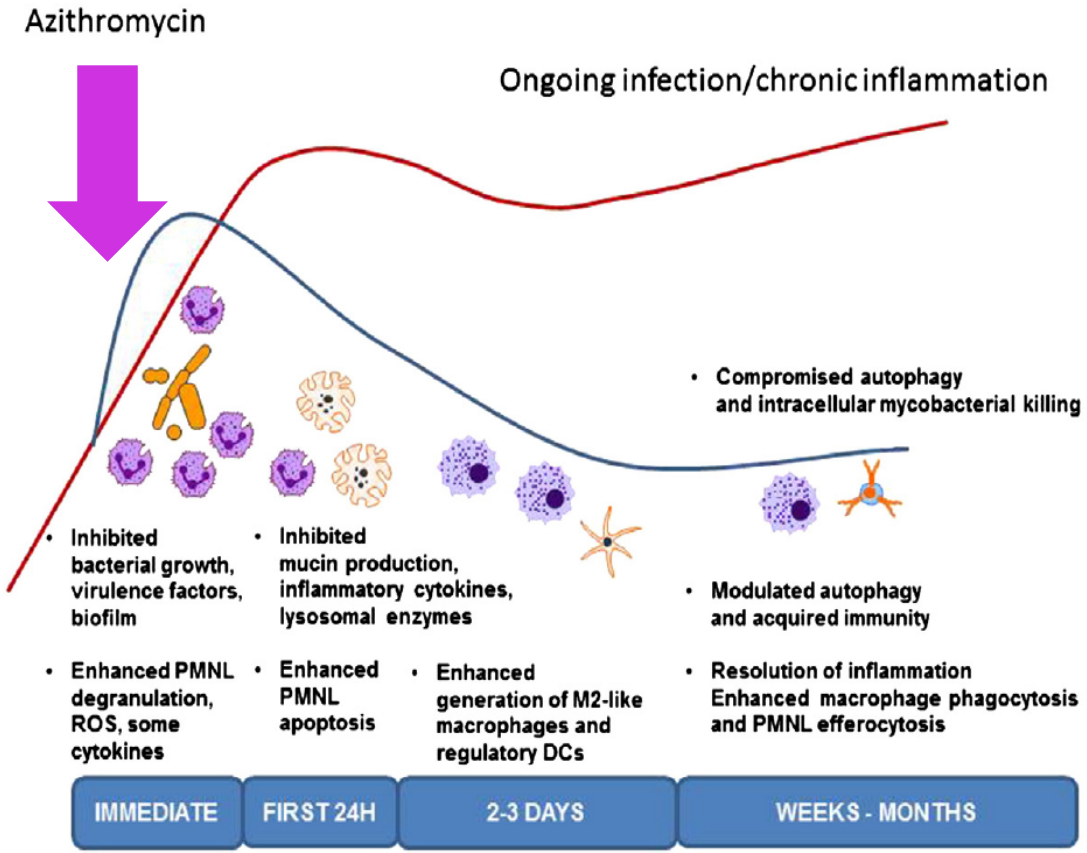




Parnham MJ, et al. Pharmacol Ther. 2014

Azithromycin: pharmacokinetic/dynamic properties?



