### **Common and Complicated Infections: When Antibiotics Fail**

### Darin Ingels, ND, FAAEM



# Fundamentals of Infection

Questions to ask yourself when you have a patient who is prone to chronic infections:

- What is it about this person that disposes him or her to these 1. infections?
- 2. What is in their environment that may create imbalance in the body's ecosystem?
- 3. What lifestyle factors are harming the patient and setting them up for illness?
- 4. What microbes are normally present in the tissues where they have the most weakness and get ill?
- 5. Is the infectious agent truly foreign or part of us?
- 6. Do we need to treat the infection or just support the immune system?

# Fundamentals of Infection

Infection is caused by the invasion and replication of microbes, the production of endogenous toxins produced by the microbe or the immune response to the microbe. Remember...there are 10X's as many microbes as cells in our bodies!

Symptoms may be precipitated by:

- Bacteria
- Viruses
- Fungi or yeasts
- Parasites
- Arthropods
- Prions
- Others?

Most of the symptoms associated with infection is the immune reaction to the infection.

### Fundamentals of Infection

We are exposed to microbes *all of the time*.

We get "infected" through eating food and drinking fluids, brushing our teeth, sexual activity, touching everything around us, breathing, etc.

Tissues one believed to be sterile, such as the bladder or small intestine are now known not to be sterile. Have we inadvertently become too sterile? Has loss of beneficial microbes actually predisposed toward persistent or chronic infections? Has the overuse of antibiotics wiped out our protective microbes?

Read "The Dirt Cure" by Dr. Shetreat-Klein.

There are two main types of OM:

- 1. Acute Otitis Media (AOM)
- 2. Otitis Media with Effusion (OME)

AOM: sudden onset with acute ear pain. Typical ear infection that brings most patients to the office for treatment.

OME: pain is rarely part of the symptom picture, but patient describes fullness in ear. Can last weeks to months.

Chronic suppurative otitis media (CSOM) is when AOM lasts longer than 2 weeks.

Causes of AOM:

- 1. Anatomy: horizontal Eustachian tubes do not allow for proper drainage. This is the most popular theory of why children get AOM.
- 2. *Allergies:* the accumulation of serous fluid in the middle ear allows for the growth of bacteria and viruses. Allergies to foods, mold, pollen, dust, animal danders and others can trigger inflammation in the middle ear.
- 3. Particulate inhalants: cigarette smoke, pollution, etc.
- 4. Other upper respiratory illnesses, such as colds, flu, etc.
- 5. Enlarged adenoids: block opening to Eustachian tube.

Causes of AOM:

AOM is primarily caused by bacteria, including:

- 1. Streptococcus pneumoniae
- 2. Haemophilus influenzae
- 3. Moraxella catarrhalis
- 4. Streptococcus pyogenes (Group A)

Viruses may also cause AOM, but are usually a part of a larger URI. Common viruses that are associated with AOM include RSV, adenovirus, coronavirus, rhinovirus and parainfluenza virus.

#### **Naturopathic Treatment: Prevention**

Prevention is the best medicine!

Find the cause...vast majority of AOM is related to allergy, so find the allergen and treat it. If you stop the fluid from accumulating, the ears stay dry and there is less liklihood of getting AOM in the first place.

Look at the patient's environment to identify triggers, including diet, home environment, school environment, family habits and hobbies.

Giving Xylitol chewing gum at a dose of 8.4-19 g per day has been shown to reduce the incidence of AOM in children attending day care.

#### **Naturopathic Treatment: Active Infection**

- 1. *Mullein oil ear drops with garlic*: warm bottle under warm water to heat oil. Place 2 drops in affected ear 3 times a day or as needed until ear pain subsides. Can add *Hypericum* to it for pain relief.
- **1.** *Vitamin A*: give 10,000 to 50,000 IU bid-tid with food for up to 7 days. Vitamin A increases secretory IgA, which lines all of the mucous membranes and supports immune function. Research suggests children more prone to AOM are deficient in vitamin A and then vitamin A supplementation may help treat AOM.<sup>1</sup>

<sup>1</sup> Lasisi AO. The role of retinol in the etiology and outcome of suppurative otitis media. Eur Arch Otorhinolaryngol. 2009 May;266(5):647-52.

