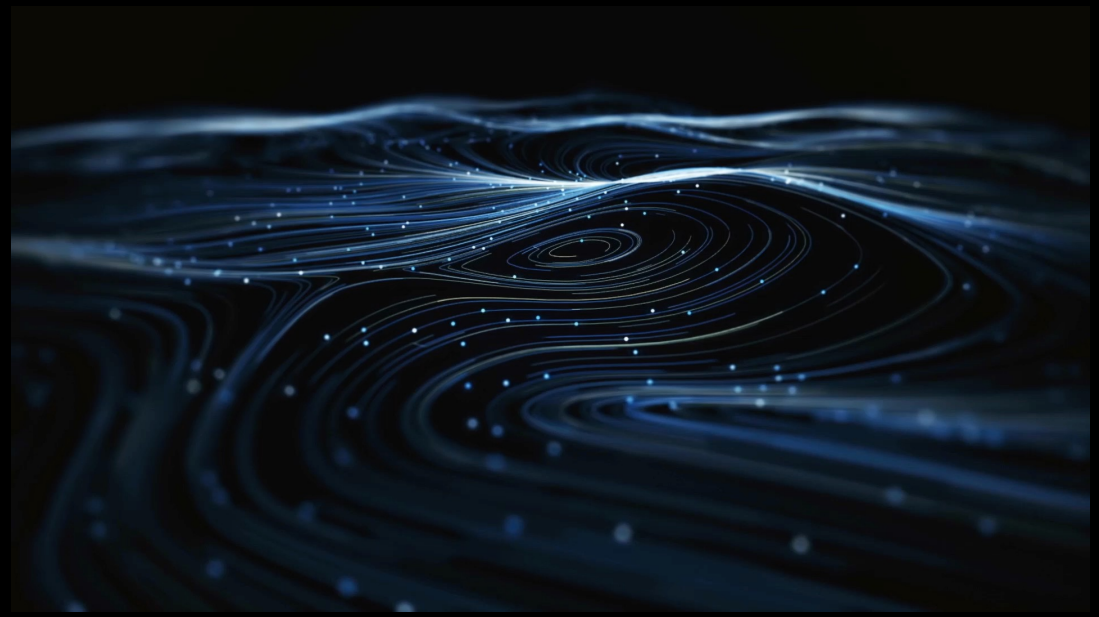
Drug repurposing for a novel disease

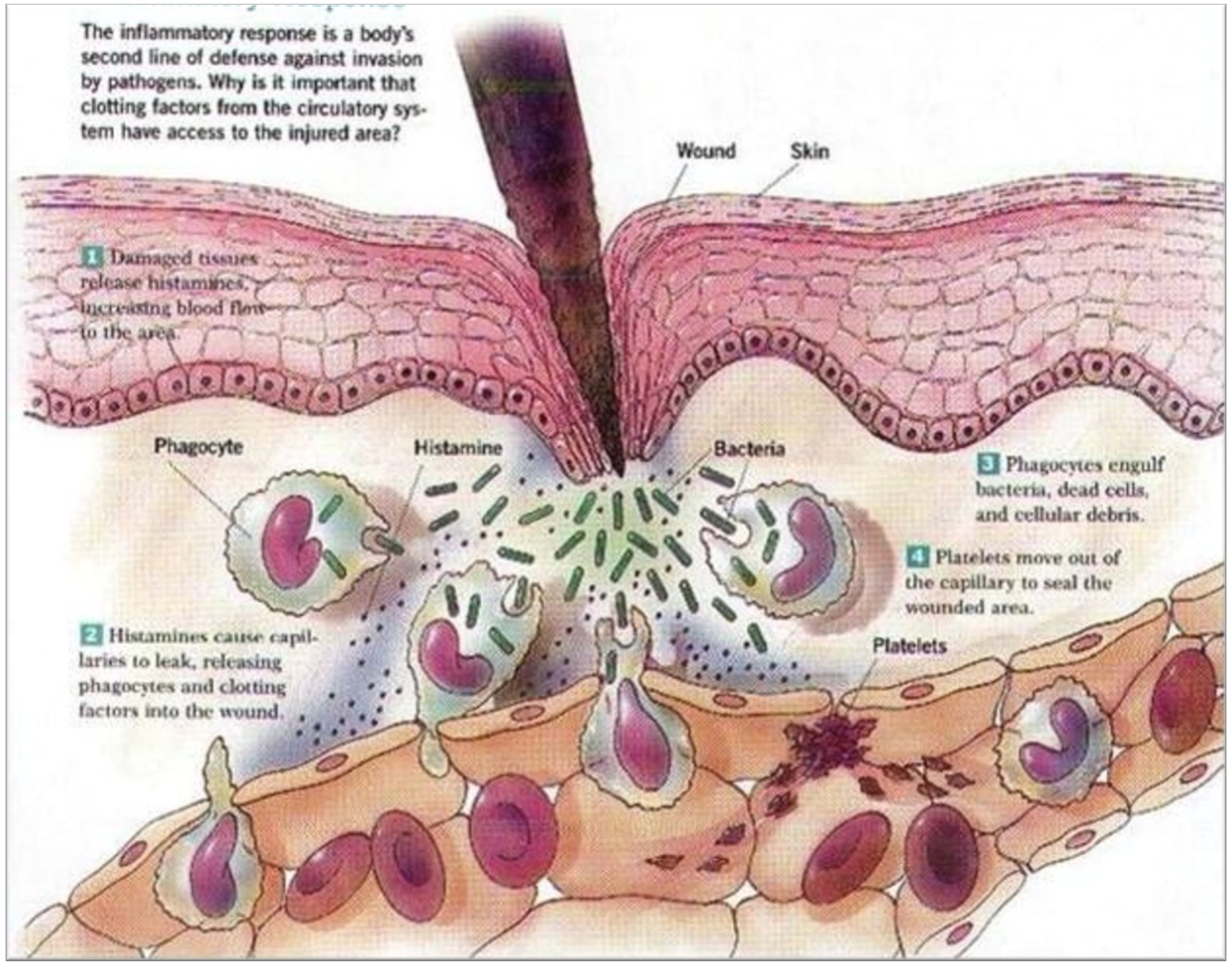
Richard Urso, M.D.