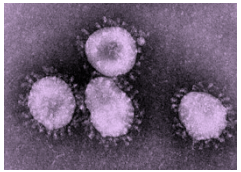


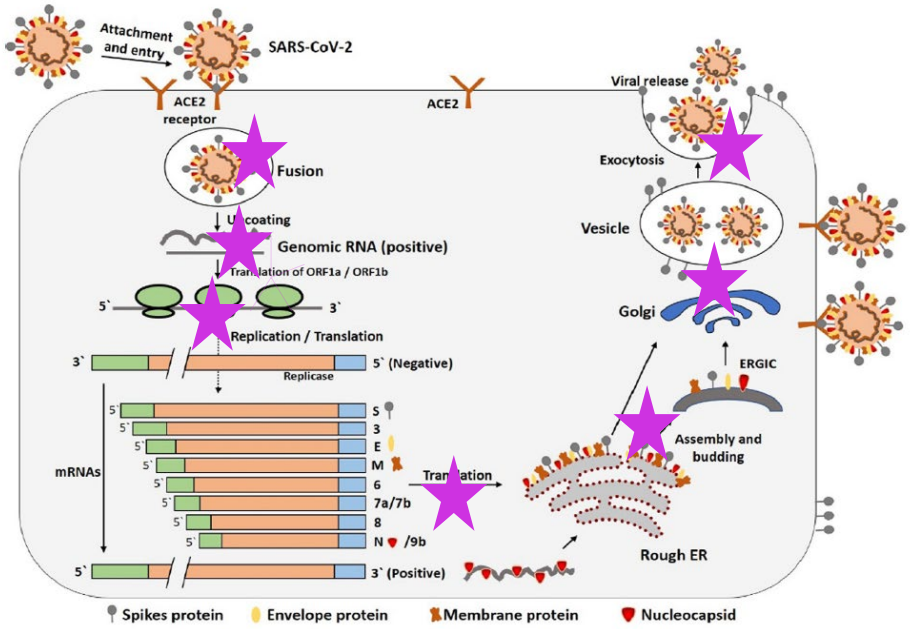
- good absorption
- rapid t_{max} (2-4h)
- high tissue concentrations (@ site of inflammation): 20X vs plasma
- intracell. 200X vs. extracell.
- long $t_{1/2}$ (>60h)
- does not induce CYPs
- PK/PD unchanged in mild/moderate hepatic impairment or renal insuff.
- Safe (QTc?, hearing loss, allergy)

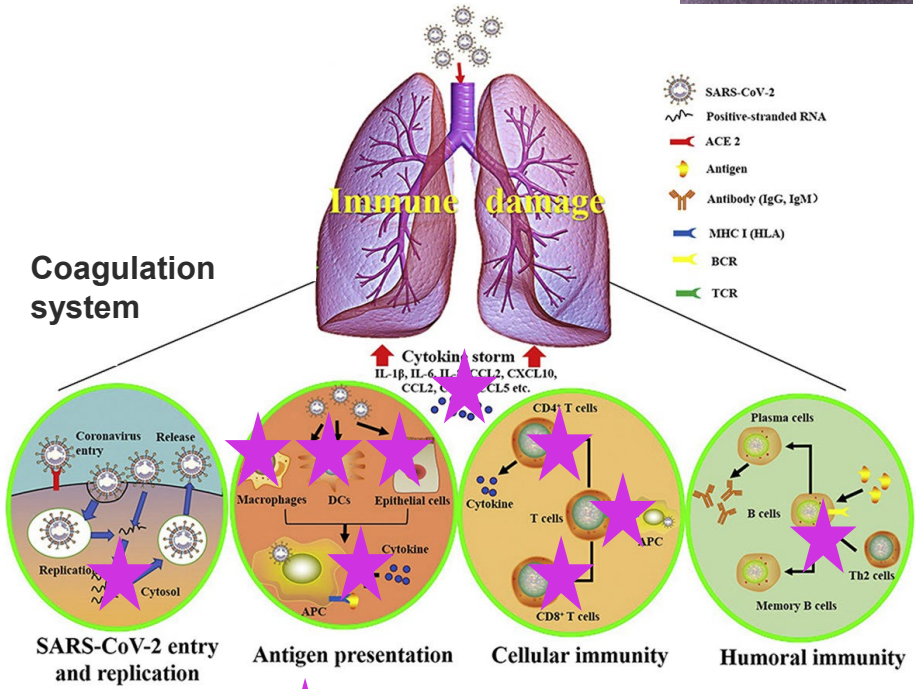
Parnham MJ, et al. Pharmacol Ther. 2014

Azithromycin: how?

