Evidence-Based Review of Natural Medicine: Focus on Respiratory Infections

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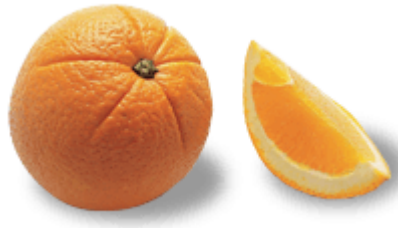
COVID-19, Respiratory Infections & Supplements?

- Many questions from both physicians and patients
  - Misleading and confusing information on web
- No proof to prevent or treat COVID-19
- This winter: pts have high concern about getting respiratory infections
  - Using many supplements currently: Questions every week
- Review data available: supplements for respiratory infections
- Adult focus
  - Some studies happen to include children: incidental, not a pediatric review

Vitamin C

- Water soluble vitamin
- Important for normal immune function
  - Vitamin C levels up to 100 x greater in WBC than in plasma
  - Lymphocyte activity, phagocyte function, leukocyte mobility
- Anti-inflammatory
  - Preclinical research:
  - ?Vitamin C decrease cytokine surge in early sepsis
    - Cytokines activate/sequester neutrophils in lung & contribute to acute respiratory distress syndrome (ARDS)
    - Fowler; JAMA 2019

Vitamin C: Oral Studies



- Scand J Infect Dis 1994
  - Systematic review of 21 RCT
  - Prevention: No change in incidence URIs
  - Acute: Decrease severity sx & duration of episodes about 23%
  - Inconsistent quality
- J Manipul Physiol Ther 1999
  - RCT 715 students (<32 yo)
  - If sx URI: vitamin C 1000 mg q 1 hr x 6 hr, then 1000 mg tid vs. control
  - Vitamin C: 85% drop in symptoms

Vitamin C: Oral Studies

- Cochrane Database Sys Rev 2013
  - Meta-analysis 29 RCT 11,306 pts
    - 5 trials w/ 598 marathon runners, skiers and soldiers on subarctic exercises:
    - Prevention: 45% lower risk URI; useful for brief periods severe exercise
  - General pop: Not helpful for routine prevention, but taken acutely may help
  - Acute:
  - Duration colds:
    - Adults: drop by 8% (3% to 12%)
    - Children: drop by 14% (7% to 21%)
  - Severity also improved

IV Vitamin C: Hospitalized Patients

- J Intensive Care 2020
  - Meta-analysis 8 clinical trials 687 mech vent pts: IV vit C (no combinations)
  - Dosage 1-6 g/day IV vitamin C
  - If ventilated >10 hr, decrease ventilation time average 25%
- Caveats:
  - Wide variety of pt situations: cardiac, burns, sepsis (2)
  - Study quality variable, dosing variable

IV Vitamin C

- Higher quality, more recent study, on ARDS w/ just vitamin C

- JAMA 2019
  - Multicenter DB RCT 167 pts w/ sepsis & ARDS <24 hours
  - IV vitamin C 50 mg/kg q6 hr vs placebo x 96 hours
  - No change in primary outcomes: CRP & organ failure scores
  - Secondary outcomes:
  - Mortality: 46.3% placebo vs. 28.8% vitamin c
  - ICU-free days: 10.7 vitamin C vs. 7.7 placebo
  - Transfer out of ICU by 168 hour: 25% vitamin c vs. 12.5 % placebo
    - Clinically significant

Vitamin C

- **Dose:**
  - Acute: 2-3 grams/day orally during sx (6 g x 1 d, then 3 g/d)
  - Prevention: data does not support
  - NIH: insufficient evidence currently regarding COVID-19

- **Side Effects:**
  - Oral:
    - Above 2 g/day- increase in GI side effects (Nausea, diarrhea, heartburn)
    - May increase risk kidney stones
  - IV:
    - Theoretical risk: IV clots in cancer pts
    - G6PD: hemolysis
    - False read for diabetics on glucometer above 15g/d IV
      - Case report of false high glucose at 10 g/day orally
      - Blood hexokinase serum glucose not affected