#### **Naturopathic Treatment: Active Infection**

- *3. Zinc*: give 15-50 mg daily with food. Research is mixed on preventing AOM and few studies on actively treating AOM with zinc supplementation.
- **3.** *Vitamin C*: give 500 -1000 mg 3 times a day to help support immune function. Research shows that children with AOM tend to have low antioxidant stores, so giving antioxidants may help reduce incidence of AOM. Vitamin C also helps boost immune function.<sup>1</sup>

<sup>1</sup>Yilmaz T1, Koçan EG, Besler HT, Yilmaz G, Gürsel B. The role of oxidants and antioxidants in otitis media with effusion in children. Otolaryngol Head Neck Surg. 2004 Dec;131(6):797-803.

#### **Naturopathic Treatment: Active Infection**

- **5.** *Probiotics*: *Streptococcus salivarius* K12. Give 1 billion col/tab at night. Reduced AOM by almost 43%.<sup>1</sup> This has also been developed as a nasal spray and shown to be effective. Other studies found conflicting results with *Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve* 99 and *Propionibacterium freudenreichii.*, but did find benefit with *Lactobacillus rhamnosus* GG when combined with *Bifidobacterium lactis* Bb-12.
- 5. *Essential oils*: there is some anecdotal evidence that placing essential oils into the affected ear may help. These include thyme, eucalyptus and basil oils. Research has only been done on basil oil.<sup>2</sup> Essential oils should be mixed with a carrier oil to reduce irritation.

<sup>1</sup> DiPierro F, DiPasquale D, DiCicco M. Oral use of *Streptococcus* salivarius K12 in children with secretory otitis media: preliminary results of a pilot, uncontrolled study. Int J Gen Med. 2015: 8; 303-308.

<sup>2</sup> Kristinsson KG1, Magnusdottir AB, Petersen H, Hermansson A. Effective treatment of experimental acute otitis media by application of volatile fluids into the ear canal. J Infect Dis. 2005 Jun 1;191(11):1876-80. Epub 2005 Apr 29.

#### **Naturopathic Treatment: Active Infection**

- 5. Botanical therapy:
- *Echinacea angustifolia*: use 1:1 tincture. Give 9-15 ml per day in divided doses.
- *Lomatium dissectum*: use lomatium isolate as a resin in the whole plant can causes a measles-like rash. Give 6-12 drops twice a day in water.
- *Hydrastis canadensis:* contains alkaloids, like berberine, which have antimicrobial effects. Use 1:5 tincture. Give 15-30 drops 3 times a day. Very bitter.
- *Baptisia tinctoria* or *Galium aparine* for reducing tonsillar swelling. Use 1:3 tincture. Give 5-7 ml 3 times per day.

### **Naturopathic Treatment: Active Infection**

### 6. Homeopathic therapy:

- Aconite 30C: pain, restless, irritable, skin dry and hot.
- Belladonna 30C: right side, rapid onset, redness, thirstless.
- Chamomilla 30C: worse at night, worse bending over, screaming and inconsolable. One cheek red, one white.
- Ferrum phos 30C: high fever, few other symptoms. Use when belladonna fails
- Hepar sulph 30C: left to right, thick pus, smelly, chilly.
- Kali mur 30C: lots of catarrh, hearing loss.
- Pulsatilla 30C: thick, green/yellow discharge, whining.

### **Naturopathic Treatment: Active Infection**

- 6. Physiotherapy:
- Eustachian tube massage
- Wet sock treatment
- Onion "ear muffs"
- Cervical adjustment to C2/C3
- Lymphatic drainage
- Gua Sha

UTI's are most common in women >children> men, mostly due to short urethra in women.

Infections are generally caused by bacteria, especially:

- 1. Escherichia coli
- 2. Klebsiella pneumoniae
- 3. Proteus mirabilis
- 4. Pseudomonas aeruginosa
- 5. Any coliform bacteria
- 6. Ureaplasma urealyticum
- 7. Candidal infections rare (need to ask for specific culture)

The Urinary Microbiota

It has long been taught that the bladder is sterile, but emerging evidence shows that it is not. Standard urinary testing does not account for slow growing organisms, anaerobes or potential commensal non-bacterial microbes.