Influenza (H1N1, other), RSV, Rhino, Parainfluenza, Zika, Sendai, Ebola





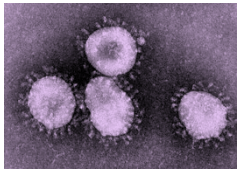


★ **Attenuation of viral replication**

★ **Attenuation of immune pathology**

Parnham MJ, et al. Pharmacol Ther. 2014

Azithromycin: the evidence?



Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial

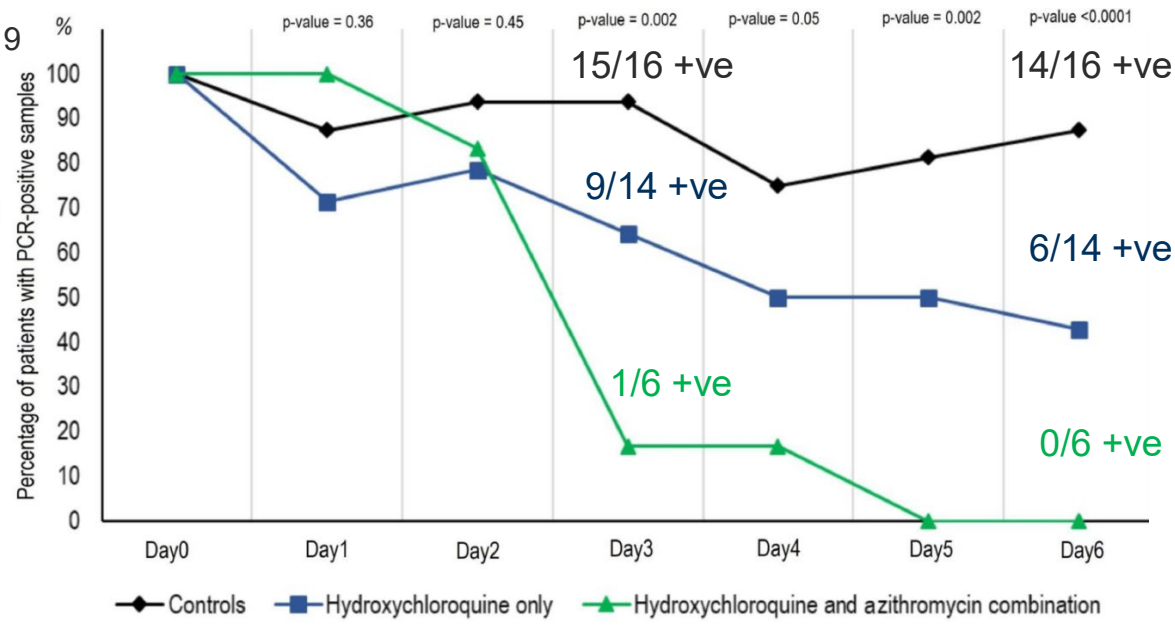
Proportion of patients with 'virological cure' (negative nasopharyngeal PCR)

Hospitalized, proven COVID-19
(Marseille, Nice, Briançon, Avignon)

200mg 3X/d 10d
(Marseille)
6/20 lost in FU

500mg d1 + 250mg d2-5
(Marseille)

16.7% asympt.
61.1% URTI
22.2% LRTI

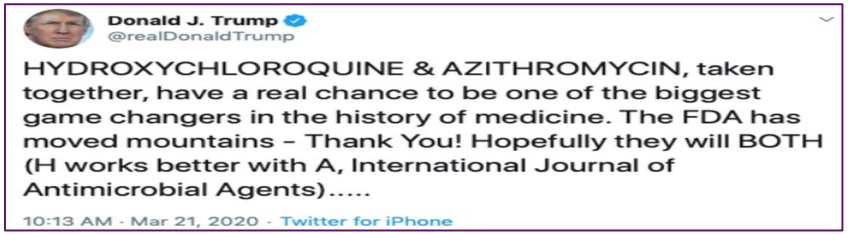


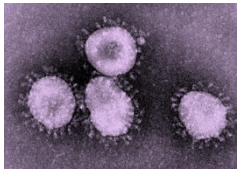
viral shedding in COVID-19 in China ±20d (max. 37d)

1/6 positive at day 6 received AZI at day 8: 'cured' day 9

1/6 again +ve at low titer at day 8

Azithromycin: the facts?



