

# Zinc

## A Review of Pertinent Drug Information for SARS-CoV-2

**Monica V. Mahoney, PharmD, BCPS AQ-ID, BCIDP**  
**Clinical Pharmacy Specialist, Beth Israel Deaconess Medical Center**  
**[mmahoney@bidmc.harvard.edu](mailto:mmahoney@bidmc.harvard.edu)**

 **@mmPharmD**

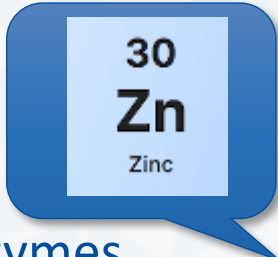
*Data as of Feb 20, 2021*



# Zinc

# Chemistry & Metabolism

- Trace element
- Cellular metabolism:
  - Required for catalytic activity of ~100 enzymes
  - Immune function
  - Protein synthesis
  - Wound healing
  - DNA synthesis
  - Cell division



1 H Hydrogen																	2 He Helium
3 Li Lithium	4 Be Beryllium															10 Ne Neon	
11 Na Sodium	12 Mg Magnesium															18 Ar Argon	
19 K Potassium	20 Ca Calcium	21 Sc Scandium	22 Ti Titanium	23 V Vanadium	24 Cr Chromium	25 Mn Manganese	26 Fe Iron	27 Co Cobalt	28 Ni Nickel	29 Cu Copper	30 Zn Zinc	31 Ga Gallium	32 Ge Germanium	33 As Arsenic	34 Se Selenium	35 Br Bromine	36 Kr Krypton
37 Rb Rubidium	38 Sr Strontium	39 Y Yttrium	40 Zr Zirconium	41 Nb Niobium	42 Mo Molybdenum	43 Tc Technetium	44 Ru Ruthenium	45 Rh Rhodium	46 Pd Palladium	47 Ag Silver	48 Cd Cadmium	49 In Indium	50 Sn Tin	51 Sb Antimony	52 Te Tellurium	53 I Iodine	54 Xe Xenon
55 Cs Cesium	56 Ba Barium	*	72 Hf Hafnium	73 Ta Tantalum	74 W Tungsten	75 Re Rhenium	76 Os Osmium	77 Ir Iridium	78 Pt Platinum	79 Au Gold	80 Hg Mercury	81 Tl Thallium	82 Pb Lead	83 Bi Bismuth	84 Po Polonium	85 At Astatine	86 Rn Radon
87 Fr Francium	88 Ra Radium	**	104 Rf Rutherfordium	105 Db Dubnium	106 Sg Seaborgium	107 Bh Bohrium	108 Hs Hassium	109 Mt Meitnerium	110 Ds Darmstadtium	111 Rg Roentgenium	112 Cn Copernicium	113 Nh Nihonium	114 Fl Flerovium	115 Mc Moscovium	116 Lv Livermorium	117 Ts Tennessine	118 Og Oganesson
			57 La Lanthanum	58 Ce Cerium	59 Pr Praseodymium	60 Nd Neodymium	61 Pm Promethium	62 Sm Samarium	63 Eu Europium	64 Gd Gadolinium	65 Tb Terbium	66 Dy Dysprosium	67 Ho Holmium	68 Er Erbium	69 Tm Thulium	70 Yb Ytterbium	71 Lu Lutetium
			89 Ac Actinium	90 Th Thorium	91 Pa Protactinium	92 U Uranium	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium	103 Lr Lawrencium

# Zinc

# Doses & Toxicity

## Recommended Daily Intake:

Age	Male	Female
0-6 months	2 mg	2 mg
7-12 months	3 mg	3 mg
1-3 years	3 mg	3 mg
4-8 years	5 mg	5 mg
9-13 years	8 mg	8 mg
14-18 years	11 mg	9 mg
19+ years	11 mg	8 mg

## Tolerable Upper Intake Levels:

Age	Male	Female
0-6 months	4 mg	4 mg
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1-3 years	7 mg	7 mg
4-8 years	12 mg	12 mg
9-13 years	23 mg	23 mg
14-18 years	34 mg	34 mg
19+ years	40 mg	40 mg

- N / V / D
- ↓ appetite
- Abdominal cramping
- Headaches
- ↓ copper levels
- Altered iron function
- ↓ immune function



# Zinc Salts

Equivalent to 1 mg  
elemental zinc ...