Newer quantitative technologies and DNA sequencing may provide better insight into what is "normal" in the bladder and may have some individual variance.<sup>1</sup>

<sup>1</sup>Brubaker L, Wolfe AJ. The new world of the urnianry microbiota in women. Am J Obstet Gynecol 2015;213:644-649.

#### **Naturopathic Treatment**

- 1. **D-mannose**: ONLY useful for *E.coli* infections. Can use powder or caps. Give 3 day dosing with higher doses on day 1 and tapering to day 3. D-mannose binds to fimbria on *E.coli* and prevents attachment to bladder wall.
- 1. Uva ursi: Arctostaphylos uva ursi. Arbutin in uva ursi is activated in alkaline urine to make antispetic hydroquinone. Also contains tannins, which have astringent effect. Use standardized extract to 20% arbutin. Give 600 mg bid-tid. Use cautiously in pregnancy, since has mild oxytocic effects.
- 1. *Tri-salts*: bicarbonate formula to alkalinize the urine. Bacteria generally like acid environment to thrive. Give 2 caps 3 times a day. Reduce dose if gets loose stool.

#### Naturopathic Treatment\

- 4. *Cranberry juice extract*: many studies showing it is effective for prevention and treatment of UTI's. Can use unsweetened juice or capsules. Take 250-300 ml of juice tid or 200 mg bid of concentrated capsules. Does not kill bacteria, but inhibits growth and attachment to bladder wall.<sup>1</sup> Cranberry extract has also been shown to be effective in preventing UTI's in children, especially those with urogenital abnormalities.<sup>2</sup>
- **5.** *Vitamin C*: little research. May need very high oral doses to be effective. High dose vitamin C of up to 10g a day may be needed to be effective. It is bacteriostatic at high doses.<sup>3</sup>

<sup>1</sup> Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. Can J Urol 2002;9:1558-1562.

<sup>2</sup> Durham SH, Stamm PL, Eiland LS. Cranberry products for the prophylaxis of urinary tract infections in pediatric patients. Ann Pharmacother 2015;49:1349-1356.

<sup>3</sup> Gupta GCD, Guha BC. The effect of vitamin C and certain other substances on the growth of micro-organisms. Ann Biochem Exp Med 1941;1:14-26.

#### **Naturopathic Treatment**

6. *Probiotics*: *Lactobacillus acidophilus* LbK3, *Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 have all been shown to help prevent and treat UTI's. A popular formula contains *L. rhamnosus* GR-1 and *L. reuteri* RC-14. Give 1 cap bid-tid or may use intravaginally at 1 cap hs. <sup>1,2,3</sup>

<sup>1</sup> Gardiner GE, Heinemann C, Bruce AW et al. Persistence of Lactobacillus fermentum RC-14 and Lactobacillus rhamnosus GR-1, but not L. rhamnosus GG in the human vagina as demonstrated by randomly amplified polymorphic DNA. Clin Diagn Lab Immunol 2002:9;92-96.

<sup>2</sup> Cadieux P, Burton J, Gardiner G et al. Lactobacillus strains and vaginal ecology. JAMA 2002:287;1940-1941.

<sup>3</sup> Reid G, Bruce AW. Selection of Lactobacillus strains for urogenital probiotic applications. J Infect Dis 2001:183(Suppl 1):S77-S80.

#### **Naturopathic Treatment**

7. Zea mays (corn silk): contains flavones that inhibit the adherence of *E. coli* to the bladder wall.<sup>1</sup> Zea mays is traditionally used as a hot tea. The corn silk steeped in hot water for 10 minutes, strained and then drink the residua fluid. Have patients drink 3-6 cups per day.