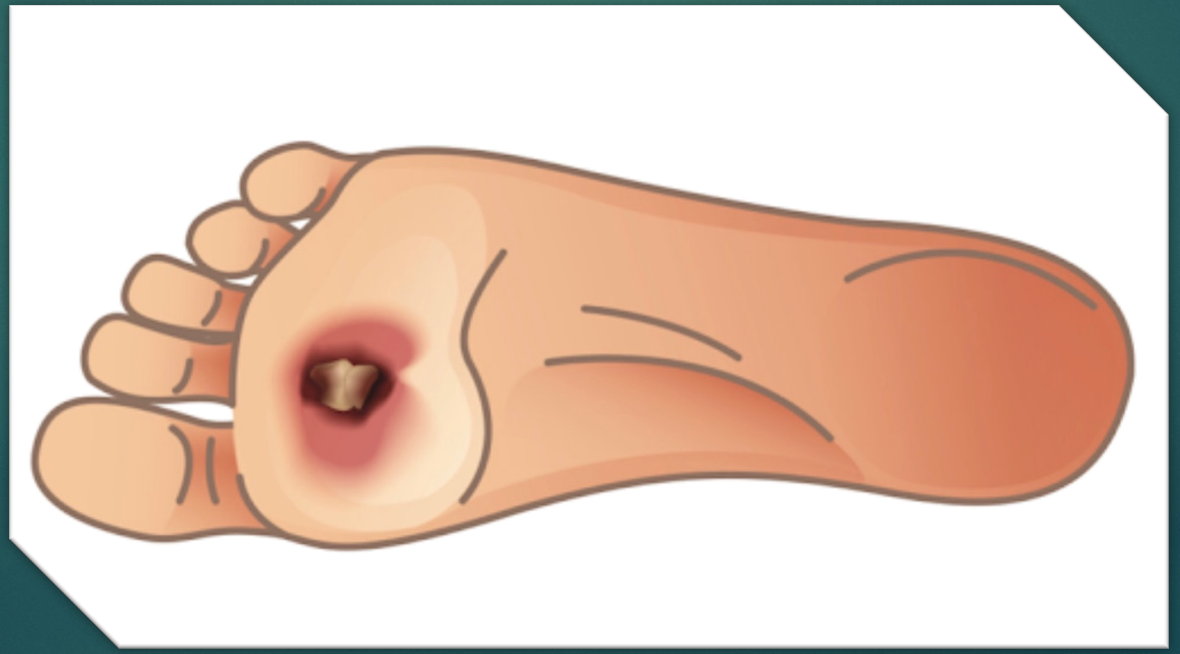
Current regimen for Delta

- IVM and/or HCQ
- Azithromycin
- Prednisone
- Cyproheptadine
- Famotidine
- Montelukast
- Dutasteride
- +/- fenofibrate
- +/- colchicine
- Baby aspirin
- Vitamin D3
- Melatonin

Also: No carb. Broth. Water. Steak. Fish or chicken. No sugar for as long as the patient is on prednisone.