Zinc acetate ... 2.8 mg  
Zinc gluconate ... 7.14 mg  
Zinc sulfate ... 4.4 mg

## Common Zinc Salt Products

- Zinc gluconate lozenge ... 13.3 mg elemental zinc
- Zinc sulfate 220 mg ... 50 mg elemental zinc



# Zinc & Infectious Diseases

12-month placebo-controlled trial:

## Population



**49**  
**elderly**  
**patients**

## Intervention



**45 mg**  
**zinc/day**  
**vs.**  
**Placebo**

## Results



**Infection**  
**rate:**  
**29% vs. 88%**

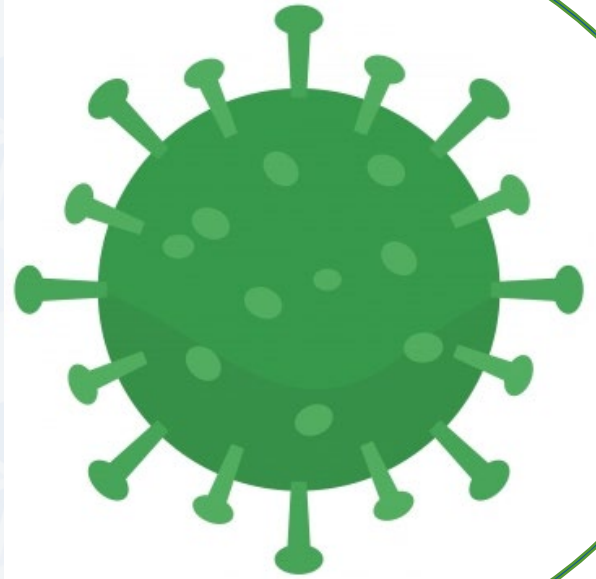
## Infection Types



- **Cold**
- **URI**
- **Fever**
- **Flu**



# The Common Cold



Rhinovirus

Influenza

Adenovirus

Parainfluenza

RSV

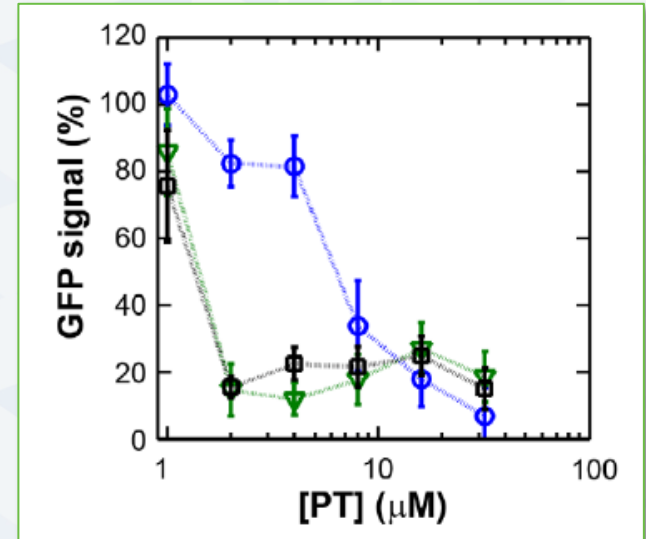
Enterovirus

**Coronavirus**



# Zinc & SARS-CoV

- Pyrithione (PT): zinc ionophore
  - Transports zinc intracellularly
- $\uparrow$  zinc via  $\uparrow$  PT =  $\emptyset$  replication of SARS-CoV
  - RNA synthesis catalyzed by an RNA-dependent RNA polymerase (RdRp)
  - $\emptyset$  RdRp elongation
  - $\downarrow$  template binding