<sup>1</sup> Rafsanjany N, Sendeker J, Lechtenberg M et al. Traditionally used medicinal plants against uncomplicated urinary tract infections: Are unusual, flavon-4-ol- and derhamnosylmaysin derivatives responsible for the antiadhesive activity of extracts obtained from the stigmata of Zea mays L. against uropathogenic E. coli and Benzethonium chloride as frequent contaminant faking potential antibacterial activities? Filoterapia 2015;105:246-253.

#### **Naturopathic Treatment**

8. *Green tea (Camilla sinensis)*: in-vitro studies show that many of the polyphenolic compounds in green tea have antimicrobial activity against uropathogens. The catechins also have a synergistic effect with many antibiotics, such as amoxicillin, sulfamethoxazole, azithromycin, methicillin, levofloxacin and ciprofloxacin. One cup of Japanese green tea provides 150 mcg of EGC and bactericidal activity is noted at microgram doses.

<sup>1</sup> Noormandi A, Dabaghzadeh F. Effects of green tea on *Escherichia coli* as a uropathogen. J Tradit Complement Med 2015;5:15-20.

#### **Naturopathic Prevention**

- 1. Avoid cigarette smoke.
- 2. Avoid pollutants.

<sup>1</sup> Seibel J, Pergola C, Werz O, Kryshen K, Wosikowski K, Lehner MD, Haunschild J. Bronchipret® syrup containing thyme and ivy extracts suppresses bronchoalveolar inflammation and goblet cell hyperplasia in experimental bronchoalveolitis. Phytomedicine. 2015 Dec 1;22(13):1172-7.

### **Naturopathic Treatment**

 Thyme and Ivy Extract: animal models shows that extracts of thyme and ivy leaf extract help reduce bronchitis by inhibiting 5-lipoxygenase and reducing leukocyte infiltration in the lungs. Also reduces goblet cell numbers, so decreases mucus formation.<sup>1</sup>

#### Give 1 tsp tid-qid for children and 1T tid-qid for adults.

<sup>1</sup> Seibel J, Pergola C, Werz O, Kryshen K, Wosikowski K, Lehner MD, Haunschild J. Bronchipret® syrup containing thyme and ivy extracts suppresses bronchoalveolar inflammation and goblet cell hyperplasia in experimental bronchoalveolitis. Phytomedicine. 2015 Dec 1;22(13):1172-7.

#### **Naturopathic Treatment**

2. *NAC (N-acetylcysteine)*: a recent meta-analysis showed that giving >1200 mg per day of NAC helps prevent chronic bronchitis in those prone to airway obstruction, where 600 mg per day may be beneficial in those who get bronchitis and no airway obstruction. NAC is well tolerated with minimal side effects.<sup>1</sup> If using NAC long-term, give zinc as NAC can deplete zinc. NAC also has antiinflamatory effects.<sup>2</sup>

<sup>1</sup> Cazzola M, Calzetta L, Page C et al. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. Eur Respir Rev. 2015 Sep;24(137):451-61.

<sup>2</sup> Gillssen A. Anti-inflammatory efficacy of N-acetylcysteine and therapeutic usefulness. Pneumologie. 2011 Sep;65(9):549-57.

### **Naturopathic Treatment**

3. Inhaled glutathione: it is known that environmental pollution causes oxidative damage that can exacerbate COPD and bronchitis. Although no specific human trials have been done on inhaled glutathione, it is postulated that using inhaled glutathione may reduce oxidative stress and protect against mucosal damage and modulate the immune response in the lungs.<sup>1</sup>

I have personally used inhaled glutathione with success in chronic bronchitis and asthma patients. Use 60 mg/ml daily in children up to 200 mg/ml in adults.

<sup>1</sup>Allen J. Inhaled glutathione for the prevention of air pollution-related health effects: a brief review. Altern Ther Health Med. 2008 May-Jun;14(3):42-4.

#### **Naturopathic Treatment**

4. *Magnesium*: research shows that infants with chronic bronchitis have low serum and RBC magnesium levels, while urine magnesium excretion is high.<sup>1</sup> Although it is unclear if the hypomagnesemia is causative of chronic bronchitis, supplementing is reasonable.