Zinc: Mechanism of Action

- Important for immune function
- Wound healing & resistance to infection
- Inhibits replication of a SARS-coronavirus **in vitro**
  - Te Velthuis AJ, PLoS Pathog 2010 Nov 4; 6 (11)

- 300 different enzymes: reproduction, growth & development, thyroid etc.
- Found in meat/seafood/dairy/nuts/legumes
  - Phytates can bind

Zinc Deficiency

- Elderly – especially in nursing home
- Vegetarian
- Medications:
  - ACE inhibitors/ARB
  - Thiazide diuretics
  - Acid blockers (PPI etc)
- Medical issues: diarrhea etc.
- Adult US RDA: 11 mg

Zinc: Treat Upper Respiratory Infection

- Ann Int Med 1996
  - DB RCT 100 employees Cleveland Clinic URI w/in 24 hr
  - Zinc gluconate lozenge 13.3 mg q 2hr vs. placebo during sx
  - Zinc: shorter duration of sx (approx 40%)
- J Int Med Res 1992
  - DB RCT 73 young adults: lozenge shortened duration about 50% vs. placebo
- J Antimicrob Chemother 1987
  - DB RCT 57 pt inoculated w/ rhinovirus: zinc gluconate lozenge 23 mg q2hr for 4.5 d vs. placebo
  - Zinc:
  - Decreased likelihood of infection
  - Shortened duration of sx

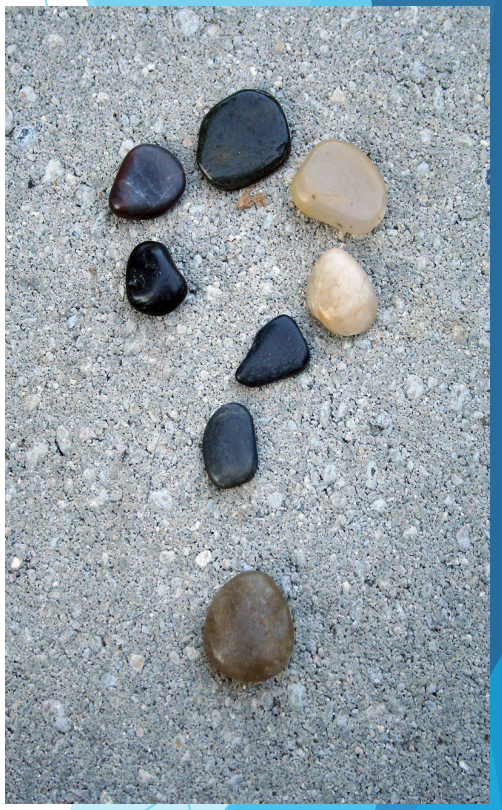
Zinc: Prevention in Elderly

- Low zinc status common in elderly, worse in nursing home
- Nutr Rev 2010
  - 578 pts in 33 nursing homes categorized by low <70 or NL > 70 ug/dl zinc levels x 1 yr
  - NL zinc:
    - **50% lower ABX use; Lower incidence & Shorter duration PNA**
    - **All cause mortality 39% lower**
- Ann Nutr Metab 1997
  - DB RCT 81 elderly pts at geriatric center x 2 yrs
  - Placebo **vs**. selenium 200 mcg/zinc 20 mg **vs**. vit c 120 mg/b carotene 6 mg/a tocoph 15 mg **vs** combin
- >75% of patients: Baseline low: vit C, folate, selenium, zinc
- Zinc: less infectious events x 2 years

Zinc: Dose and Side Effects

- Dose:
  - Acute: zinc acetate/gluconate lozenge 9-24 mg q 2 hr during symptoms x 4 days
    - Avoid other lozenge with mannitol/sorbitol: decrease ionization
    - Max dose per day 40 mg in adults & only for 5 days
  - Prevention in deficiency: zinc gluconate 20 mg/day
  - NIH: insufficient evidence currently regarding COVID-19
- Side effects:
  - Do not use zinc nasal spray: anosmia
  - Lozenge: bad taste, nausea
  - Zinc >40 mg/day: copper deficiency