Steps of the Inflammatory Response



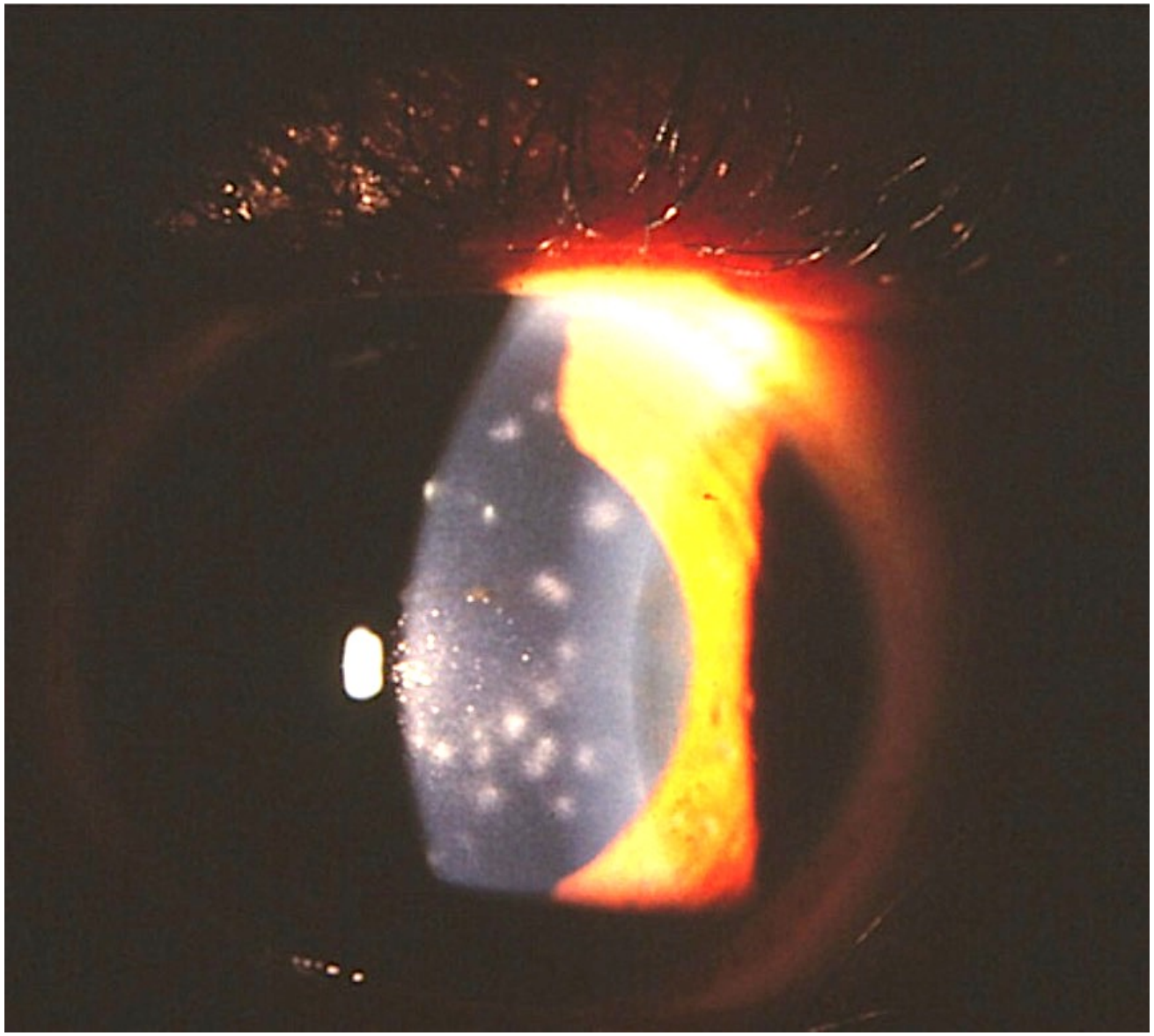
Repurposed drugs

- Eplerenone
- Spironolactone
- Losartan
- Dapsone
- HCQ/CQ
- Cyclosporin
- Macrolide ABX
- Fenofibrate
- Cholecalciferol
- Fenbendazole
- Triamcinolone
- Cyproheptadine
- Mitomycin
- Ivermectin
- Colchicine
- Cromolyn sodium
- Doxycycline
- Nerve Growth Factor

Conditions treated with repurposed drugs

- DR, vascular disease
- Cancer
- Sjogren's
- Fibrosis
- Scarring
- Chronic wounds
- Hordeolum
- Viruses
- Pterygium
- Keratitis
- GVHD
- Epiphora
- MGD
- Keloid

COVID: Biphasic disease



Why steroids for a virus?