$\uparrow$  PT  $\downarrow$  green-fluorescent protein-marked SARS-CoV.  
Blue = 0  $\mu\text{M}$ ; green = 1  $\mu\text{M}$ ; black = 2  $\mu\text{M}$  ZnOA<sub>2</sub>



# Zinc & Chloroquine

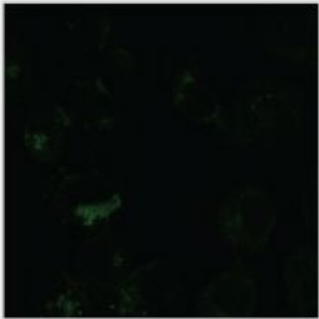
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PLOS ONE

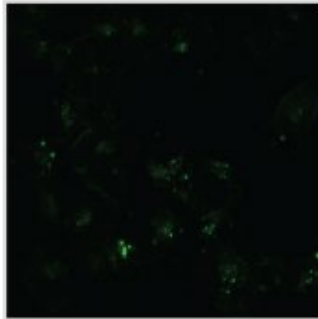
## Chloroquine Is a Zinc Ionophore

- Chloroquine enhanced intracellular zinc uptake
- Zinc enhanced cytotoxic activity of chloroquine

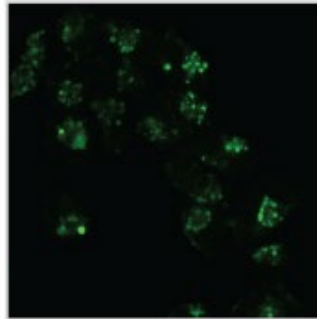
Control



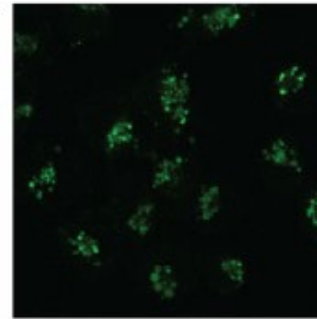
50  $\mu\text{M}$   $\text{ZnCl}_2$



300  $\mu\text{M}$  ChQ  
+5  $\mu\text{M}$   $\text{ZnCl}_2$



300  $\mu\text{M}$  ChQ  
+50  $\mu\text{M}$   $\text{ZnCl}_2$



FluoZin-3

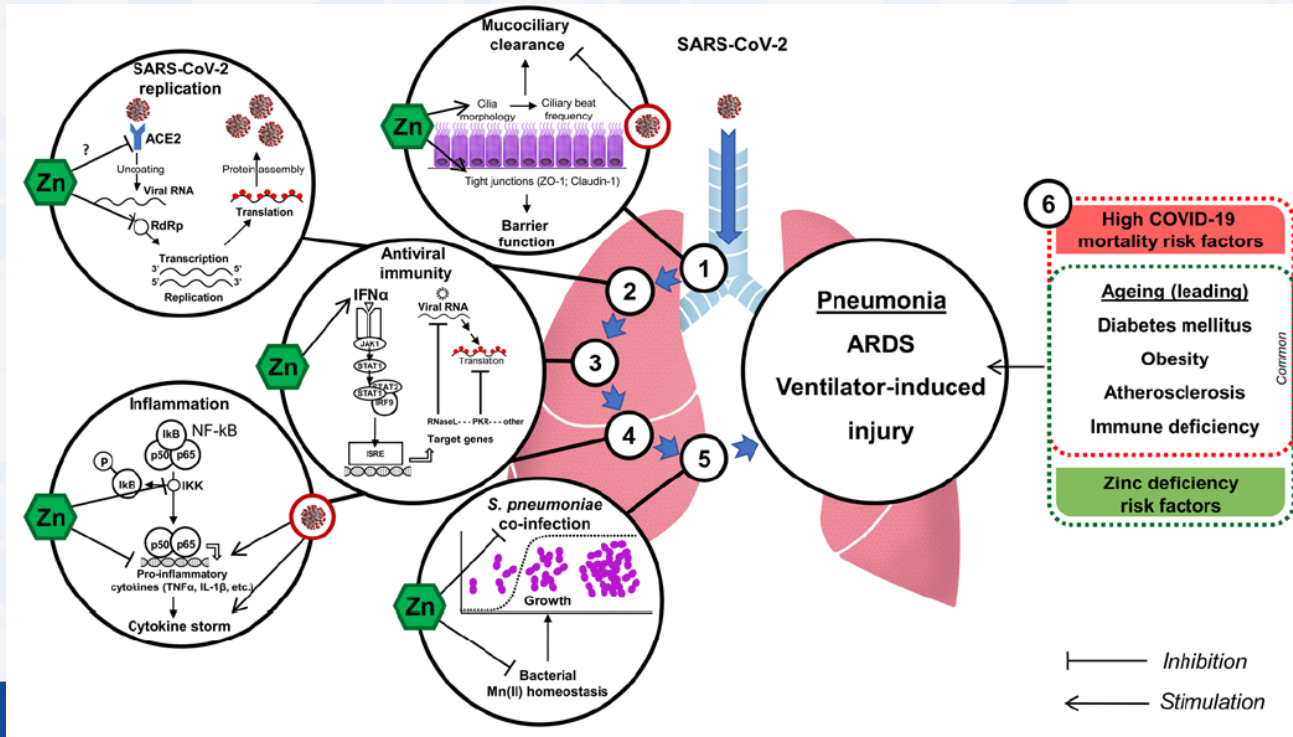