Bottom Line: Vitamin C & Zinc



- Vitamin C: acutely may benefit URI
- Vitamin C: data does not support prevention except in extreme athletes

- Zinc: acutely may benefit
- Zinc: data for elderly for prevention (including in nursing home), especially if deficient

- Must start as soon as possible

Elderberry

- Sambucus nigra:
  - Medicinal
  - Found on east coast and Europe
- Sambucus racemosa
  - Native to Pacific northwest
  - Not used medicinally
- Berries must be cooked

Elderberry: Mechanism of Action

- Kills several different strains of influenza, including H1N1 “swine flu” in vitro
- ?Concern about increasing cytokines
  - Eur Cytokine Netw. 2001 Apr-Jun;12(2):290-6
- However, also study suggesting decreases cytokines
  - Phytomedicine. 2016 Oct 15;23(11):1198-210
- High in anthocyanins
  - Anti-inflammatory; antioxidant; quench free radicals
    - Food Nutr Res. 2017; 61(1): 1361779

Elderberry: Acute Respiratory Infection

- J Altern Complement Med. 1995
  - DB RCT 27 children/adults w/ flu:
    - Sambucol 2 tbsp/d (child); 4 tbsp/d (adult) x 3 d
  - Decrease sx by >91%, including fever
  - Resolved sx in 2 days (vs. 6 days placebo)

- J Int Med Res. 2004
  - DB RCT 63 adults w/ flu:
  - 15 ml elderberry syrup 4x/d vs. placebo x 5 d
  - Drop duration symptoms by 56% vs placebo
  - Less rescue medication

Elderberry: Acute Respiratory Infections

- Curr Ther Res Clin Exp 2015
  - DB RCT multicenter 473 pt
  - Oseltamivir 75 mg bid 5 d vs. Echinaforce Hotdrink 10 d
  - Similar efficacy
  - Elderberry juice combination product

- Online J Pharmacology and Pharmacokinetics 2009
  - DB RCT 64 adults w/ flu 175 mg elderberry lozenge qid vs. placebo x 2 d
  - Elderberry: Drop fever, HA, muscle ache, cough, nasal congestion sx
  - At 2 days: 28% complete resolution in elderberry; 0% in placebo

Elderberry:
Travel and Respiratory Infections

- Nutrients 2016
  - DB RCT 312 adults on international flight
  - Elderberry cap: 600 mg 8 d prior & 900 mg during - 5 d after vs placebo
  - Drop severity URI by 58%
  - Drop duration by about 2 d

Elderberry: Dose and Side Effects

- **Dose:**
  - Range in product quality
  - Sambucol in studies N/A: Sambucol Black Elderberry syrup 1 tbsp 4x/d at onset sx
  - New Chapter: Elderberry Force: met USP standards: 335 mg/cap
    - Consumerlab.com
- Must start asap: ideally within first day
- **Side Effects:**
  - Do not consume raw berries:
    - Cyanogenic glycosides inactivated by cooking
  - Diarrhea, nausea
  - Allergy (elderberry flower)

Probiotics: General Information

- Living microbes: provide benefit to host
- Respiratory infections:
  - Lactobacillus and Bifidobacteria: most studies
- Mechanism
  - Block pathogenic organisms from binding and growing
  - Modulate non-specific cellular and humoral immunity
  - Secrete chemicals to kill pathogens: bacteriocins, H2O2, lactic acid, acetic acid
    - L plantarum in mice ->H1N1 influenza virus: drop lung viral load; increase survival
      - Int Immunopharmacol 2009 Aug; 9(9)
    - L casei Shirota -> antiviral against coronavirus causing GI sx known as TGEV
      - Int J Food Microbiol. 2010 Jul 31;141 Suppl 1:S91-7