### Give 200 mg bid to children and TBT to adults.

<sup>&</sup>lt;sup>1</sup> Bednarek A, Pasternak K, Karska M. Evaluation of blood serum, erythrocyte and urine magnesium concentrations in babies with pneumonia or bronchial obstructive bronchitis. Magnes Res. 2003 Dec;16(4):271-80.

### **Naturopathic Treatment**

#### 5. Elderberry:

Elderberry (*Sambucus nigra*) has historical use for respiratory illnesses such as bronchitis, colds and flu. It has natural antiviral and antiinflamatory activity. It induces the release of infectionfighting cytokines. The antiinflamatory effects in the bronchioles make it useful for viral and bacterial infections of the lungs, including bronchioltitis, bronchitis, pneumonia and reactive airway disease.

Give 1 tsp tid-qid for children and 1T tid-qid for adults.

#### **Naturopathic Treatment**

6. Andrographis paniculata: in-vitro studies show andrographolide upregulates human  $\beta$ -defensin-2, an inducible antimicrobial peptide that is important in innate immunity. The result is an increase in NF- $\kappa$ B, which control cellular immunity and cytokine production.<sup>1</sup> One study found an extract of *andrographis* help reduce the duration of illness in uncomplicated URI by more than 2 days.<sup>2</sup>

*Andrographis* has known antiviral effects against HSV, influenza, campylobacter, skin yeast, Group B strep and other microbes. Because of its anti-inflammatory effects, it is used for other inflammatory conditions like RA and UC.

#### Give 200-500 mg qd-bid of a 5% standardized extract.

<sup>1</sup>Shao ZJ, Zheng XW, Feng T et al. Andrographolide exerted its antimicrobial effects by upregulation of human  $\beta$ -defensin-2 induced through p38 MAPK and NF- $\kappa$ B pathway in human lung epithelial cells. Can J Physiol Pharmacol. 2012 May;90(5):647-53.

<sup>2</sup> Saxena RC, Singh R, Kumar P et al. A randomized double blind placebo controlled clinical evaluation of extract of Andrographis paniculata (KalmCold) in patients with uncomplicated upper respiratory tract infection. Phytomedicine. 2010 Mar;17(3-4):178-85.

#### **Naturopathic Treatment**

7. *Vitamin C*: most of the research on vitamin C is with respect to the common cold, but one randomized study found vitamin C helped reduced severity and duration of bronchitis in elderly people who were hospitalized.<sup>1</sup> Of note, these patients were shown to have low serum vitamin C levels and were only supplemented with 200 mg per day.

It is generally recommended to give at least 1000 mg per day to adults, but higher doses may be helpful.

<sup>1</sup> Hemilä H, Douglas RM. Vitamin C and acute respiratory infections. Int J Tuberc Lung Dis. 1999 Sep;3(9):756-61.

#### **Naturopathic Treatment**

**8.** *Myers cocktail*: Dr. John Myers made this formula popular in the 1970's and has been used by thousands of physicians around the world since. The cocktail is a combination of vitamin C, magnesium chloride, calcium gluconate, thiamine, vitamin B6, vitamin B12, calcium pantothenate, vitamin B complex and dilute HCL.<sup>1</sup>

It is theorized that the higher doses of nutrients exert pharmacologic effects, including stimulating immune function.

Dr. Alan Gaby has treated over 1000 patients with this IV mix with clinical success and minimal side effects, mostly due to doing IV push too quickly and causing flushing or nausea.

<sup>1</sup> Gaby AR. Intravenous nutrient therapy: the "Myers' cocktail". Altern Med Rev. 2002 Oct;7(5):389-403.

### **Naturopathic Treatment**

Other possible treatments:

- Vitamin A : increases secretory IgA.
- Zinc: boosts immune function.
- Oral glutathione: raise tissue glutathione.
- Essential oils: thyme, oregano, artemisia
- Cupping: increase blood flow to chest
- Constitutional hydrotherapy: applying alternating hot and cold towels to chest and back.