 SIDP

SOCIETY OF INFECTIOUS  
DISEASES PHARMACISTS





# Proposed Mechanisms of Action



# Zinc & COVID-19 Outcomes



Healthy volunteer  
n=45

vs.



COVID-19 +  
n=47

30  
**Zn**  
Zinc

Median:  
105.8 mcg/dL

30  
**Zn**  
Zinc

Median:  
74.5 mcg/dL




# Zinc & COVID-19 Outcomes




Healthy volunteer  
n=45


vs.



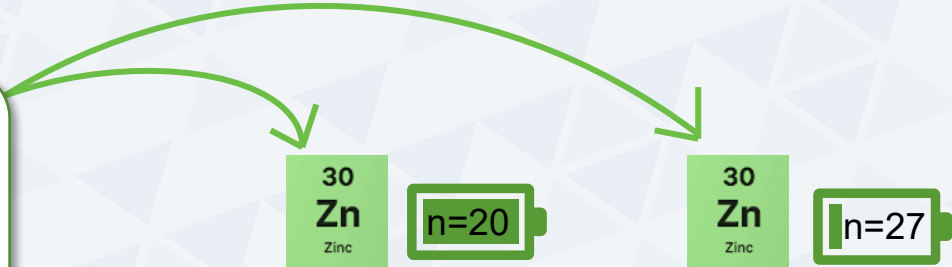
COVID-19 +  
n=47



Median:  
105.8 mcg/dL



Median:  
74.5 mcg/dL



<b>Complications</b>	<b>30.0%</b>	<b>70.4%</b>	<b>p=0.009</b>
<b>Corticosteroids</b>	<b>10.0%</b>	<b>44.5%</b>	<b>p=0.022</b>
ARDS	0%	18.5%	p=0.063
Hypotension	0%	14.8%	p=0.126
Sepsis	0%	3.7%	p=1.0
ICU	10.0%	25.9%	p=0.266
Death	<b>0%</b>	18.5%	p=0.06
<b>LOS &gt;7 days</b>	<b>30.0%</b>	<b>59.3%</b>	<b>p=0.047</b>