Probiotics:
Prevention of Respiratory Infections

- Cochrane Database Syst Rev 2015
  - Meta-analysis 12 RCT 3720 pts
  - Drop number acute respiratory infx
  - Shorter duration, less antibiotic use

- Cochrane Database Syst Rev 2011
  - Decrease odds of 3 or more acute respiratory infx by 43%

Probiotics:
Prevention of Respiratory Infections

- BMJ 2001
  - DB RCT 571 healthy children ages 1-6 yo x 7 months
  - Culturelle (specific Lactobacillus) vs. placebo (added to milk)
- Probiotic:
  - 16% drop in incidence of respiratory infections
  - 17% drop in incidence of complicated

    upper respiratory infections and lower respiratory infections
  - 19% drop in need for antibiotics

Probiotics:
Prevention of Respiratory Infections

- Pediatrics 2009
  - DB RCT of 80 school children (8 – 13 yo)
  - Lactobacillus + HOWARU Bifido vs placebo x 3 months
- Probiotic:
  - Drop risk of fever/cough/rhinorrhea by 45% vs. placebo
  - Shorter duration of symptoms; less school absence

- Eur J Nutr 2017
  - RCT 96 male workers (aged 30-49yo)
  - Lactobacillus casei strain Shirota-fermented milk vs. placebo x 12 wks
- Probiotic:
  - Drop incidence of respiratory infection by 26.3%
  - Shorter duration of symptoms by 2.2 days

Probiotics: Dose and Side Effects

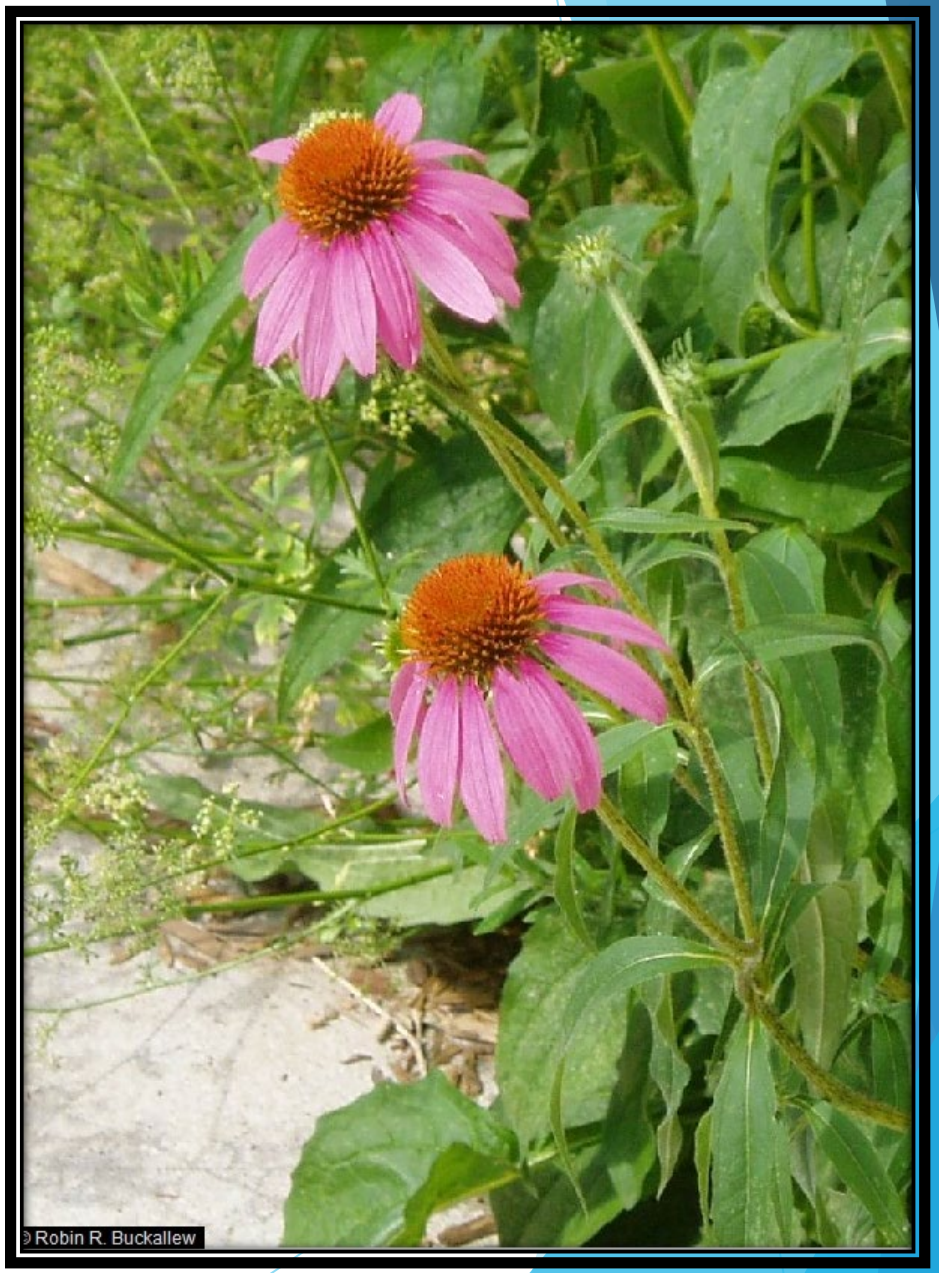
- **Dose:** 1- 5 billion/d for URI prevention
- **Side effects**
  - Well tolerated
  - Gas/bloating in first few days
  - Quality matters:
    - Examples of standardized species probiotics w/ studies:
      - Culturelle (Lactobacillus GG)
      - HOWARU (Bifidobacteria)
      - Shirota probiotic (Yakult) (Lactobacillus caei Shirota)