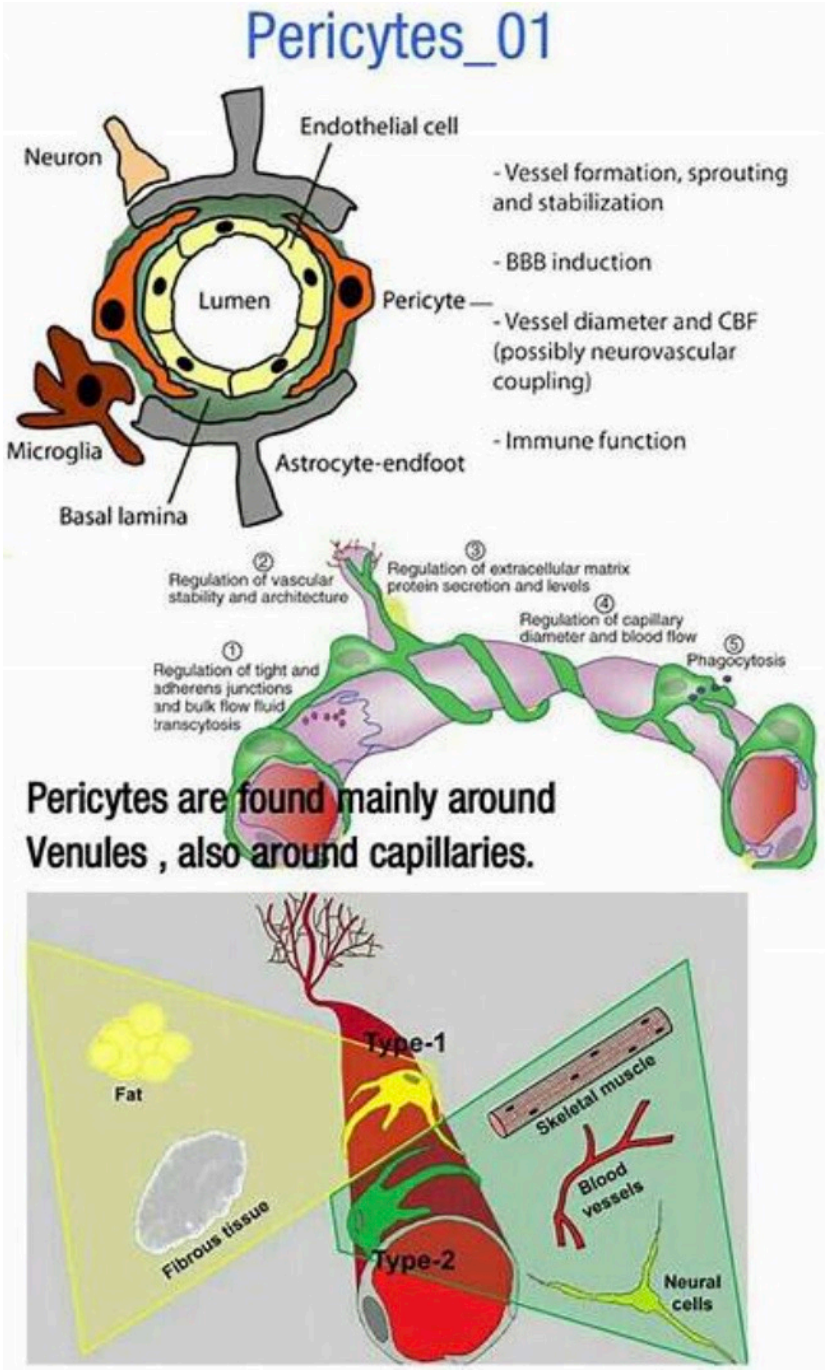
Title: SARS-CoV-2 virus culture from the upper respiratory tract: Correlation with viral load, subgenomic viral RNA and duration of illness.

Authors: Ranawaka APM Perera[1], Eugene Tso[3], Owen TY Tsang[4], Dominic NC Tsang[5], Kitty Fung[3], Yonna WY Leung[1], Alex WH Chin[1], Daniel KW Chu[1], Samuel MS Cheung[1], Leo LM Poon[1], Vivien WM Chuang[2], Malik Peiris[1].

Abstract

In 68 respiratory specimens from a cohort of 35 COVID-19 patients, 32 of them with mild disease, we found SARS coronavirus-2 virus culture and sub-genomic RNA was rarely detectable beyond 8 days after onset of illness although virus RNA by RT-PCR remained detectable for many weeks.

In respiratory specimens of COVID-19 patients mainly with mild disease culturable SARS-CoV-2 and subgenomic RNA (good indicator of replication) was rarely detectable beyond 8 days after onset of illness although virus RNA by RT-PCR remained for up to 70 days.