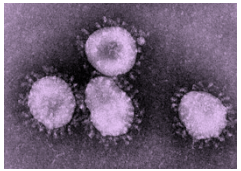


- Non-randomized, multi-center convenience sampling
- PCR-analysis not standardized/uniform
- ‘Study-period’ 14 days…
- AZI added ‘to prevent bacterial super-infection’
- Secondary endpoint-data @D14?
  - virological clearance
  - clinical follow-up (T°, RR, hospital stay, mortality)
  - occurrence of side-effects
- Journal’s Editor-in-Chief (JM. Rolain) = both the paper’s coauthor and the main author’s (D. Raoult) subordinate

Received 16 March 2020, Accepted 17 March 2020, Available online 20 March 2020.

Gautret P, et al. Int J Antimicrob Agents. 2020

Azithromycin: the facts?

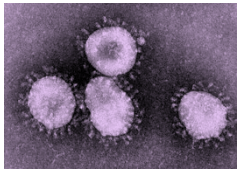


“cavete consules quod tarpeia rupes proxima est capitolio”
(beware advisors, because one's fall from grace can come swiftly)



Gautret P, et al. Int J Antimicrob Agents. 2020

Azithromycin: the evidence?



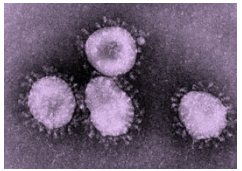
No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection

- 11 consecutive patients hospitalized for COVID-19 (Paris)
- HQ (600 mg/d for 10 days) + AZI (500 mg day 1, 250 mg days 2-5)

- 1 patient died and 2 upgraded to ICU (<5d)
- SARS-CoV2 RNA in +ve 8/10 patients on day 5-6

Molina JM, et al. Médecine et Maladies Infectieuses 2020

Azithromycin: the evidence?



Macrolides in critically ill patients with Middle East Respiratory Syndrome

- retrospective analysis, multi-center cohort
- 90-day mortality, MERS-CoV RNA clearance
- 349 critically ill MERS patients
- 136 (39%) received macrolides: azithromycin in 97/136 (71.3%)
- started at D0 or D1 in ICU in 76.5% of cases

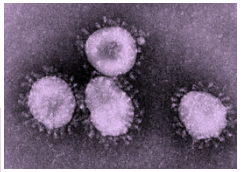
- No reduction of 90-day mortality (group adjusted OR*: 0.84; 95% CI: 0.47–1.51; P=0.56)
- No difference in MERS-CoV RNA clearance (adjusted HR: 0.88; 95%CI:0.47–1.64;P=0.68)

* Multivariable logistic regression analysis, with macrolide therapy as independent variable.
The model included **baseline variables** of clinical interest, decided a priori, and significant co-variables at the univariable level (P <0.2) that included: BMI, SOFA score at admission to ICU, community-acquired (versus hospital-acquired) infection, healthcare worker-associated infection, NIV at ICU admission, malignancy, chronic pulmonary disease, and liver disease).

BUT: On admission to ICU, baseline characteristics of patients who received and did not receive macrolides were **similar**!

Arabi YM, et al. Int J Infect Dis. 2019

Azithromycin: the evidence?



Macrolides in critically ill patients with Middle East Respiratory Syndrome

Table 2
ICU course and outcomes among critically ill patients with Middle East Respiratory Syndrome (MERS) who received or did not receive macrolide therapy.