SOCIETY OF INFECTIOUS  
DISEASES PHARMACISTS



# Zinc in SARS-CoV-2

+ COVID 19  
Hospitalized



Txt + Zinc (n=196)

Control (n=46)

April 11, 2020

	Txt + Zinc	Control
<b>HCQ</b>	191 (97.4)	32 (69.6)
<b>Lopinavir/ritonavir</b>	114 (58.1)	13 (28.3)
<b>IL-6 inhibitor</b>	71 (36.2)	9 (19.6)
<b>Steroids</b>	56 (28.6)	6 (13.0)



# Zinc in SARS-CoV-2

## ↑ risk of in-hospital mortality:

- Older age
- Male sex
- ↑ severity of illness

## ↓ risk of in-hospital mortality:

- IL-6 inhibitor

**Mortality: Zinc: 37.2% vs. Control: 45.7% (NS)**

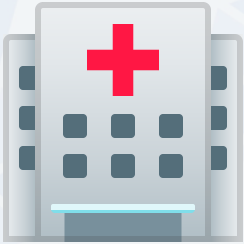
## Conclusion:

*“Our analyses demonstrate the lack of a causal association between zinc and the survival of hospitalized patients with COVID-19”*



# Zinc in SARS-CoV-2

+ COVID 19  
Hospitalized



Hydroxychloroquine + Azithromycin

n=521

HCQ + Azithro + Zinc

n=411

March 2, 2020

March 25, 2020

April 5, 2020

Hydroxychloroquine 400mg x 1 then 200 mg PO BID; Azithromycin 500 mg PO daily; Zinc sulfate 220 mg PO daily; all x 5 days



SOCIETY OF INFECTIOUS  
DISEASES PHARMACISTS

Carlucci PM et al. J Med Microbiol. 2020;69:1228-34. doi: 10.1099/jmm.0.001250



# Zinc in SARS-CoV-2

## Univariate Analysis

- Hospital LOS
- MV duration
- O<sub>2</sub> flow rate
- FiO<sub>2</sub>



## Bivariate Analysis

- ↓ Mortality/hospice  
OR 0.511, 95% CI 0.359-0.726
- ↓ Need for ICU  
OR 0.545, 95% CI 0.362-0.821
- ↓ Need for invasive ventilation  
OR 0.562, 95% CI 0.354-0.891

	<u>Zinc</u>	<u>No Zinc</u>
ICU:	73.6%	74.4%
Ward:	6.9%	13.2%



# Zinc in SARS-CoV-2

## Conclusions:

- Zinc + hydroxychloroquine/azithromycin decreased mortality in a non-ICU population
- Zinc may have a role in preventing progression to severe disease
  - May not be effective once “cytokine storm” occurs
- ***“This study should not be used to guide clinical practice. Rather ... support the initiation of future randomized clinical trials...”***





# COVID A to Z: RCT

+ COVID 19  
Outpatient



Vit C 8000 mg/day

Zinc 50 mg QHS

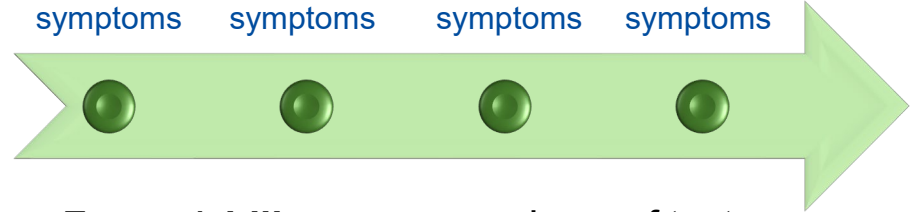
Both therapies

Usual care

Day 28

## Weekly Symptom Questionnaire

0 no symptoms    1 mild symptoms    2 moderate symptoms    3 severe symptoms



- Fevers/chills
- Shortness of breath
- Cough
- Fatigue
- Muscle/body aches
- Headache
- Loss of taste
- Loss of smell
- Congestion/runny nose
- Nausea
- Vomiting
- Diarrhea