Outside in or inside out?

Mesenchymal Stem Cells, Fibroblasts and Pericytes: Different Functional States of the Same Cell?.

Dimas T. Covas, MD, PhD, Rodrigo A. Penepucci,
Aparecida M. Fontes, PhD, Maristela Orellana,
Karen L. Prata, MD, Luciano Neder, MD, PhD,
Luiz C. Perez, MD, PhD, Rita C. Carrara, PhD, Amelia G. Araujo,
Marco A. Zago, MD, PhD

Review

Potential Usefulness of Losartan as an Antifibrotic Agent and Adjunct to Platelet-Rich Plasma Therapy to Improve Muscle Healing and Cartilage Repair and Prevent Adhesion Formation

Johnny Huard et al. Orthopedics. 2018.

Editor's Note: This article was published on May 21, 2020, at NEJM.org.

ORIGINAL ARTICLE

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., et al.

The American Journal of Pathology

American Society for Investigative Pathology

COVID-19 Vasculopathy: Mounting Evidence for an Indirect Mechanism of Endothelial Injury

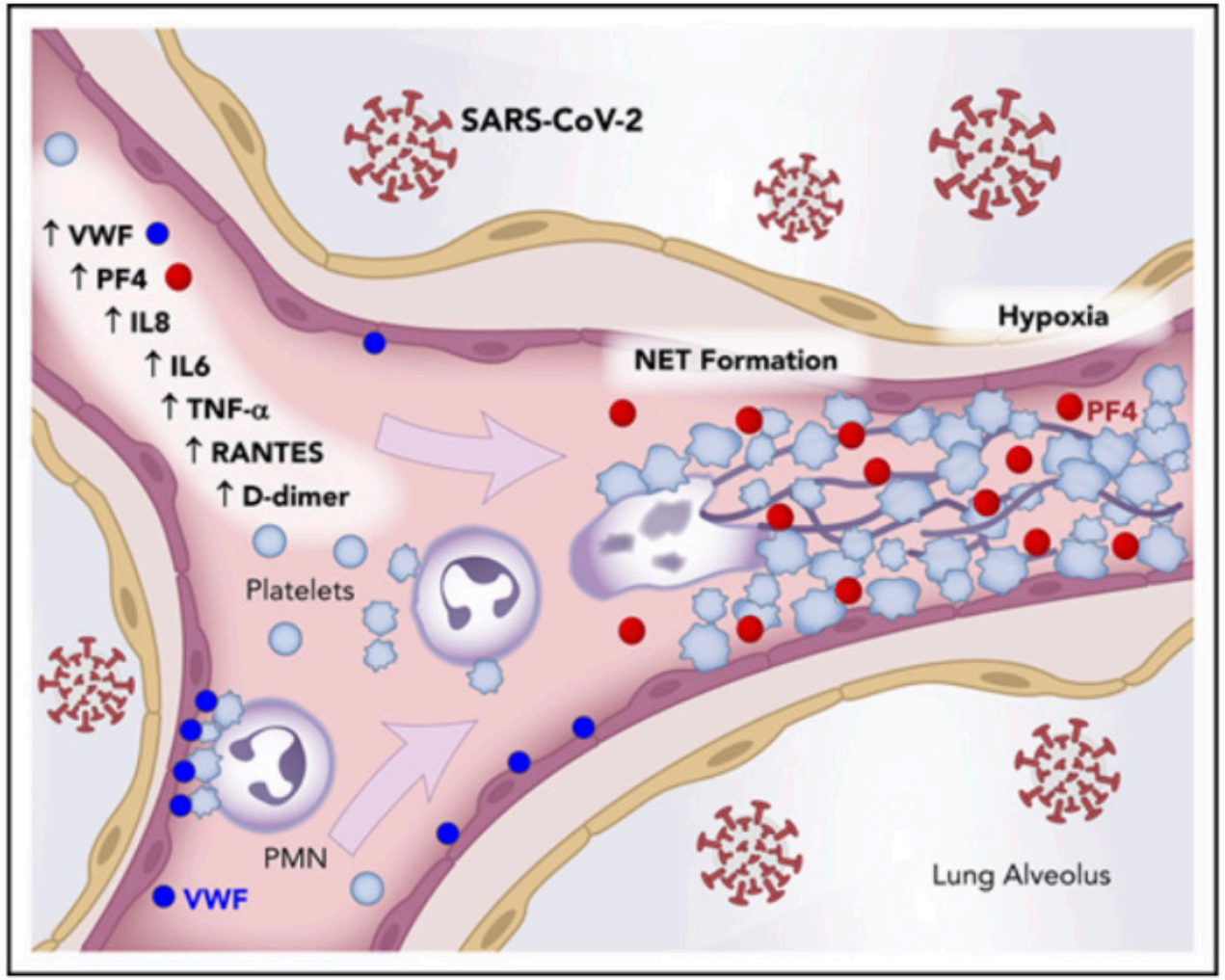
Roberto F. Nicosia, Giovanni Ligresti, [...], and Domenico Ribatti