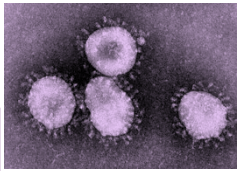
Variables	Macrolide group (n = 136)	No macrolides group (n = 213)	P-value
Non-invasive positive pressure ventilation, n (%)	49 (36.0)	57 (26.8)	0.07**
Invasive ventilation, n (%)	117 (86.0)	180 (84.5)	0.70**
Neuromuscular blockade, n (%)	59 (43.4)	74 (34.7)	0.11**
High-frequency oscillation ventilation, n (%)	19 (14.0)	7 (3.3)	0.0002**
ECMO, n (%)	10 (7.4)	12 (5.6)	0.52**
Nitric oxide, n (%)	23 (16.9)	21 (9.9)	0.05**
Prone positioning, n (%)	18 (13.2)	15 (7.0)	0.05**
Vasopressors, n (%)	107 (78.7)	169 (79.3)	0.88**
Antivirals, n (%)	118 (86.8)	169 (79.3)	0.08**
Oseltamivir, n (%)	99 (72.8)	97 (45.5)	< 0.0001**
Corticosteroids, n (%)	76 (55.9)	102 (47.9)	0.15**
Intravenous immunoglobin, n (%)	15 (11.0)	9 (4.2)	0.01**
Renal replacement therapy, n (%)	79 (58.1)	95 (44.6)	0.01**
ICU mortality, n (%)	81 (59.6)	146 (68.5)	0.09**
Hospital mortality, n (%)	86 (63.2)	151 (70.9)	0.14**
90-day mortality, n (%)	82 (60.3)	150 (70.4)	0.05**
MERS-CoV RNA clearance[a], days, median (Q1, Q3)	26 (19, 33)	21 (17, 28)	0.93
ICU length of stay, days, median (Q1, Q3)	11 (6, 21)	8 (5, 17)	0.09^
Hospital length of stay, days, median (Q1,Q3)	16 (8.5, 34)	20 (11, 35)	0.08^
Invasive ventilation duration, days, median (Q1, Q3)	11 (6, 18)	8 (4, 15)	0.04^

ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit.

Sicker

Arabi YM, et al. Int J Infect Dis. 2019

Azithromycin: the evidence?



Macrolides in critically ill patients with Middle East Respiratory Syndrome

Table 2
ICU course and outcomes among critically ill patients with Middle East Respiratory Syndrome (MERS) who received or did not receive macrolide therapy.

Variables	Macrolide group (n = 136)	No macrolides group (n = 213)	P-value
Non-invasive positive pressure ventilation, n (%)	49 (36.0)	57 (26.8)	0.07**
Invasive ventilation, n (%)	117 (86.0)	180 (84.5)	0.70**
Neuromuscular blockade, n (%)	59 (43.4)	74 (34.7)	0.11**
High-frequency oscillation ventilation, n (%)	19 (14.0)	7 (3.3)	0.0002**
ECMO, n (%)	10 (7.4)	12 (5.6)	0.52**
Nitric oxide, n (%)	23 (16.9)	21 (9.9)	0.05**
Prone positioning, n (%)	18 (13.2)	15 (7.0)	0.05**
Vasopressors, n (%)	107 (78.7)	169 (79.3)	0.88**
Antivirals, n (%)	118 (86.8)	169 (79.3)	0.08**
Oseltamivir, n (%)	99 (72.8)	97 (45.5)	< 0.0001**
Corticosteroids, n (%)	76 (55.9)	102 (47.9)	0.15**
Intravenous immunoglobin, n (%)	15 (11.0)	9 (4.2)	0.01**
Renal replacement therapy, n (%)	79 (58.1)	95 (44.6)	0.01**
ICU mortality, n (%)	81 (59.6)	146 (68.5)	0.09**
Hospital mortality, n (%)	86 (63.2)	151 (70.9)	0.14**
90-day mortality, n (%)	82 (60.3)	150 (70.4)	0.05**
MERS-CoV RNA clearance[a], days, median (Q1, Q3)	26 (19, 33)	21 (17, 28)	0.93
ICU length of stay, days, median (Q1, Q3)	11 (6, 21)	8 (5, 17)	0.09^
Hospital length of stay, days, median (Q1,Q3)	16 (8.5, 34)	20 (11, 35)	0.08^
Invasive ventilation duration, days, median (Q1, Q3)	11 (6, 18)	8 (4, 15)	0.04^

ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit.