Bottom Line: Elderberry & Probiotics

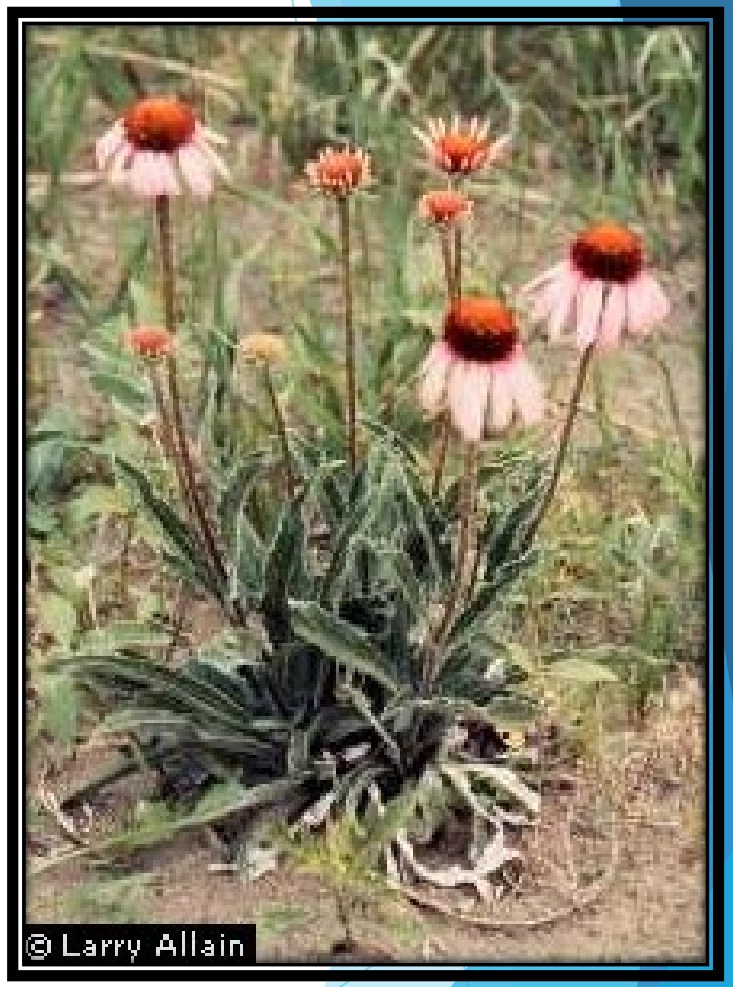
- Elderberry:
  - Acute: may benefit
  - Prevention: may benefit on plane flight to decrease symptoms if they develop
  - Need to start right away
- Probiotics:
  - Acute: may benefit
  - Prevention: may benefit