PHAGOCYTES, GRANULOCYTES, AND MYELOPOIESIS | SEPTEMBER 3, 2020

Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome

Elizabeth A. Middleton, Xue-Yan He, Frederik Denorme, Robert A. Campbell, David Ng, Steven P. Salvatore, Maria Mostyka, Amelia Baxter-Stoltzfus, Alain C. Borczuk, Massimo Loda, Mark J. Cody, Bhanu Kanth Manne, Irina Portier, Estelle S. Harris, Aaron C. Petrey, Ellen J. Beswick, Aleah F. Caulin, Anthony Iovino, Lisa M. Abegglen, Andrew S. Weyrich, Matthew T. Rondina, Mikala Egeblad, Joshua D. Schiffman, Christian Con Yost

Visual Abstract



Pharmacology Research & Perspectives / Volume 5, Issue 1
/ e00293

Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases

Md. Abdul Alim Al-Bari ✉,

In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Xueting Yao, Fei Ye, Miao Zhang, Cheng Cui, Baoying Huang, Peihua Niu, Xu Liu, Li Zhao, Erdan Dong, Chunli Song ... Show more

Author Notes

Clinical Infectious Diseases, Volume 71, Issue 15, 1 August 2020, Pages 732–739,

Cell Discovery

Correspondence | Open Access |
Published: 18 March 2020

Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro

Jia Liu, Ruiyuan Cao, [...] Manli Wang

Cell Discovery **6**, Article number: 16 (2020) | Cite

Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection

Jacques Fantini et al. Int J Antimicrob Agents. 2020 May.

Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19

Bo Yu et al. Sci China Life Sci. 2020 Oct.

Chloroquine reduces hypercoagulability in pancreatic cancer through inhibition of neutrophil extracellular traps

Brian A Boone et al. BMC Cancer. 2018.

The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro

Leon Caly et al. Antiviral Res. 2020 Jun.

The Journal of Antibiotics
Nature Publishing Group

The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article

Asiya Kamber Zaidi and Puya Dehgani-Mobaraki

Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway

Xinxin Ci et al. Fundam Clin Pharmacol. 2009 Aug.

Ivermectin for COVID-19 Treatment: Clinical Response at Quasi-Threshold Doses Via Hypothesized Alleviation of CD147-Mediated Vascular Occlusion

22 Pages
Posted: 1 Jul 2020
Last revised: 22 Aug 2021

David Scheim
US Public Health Service

Date Written: June 26, 2020

Avermectin inhibits neutrophil extracellular traps release by activating PTEN demethylation to negatively regulate the PI3K-ERK pathway and reducing respiratory burst in carp

Shufang Zheng et al. J Hazard Mater. 2020.

Three COVID-19 lung autopsies were examined for NETs and platelet involvement. We assessed NET formation ex vivo in COVID-19 neutrophils and in healthy neutrophils incubated with COVID-19 plasma. We also tested the ability of neonatal NET-inhibitory factor (nNIF) to block NET formation induced by COVID-19 plasma. Plasma MPO-DNA complexes increased in COVID-19, with intubation ($P < .0001$) and death ($P < .0005$) as outcome. Illness severity correlated directly with plasma MPO-DNA complexes ($P = .0360$), whereas Pa_{O_2}/fraction of inspired oxygen correlated inversely ($P = .0340$). Soluble and cellular factors triggering NETs were significantly increased in COVID-19, and pulmonary autopsies confirmed NET-containing microthrombi with neutrophil-platelet infiltration. Finally, COVID-19 neutrophils ex vivo

Review

Azithromycin in viral infections

Madeleine E Oliver et al. Rev Med Virol. 2021 Mar.