Need to investigate cause of diarrhea as treatment varies depending on diagnosis. Most common causes of pediatric diarrhea include:

- Rotavirus
- Other enteric viruses, including enterovirus, adenovirus, coronavirus, Norwalk virus.
- Food poisoning (salmonella, shigella, campylobacter)
- IBS
- IBD
- Celiac disease
- Food allergies

#### **Naturopathic Treatment: Diet**

- Hydration: push fluids. Use electrolyte replacement formulas. Make into popsicles for small children and infants.
- B.R.A.T diet: keep diet simple and bland until diarrhea resolves. Bananas, applesauce, rice and toast (gluten-free).
- Avoid simple carbohydrates and junk food. This includes, milk, soda or juice of all kinds.
- Feed small, frequent meals if tolerated. Make sure foods are well cooked. No raw foods or legumes.

#### **Naturopathic Treatment**

*1. Probiotics:* Use the following probiotics for pediatric gastrointestinal conditions:

Prevention of acute infectious diarrhea: Bifidobacterium lactis, Lactobacillus rhamnosus GG (LGG), and L. reuteri.

Treatment of AID: Lactobacillus GG and S. boulardii or Lactobacillus reuteri.

Prevention of antibiotic-associated diarrhea: Lactobacillus GG and S. boulardii.

Prevention of traveler's diarrhea: S. boulardii. Give 1-2 caps bid with food.

Induction and maintenance of ulcerative colitis: VSL#3. Give 2 caps bid-tid with food.

Improving symptoms of irritable bowel syndrome: Lactobacillus GG and VSL#3.

Cruchet S, Furnes R, Maruy A et al. The use of probiotics in pediatric gastroenterology: a review of the literature and recommendations by Latin-American experts. Paediatr Drugs. 2015 Jun;17(3):199-216.

#### **Naturopathic Treatment**

2. Glutamine: glutamine powder can be useful in pediatric acute diarrhea as it is a fuel source for enterocytes and enteric lymphocytes. One study found that glutamine powder at 0.3g/kg/day helped shorten the duration of diarrhea by more than 24 hours.<sup>1</sup>

Glutamine dosing should be fairly high in acute diarrhea, so an 80 lb child would get 10g/day. Adults getting chemotherapy have received as high as 30g/day.

<sup>1</sup> Yalçin SS, Yurdakök K, Tezcan I, Oner L. Effect of glutamine supplementation on diarrhea, interleukin-8 and secretory immunoglobulin A in children with acute diarrhea. J Pediatr Gastroenterol Nutr. 2004 May;38(5):494-501.

#### **Naturopathic Treatment**

3. *Carob:* carob powder is a rich source of tannins, polyphenols and fiber and has long history of use for diarrhea. One study is infants between 3-21 months with acute diarrhea were given up to 15g/day of carob powder compared with placebo. The duration of diarrhea in those receiving carob powder was reduced by almost 2 days. Cessation of vomiting, weight loss and regulation of body temperature was also more quickly normalized in those taking carob powder.<sup>1</sup>

<sup>1</sup> Loeb H, Vandenplas Y, Würsch P, Guesry P. Tannin-rich carob pod for the treatment of acute-onset diarrhea. J Pediatr Gastroenterol Nutr. 1989 May;8(4):480-5.

#### **Naturopathic Treatment**

4. Zinc: supplementation with zinc can also be effective at reducing length and severity of diarrhea. Giving 10-20 mg/kg/day of zinc helped restore normal bowel habits in hospitalized children with diarrhea.<sup>1</sup> The effect was even greater when 1500 IU of vitamin A per day was added to the treatment regimen.

On a practical note, you must give zinc with food or it can make patient nauseous. Best to give in small doses with food.

<sup>&</sup>lt;sup>1</sup> Wang Y, Gao Y, Liu Q, et al. Effect of vitamin A and Zn supplementation on indices of vitamin A status, haemoglobin level and defecation of children with persistent diarrhea. *Journal of Clinical Biochemistry and Nutrition*. 2016;59(1):58-64.

#### **Naturopathic Treatment**

5. Vitamin D: low serum levels of vitamin D have ben noted in children with acute diarrhea.<sup>1</sup> However, there are no good studies on supplementing with vitamin D as a preventive or treatment measurement for diarrhea in children.

Nonetheless, vitamin D deficiency has been indicated in numerous chronic illnesses, including IBD and IBS. It is reasonable to supplement vitamin D, especially in those with low serum vitamin D.