Echinacea: General

- Native to the USA
  - E. pallida, E. purpurea, E. angustifolia
- In vitro, kills enveloped viruses:
  - ie. RSV, coronavirus, influenza virus
    - Evid Based Complement Alternat Med 2012;2012
- Modulate non-specific and specific immune response
  - Macrophage phagocytosis
- Anti-inflammatory



Echinacea: Respiratory Infections



- Lancet Infect Dis 2007
  - Meta-analysis 14 RCT
  - Decrease odds URI by 58% and duration by 1.6 days
- Clin Ther 2006
  - Meta-analysis 3 RCT on experimentally induced URI (rhinovirus)
  - Dropped incidence by 45%
- Cochrane Database Syst Rev 2014
  - Meta-analysis 24 DB RCT 4631 pts
  - Heterogeneous: possible benefit for prevention of 10-20%
- Studies: wide variety of dose, product type, plant part, schedule used

Echinacea: Respiratory Infections

- Evid Based Complement Altern Med 2012
  - DB RCT 755 pts Echinaforce 0.9 ml tid (2400 mg) vs placebo x 4 mo
  - Increase to 5x/d (4000 mg) if sx URI
  - Drop number of colds: 59%
  - Drop duration of cold symptoms: 26%
- Experimentally induced colds:
  - Prevented colds 2/3 studies, but small sample size: not reach significance
- Treating colds, data controversial

Echinacea: Dose

- Safety?
  - Well tolerated
  - Theoretically: not if autoimmune condition
  - Allergy – daisy family
- Dose:
  - Prevention:
  - Echinaforce (A. Vogel) 0.9 ml tid (2400 mg/d)
  - Not clear for treatment

Vitamin D: Sunshine Vitamin

- Fat soluble vitamin/hormone derived from sun
- Food generally poor source, even fortified: fatty fish (mackerel, tuna etc)
- Respiratory:
  - Higher levels correlate w/ better pulmonary fxn (FEV1)
  - Decrease immune mediated inflammation of airway
    - Chest. 2005 Dec;128(6):3781

Vitamin D

- BMJ 2017
  - Meta-analysis 25 RCT 11,321 pts
    - Reduced odds of acute respiratory tract infections **in all pts** by 12% vs. placebo
    - Daily or weekly vitamin D more effective than 1x/month
    - Greatest effect in most deficient: if serum <25 nmol/L, drop odds by 42%
- Am J Clin Nutr 2010
  - DB RCT 167 children (6-15 yo) 1200 IU vit D vs. placebo x 4 mo
  - Drop risk influenza A or asthma by 42%
- Ann Int Med 2012
  - Vitamin D decreased COPD exacerbations by 43% vs placebo (if serum <10 ng/ml)

Vitamin D

- D2 (ergocalciferol) and D3 (cholecalciferol) are not equivalent
  - D2: 1/3 less potent than D3
  - Serum levels fall back to baseline quickly with D2
    - J Clin Endocrinol Metab 2004
- Dose:
  - Adult: 600-800 IU/day (US RDA); some studies: 1000 IU/day (25 mcg)
  - Upper limit: 4000 iu/day (unless malabsorption)
    - Convert to mcg = divide by 40
  - Level: best to test 25 OH vitamin D (most stable): >32 - 100 ng/ml
  - NIH: insufficient evidence currently regarding COVID-19
- Side Effects
  - Above >100 ng/ml: hypercalcemia and consequent issues, Atrial fibrillation