Macrolides

- Rhinovirus
- Influenza A
- Zika
- Ebola
- Enteroviruses
- Coronaviruses

Macrolides

IL-6, IL-1B, IL-2, TNF, NF-KB, GM-CSF, MTOR, NF-KB

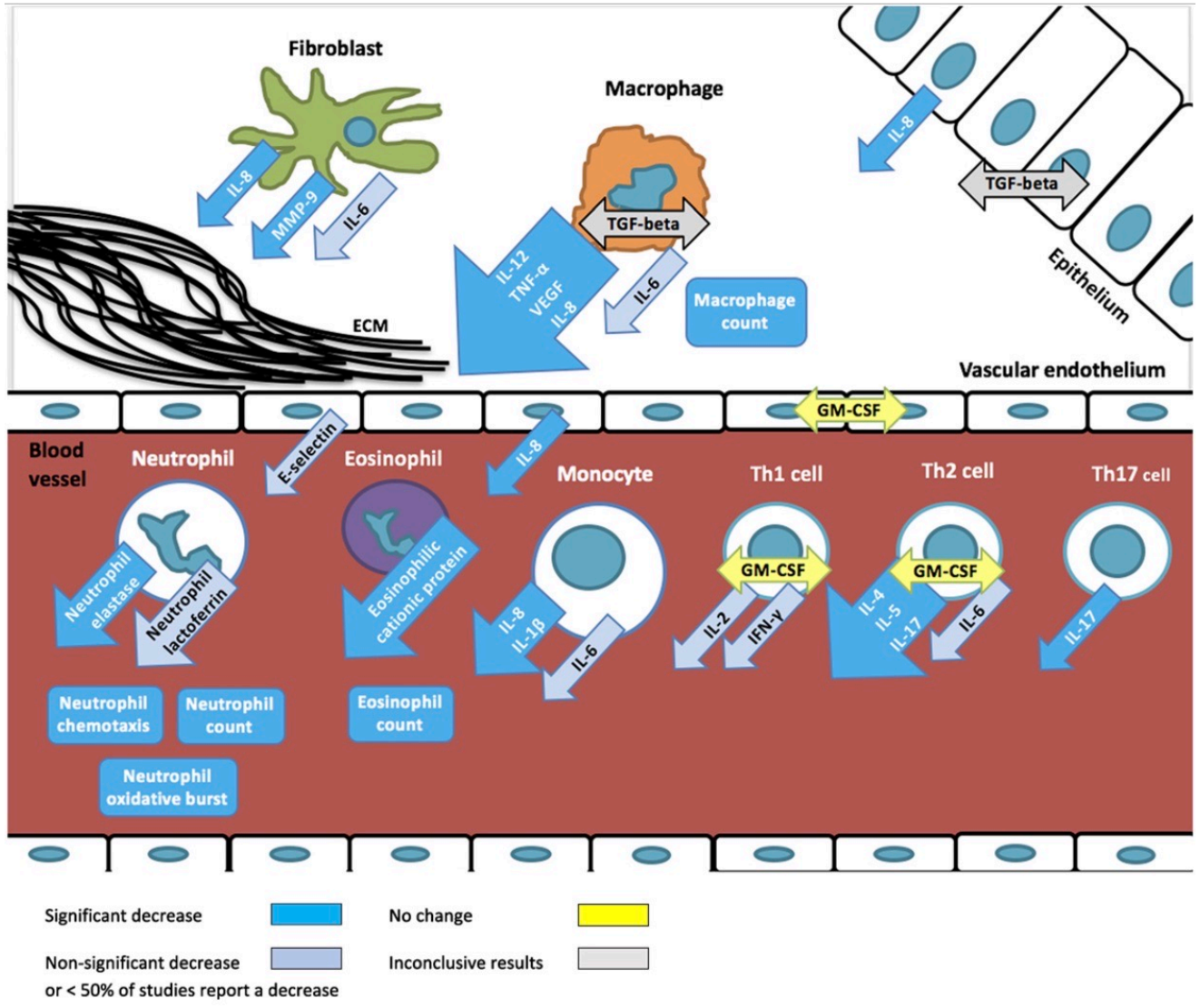
Inhibits T-cells by inhibiting calcineurin signaling

Accumulates in lysosomes affecting adhesion, degranulation, and apoptosis of neutrophils

The Immunomodulatory Effects of Macrolides—A Systematic Review of the Underlying Mechanisms

 Petra Zimmermann[1,2,3,4]*, Victoria C. Ziesenitz[5], Nigel Curtis[1,2,3] and  Nicole Ritz[2,4,5]

[1]Department of Paediatrics, The University of Melbourne, Parkville, VIC, Australia
[2]Infectious Diseases & Microbiology Research Group, Murdoch Children's Research Institute, Parkville, VIC, Australia
[3]Infectious Diseases Unit, The Royal Children's Hospital Melbourne, Parkville, VIC, Australia
[4]Infectious Diseases Unit, University of Basel Children's Hospital, Basel, Switzerland
[5]Paediatric Pharmacology, University of Basel Children's Hospital, Basel, Switzerland