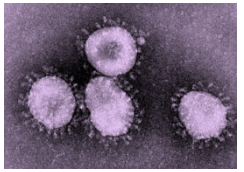
Sicker

Equal (better?)

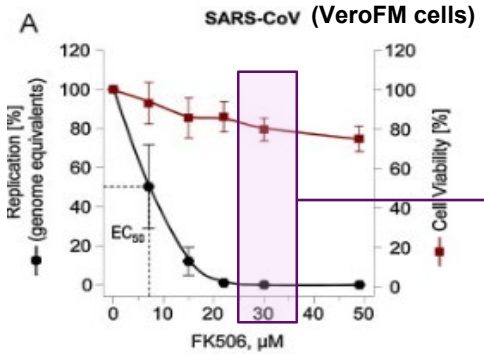


Arabi YM, et al. Int J Infect Dis. 2019

Macrolides other than azithromycin: the facts?

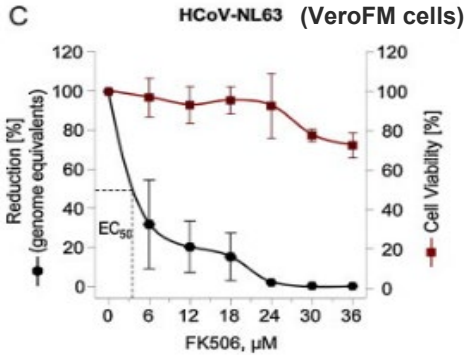


Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506



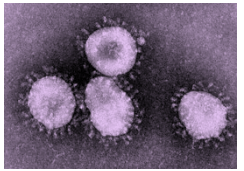
SARS-CoV-2
(J. Neyts, et al. KU Leuven)

FK506 / Tacrolimus = macrolide immunosuppressant



Carbajo-Lozoya J, et al. Virus Res. 2012

Direct Antivirals working against nCoV (DAWN) – Azithromycin



- randomized, open-label, proof-of-concept clinical trial
- multi-center (n=12, 9 Flanders/2 Brussels/1 Wallonia)

- ≥18 y
- Confirmed SARS-CoV-2 <72 h prior to randomization
- U/LRTI + CT compatible
- ward or ICU
- 'Severe' disease:
  - infiltrates on imaging
  - SpO2 ≤ 94%
  - supplemental O2 and/or mechanical ventilation

R 2:1

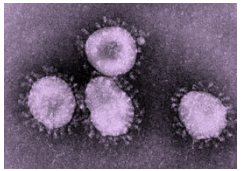
n=80 → Standard of Care

n=160 → Azithromycin (500 mg D1-5 po) + Standard of Care

Primary endpoints (ITT analysis):
- ✓ Clinical status at day 15 (WHO scale)
- ✓ Cumulative clinical status up to day 15 (WHO scale)

Exclusion:
- ALT/AST > 5 ULN
- Pregnancy / breast feeding
- Allergy to azithromycin
- LVEF ≤30%
- QT > 470 (M)/480 (F) msec
- Macrolide during last week prior to admission

Direct Antivirals working against nCoV (DAWN) – Azithromycin



- randomized, open-label, proof-of-concept clinical trial
- multi-center (n=12)

- ≥18 y
- Confirmed SARS-CoV-2 <72 h prior to randomization
- U/LRTI + CT compatible
- ward or ICU
- 'Severe' disease:
  - infiltrates on imaging
  - SpO2 ≤ 94%
  - supplemental O2 and/or mechanical ventilation

R 2:1

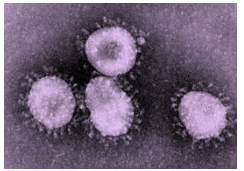
Exclusion:
- ALT/AST > 5 ULN
- Pregnancy / breast feeding
- Allergy to azithromycin
- LVEF ≤30%
- QT > 470 (M)/480 (F) msec
- Macrolide during last week prior to admission

Secondary endpoints:

- ✓ Mortality (day 15+29), time to death, date and cause of death
- ✓ Time to clinical improvement
- ✓ Duration of O2, Mech Vent, hospit stay, ICU stay
- ✓ NEWS score
- ✓ Adverse events
- ✓ Lab values on days 1, 3, 5, 8, 11, 15 and 29 (if available)
- ✓ Combined cardiac endpoint (hsTrop, ventricular arrhythmia requiring intervention, reanimation, sudden cardiac death)
- ✓ absolute QTc and delta QTc interval between baseline ECG and follow-up ECG at day 2-3
- ✓ PCR for SARS-CoV-2 on day 6 (if available)
- ✓ Functional and radiological evaluation 5-7 weeks post-discharge (Questionnaire, PFT, low dose CT, Lab, 6MWD)
- ✓ Survival status 90 days post-admission

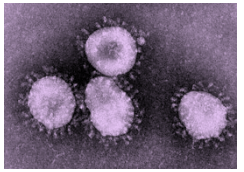
PI: R. Vos, CI: W. Janssens

Direct Antivirals working against nCoV (DAWN) – Other



- multi-center (n=12) + others
- direct working anti-virals
- reconvalescent plasma
- other …

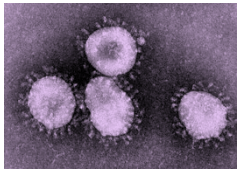
Let’s fight this virus…





…and end this horror movie

Let's fight this virus…



NCT04329832	Hydroxychloroquine vs. Azithromycin for Hospitalized Patients With Suspected or Confirmed COVID-19	Utah
NCT04334382	Hydroxychloroquine vs. Azithromycin for Outpatients in Utah With COVID-19	Utah
NCT04332107	Azithromycin for COVID-19 Treatment in Outpatients Nationwide (ACTION)	San Francisco
NCT04339426	Atovaquone and Azithromycin Combination for Confirmed COVID-19 Infection	Phoenix
NCT04329572	Efficacy and Safety of Hydroxychloroquine and Azithromycin for the Treatment of Hospitalized Patients With Moderate to Severe COVID-19	Brasil
NCT04339816	Azithromycin Added to Hydrochloroquine in Patients Admitted to Intensive Care With COVID-19: Randomised Controlled Trial (AZIQUINE-ICU)	Czech Republic
NCT04336332	Randomized Comparison of Combination Azithromycin and Hydroxychloroquine vs. Hydroxychloroquine Alone for the Treatment of Confirmed COVID-19	New Jersey
NCT04332094	Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of COVID-19 (TOCOVID)	Barcelona
NCT04335552	Phase 2 Trial of Hydroxychloroquine, Azithromycin, or Both for Treatment of Severe SARS-CoV-2 Infection	Durham
NCT04328272	Effectiveness of Hydroxychloroquine in Covid-19 Patients (Covid)	Pakistan
NCT04338698	Hydroxychloroquine, Oseltamivir and Azithromycin for the Treatment of COVID-19 Infection: An RCT (PROTECT)	Pakistan
NCT04321278	Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Coalition Covid-19 Brasil II)	Brasil
NCT04337866	Evaluation of the Effects of Ozone Therapy on Covid 19 Positive Patients	Istanbul
NCT04322396	Proactive Prophylaxis With Azithromycin and Chloroquine in Hospitalized Patients With COVID-19 (ProPAC-COVID)	Copenhagen
NCT04322123	Safety and Efficacy of Hydroxychloroquine Associated With Azythromycin in SARS-Cov-2 Virus (Coalition-I)	Brasil
NCT04324463	Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial (ACT COVID19)	Hamilton
NCT04334512	A Study of Quintuple Therapy to Treat COVID-19 Infection (HAZCpaC)	California
NCT04332835	Convalescent Plasma for Patients With COVID-19: A Randomized, Open Label, Parallel, Controlled Clinical Study (CP-COVID-19)	Bogota
NCT04323345	Efficacy of Natural Honey Treatment in Patients With Novel Coronavirus	Cairo
NCT04333355	Safety in Convalescent Plasma Transfusion to COVID-19	Monterrey
NCT02735707	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)	Utrecht