Bottom Line: Echinacea & Vitamin D

- Echinacea: studies are very mixed quality
  - May be some benefit for prevention
- Vitamin D:
  - If deficient, increases risk for respiratory infections
  - Regular dosing daily or weekly best
  - Use vitamin D3 – more effective (not ergocalciferol/vitamin D2)

Less Well Known: Brewer's Yeast

- Yeast high in nutritional value easily found OTC

- Moyad MA. J Altern Complement Med. 2010 Feb;
  - DB RCT 112 pts with no recent influenza vaccine 500 mg brewers yeast (Epicor) vs. placebo x 12 weeks
  - **Decrease incidence of URI or influenza by 10-20% over 12 weeks**
  - No change in severity of symptoms
- Side Effects
  - Well tolerated and safe – considered a food
  - Contraindicated with MAO inhibitors b/c of tyramine

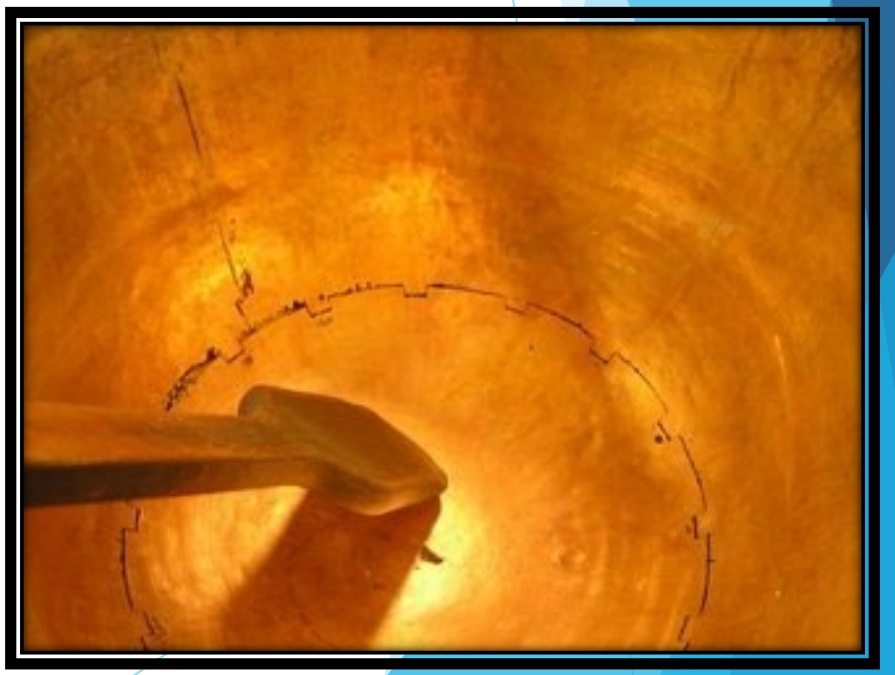
Avoid

- Colloidal silver
  - Solution of silver particles:
    - “Blue man syndrome”
    - Chronic use:
      - Permanent grayish color skin, seizure, leukemia

- “Miracle Mineral Solution”
  - 28% sodium chlorite with water = drinking bleach
    - Nausea, vomiting, diarrhea, death

Data Suggests Ineffective

- Vitamin A
  - No decrease in respiratory infections (children)
    - J Pediatr. 2003: meta-analysis 9 RCT; Cochrane Database Syst Review 2008
  - No decrease severity or incidence pneumonia
    - Bull World Health Organ. 1995: large scale meta-analysis by WHO
  - Liver injury etc. (preformed vitamin A)
    - Adult UL: 10,000 IU/d retinol/retinyl ester; child: age dependent
- Copper
  - No data for respiratory illness
  - Adult UL:10 mg/d; child: age dependent
  - Liver damage



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