Fibroblast
Macrophage
IL-8
MMP-9
IL-6
TGF-beta
IL-12
TNF-α
VEGF
IL-8
IL-6
Macrophage count
IL-8
TGF-beta
Epithelium
ECM
Vascular endothelium
GM-CSF
Blood vessel
Neutrophil
E-selectin
Eosinophil
IL-8
Monocyte
Th1 cell
Th2 cell
Th17 cell
Neutrophil elastase
Neutrophil lactoferrin
Eosinophilic cationic protein
IL-8
IL-1β
IL-6
GM-CSF
IL-2
IFN-γ
GM-CSF
IL-4
IL-5
IL-17
IL-6
IL-17
Neutrophil chemotaxis
Neutrophil count
Eosinophil count
Neutrophil oxidative burst
Significant decrease
No change
Non-significant decrease
or < 50% of studies report a decrease
Inconclusive results

International Journal of Antimicrobial Agents

Volume 55, Issue 6, June 2020, 106007

Excessive lysosomal ion-trapping of hydroxychloroquine and azithromycin

Hartmut Derendorf ✉

Pulmonary Pharmacology & Therapeutics

Elsevier

Antihistamines and azithromycin as a treatment for COVID-19 on primary health care – A retrospective observational study in elderly patients

Juan Ignacio Morán Blanco, Judith A. Alvarenga Bonilla, [...], and Karina Villar Gómez de las Heras

Cytokine Storm Syndrome in SARS-CoV-2 Infections: A Functional Role of Mast Cells

Bahareh Hafezi, Lily Chan, [...], and Khalil Karimi

Famotidine

Disrupts histamine crosstalk in mast cells, neutrophils, and eosinophils

- Decreases TLR3 leading to decreased IRF3, NF-KB, CCL-2, IL-6

Acts on viral replication proteases and chymotrypsin-like proteases

Inhibits cytokine release

Famotidine inhibits toll-like receptor 3-mediated inflammatory signaling in SARS-CoV-2 infection

Rukmini Mukherjee et al. J Biol Chem. 2021 Aug.

Cyproheptadine

H1 receptor Antagonist

Serotonin antagonist

- Platelets

Anti-cholinergic

Cyproheptadine is an H1 blocking antihistamine, but it also has serotonin receptor blocking activity. Specifically, it acts to block 5-HT1A and 5-HT2A receptors, which are the receptors responsible for the symptoms of serotonin syndrome.

Montelukast/Singulair

Cysteinyl leukotriene receptor antagonist

Suppresses inflammatory cytokine release

- IL-1B + IL-8

Binds the terminal site of the virus primary protease enzyme

The association between obesity and poor outcome after COVID-19 indicates a potential therapeutic role for montelukast

Muhammad Qutayba Almerie et al. Med Hypotheses. 2020 Oct.

Fenofibrate

Anti-viral	• Destabilizes RBD and inhibits binding to ACE2 • Reduced viral infection by 70% in tissue culture
Anti-inflammatory- NF-KB, NRLP3	
Anti-Thrombotic	• Down-regulation of genes in the complement cascade • Inhibits platelet activation and via suppression of thromboxane A2 receptor RAC
Anti-Tumor	• Neuro-ectodermal anti-tumor • Solid tumors

The Hyperlipidaemic Drug Fenofibrate Significantly Reduces Infection by SARS-CoV-2 in Cell Culture Models

Scott P Davies et al. Front Pharmacol. 2021.

Fenofibrate, a PPARα agonist, protect proximal tubular cells from albumin-bound fatty acids induced apoptosis via the activation of NF-kB

Nan Zuo et al. Int J Clin Exp Pathol. 2015.

Article | Open Access | Published: 20 May 2021

Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease

Maheshwar Lakkireddy, Srikanth Goud Gadiga,

[...] Manohar Kandakatla

Complementary Therapies in Medicine

Volume 54, November 2020, 102579

Association between serum vitamin D levels and venous thromboembolism (VTE): A systematic review and meta-analysis of observational studies

Jia Wan [a, 1] ... Yan Chu [a]

Early Antiandrogen Therapy With Dutasteride Reduces Viral Shedding, Inflammatory Responses, and Time-to-Remission in Males With COVID-19: A Randomized, Double-Blind, Placebo-Controlled Interventional Trial (EAT-DUTA AndroCoV Trial – Biochemical)

Flavio A Cadegiani, John McCoy, [...], and Andy Goren

Current regimen for Delta

- IVM and/or HCQ
- Azithromycin
- Prednisone
- Cyproheptadine
- Famotidine
- Montelukast
- Dutasteride
- +/- fenofibrate
- +/- colchicine
- Baby aspirin
- Vitamin D3
- Melatonin

Also: No carb. Broth. Water. Steak. Fish or chicken. No sugar for as long as the patient is on prednisone.

We’re always going to be faced with new and untreatable disorders, and often the answers are already in our toolbox.