# COVID A to Z: RCT

## Results:



Interim Analysis @ 40% = Terminated for Futility

**Primary Endpoint: Time (days) to 50% ↓ symptom severity score**

<u>Vit C:</u>	<u>Zinc:</u>	<u>Both:</u>	<u>Usual:</u>
5.5 days	5.9 days	5.5 days	6.7 days

## Conclusions:

*“The addition of vit C, zinc, or both did not shorten the duration of COVID-19 symptoms”*



# Current Zinc-COVID-19 Trials

## Treatment:

### NCT04392427

- Nitazoxanide
- Ribavirin
- Ivermectin
- Zinc

### NCT04641195

- Zinc
- Vit D

### NCT04342728

- Zinc
- Vit C

### NCT04468139

- Quercetin
- Bromelain
- Zinc
- Vit C

### NCT04558424

- Zinc
- Vit C

### NCT04323228

- Vit A
- Vit C
- Vit E
- Selenium
- Zinc

### NCT04621461

- HCQ
- Azithromycin
- Zinc

### NCT04323228

- Vit C
- HCQ
- Azithromycin
- Zinc
- Vit D
- Vit B12

### NCT04584567

- Zinc
- Vit D

### NCT04542993

- Zinc
- Resveratol

### NCT04507867

- Nutritional supplement (with zinc)

## Prophylaxis:

### NCT04551339

- Zinc

### NCT04335084

- HCQ
- Zinc
- Vit C
- Vit D

### NCT04584567

- Doxycycline
- Zinc

### NCT04590274

- HCQ
- Zinc
- Azithromycin
- Vit C
- Vit D
- NAC
- Elderberry
- Quercetin

### NCT04446104

- HCQ
- Ivermectin
- Zinc
- Vit C
- Povodine iodine

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- N / V / D
- ↓ appetite
- Abdominal cramping
- Headaches
- ↓ copper levels
- Altered iron function
- ↓ immune function



# Zinc

# Drug Interactions

- Zinc is a polyvalent cation – caution with oral co-administration
- **HIV medications:** bicitgravir, dolutegravir, elvitegravir, raltegravir
- **Antibiotics:** quinolones, tetracyclines
- **Diuretics:** (chlorthalidone, hydrochlorothiazide) may ↑ urinary zinc excretion
- ↑ iron may ↓ zinc
- ↑ zinc may ↓ copper



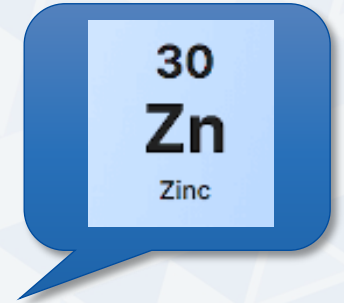
# COVID-19 Guidelines

Guideline	Zinc	Citation
IDSA (Infectious Diseases Society of America)	<b>No mention</b>	<a href="https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/">https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/</a>
WHO (World Health Organization)	<b>No mention</b>	<a href="https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected">https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected</a>
SCCM (Society of Critical Care Medicine – Surviving Sepsis Campaign)	<b>No mention</b>	<a href="https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US">https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US</a>
NICE (National Institute for Health and Care Excellence)	<b>No mention</b>	<a href="https://www.nice.org.uk/covid-19">https://www.nice.org.uk/covid-19</a>
NIH (National Institutes of Health)	<ul style="list-style-type: none"><li>• <b>Txt: insufficient data</b></li><li>• <b>Ppx: remain within RDA dosing</b></li></ul>	<a href="https://covid19treatmentguidelines.nih.gov/introduction/">https://covid19treatmentguidelines.nih.gov/introduction/</a>



# Summary

- Zinc is a trace element
- Body of evidence in COVID-19:
  - 2 retrospective studies → *no appreciable benefit*
  - Additional studies pending
- National treatment guidelines → *do not recommend use*



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