<sup>1</sup>Talachian E, Bidari A, Noorbakhsh S, Tabatabaei A, Salari F. Serum levels of vitamins A and D, and zinc in children with acute diarrhea: A cross-sectional study. *Medical Journal of the Islamic Republic of Iran*. 2015;29:207.

#### **Naturopathic Treatment**

**6.** *Botanicals*: there are no randomized studies on most botanicals for pediatric diarrhea, but these herbs have a long historical use and are GRAS. These herbs have astringent, demulcent and anti-inflammatory effects.

- Ulmus fulva (Slippery Elm): use cold infusion.
- Althea officinalis (Marshmallow): use cold infusion.
- Geranium maculatum (Cranesbill): use tincture.
- Achillea millefolium (Yarrow): use tea or tincture.
- *Rubus macropetalus (Black raspberry root):* use tincture.
- Filipendula ulmaria (Meadowsweet): use tea or caps.

#### **Naturopathic Treatment**

#### 7. *Homeopathics:* use low potency, 12C or 30C.

**Podophyllum**: Main remedy for acute diarrhea. Sudden urgency for a stool with profuse, offensivesmelling stools. Explosive diarrhea. Large thirst for cold liquids.

*Arsenicum album*: Main remedy for diarrhea caused by food poisoning or from viral diseases. The diarrhea is worse after eating or drinking, and is usually accompanied by nausea, vomiting, burning or cramping pains in the abdomen. Chilly. Thirsty, but sips fluids.

*Aloe socotrina* : Accidental leaking of stool after passing gas. Have a lot of sputtering during its release. Stools is very mucousy and like Jell-O.

*Veratrum album*: Profuse, painful diarrhea that is forcibly evacuated. Chilly people, but they crave ice and cold drinks. Profuse sweating with chills, with projectile vomiting.

*Chamomilla*: Diarrhea, in children with extreme irritability during their illness. Green, foul smelling diarrhea. Wants to be carried.

*Calcarea carbonica:* Most commonly given to infants. Pale, lethargic infants who sweat profusely on head. Desires eggs and indigestible things like chalk or dirt.

*Cinchona officinalis*: Diarrhea with great bloating, indigestion, and general weakness. The symptoms are noticeably worse at night, in hot weather, and after nursing.

\* Adopted from Dana Ullman, MPH C&C Infections 2/4/18: Darin Ingels, ND



Manuka honey: the hydrogen peroxide found in honey creates hydroxyl free radicals which inhibit growth of MRSA and also disrupt intact DNA. Studies also show in inhibits the growth of vancomycin-resistant enterococcus.<sup>1</sup>

The active ingredient in manuka honey is methylglyoxal (MG), a compound found in most types of honey, but usually only in small quantities. Medical grade Manuka honey has a higher concentration of methylglyoxal by up to 10X's more than regular honey.

This is a very safe, effective treatment for MRSA, especially for lesions around a child's mouth.

<sup>1</sup> Brudzynski K, Lannigan R. Mechanism of Honey Bacteriostatic Action Against MRSA and VRE Involves Hydroxyl Radicals Generated from Honey's Hydrogen Peroxide. Frontiers in Microbiology. 2012;3:36.



2. Ursolic acid-containing oils: ursolic acid is found in many plants and fruits, including the skin of apples, Holy Basil, bilberry, cranberry, elder flower, oregano, peppermint, rosemary, thyme, lavender and hawthorn.

Ursolic acid disrupts bacterial reproduction cycles in-vitro, so may help kill organism. There are no human studies on ursolic acid and MRSA, but concentrated essential oils have been used clinically with success.

Wang CM, Jhan YL, Tsai SJ, Chou CH. The Pleiotropic Antibacterial Mechanisms of Ursolic Acid against Methicillin-Resistant Staphylococcus aureus (MRSA). Molecules. 2016 Jul 7;21(7).



3. Licorice (Glycyrrhiza glabra): in-vitro and in-vivo studies show licorice has a synergistic effect with some  $\beta$ -lactam drugs and improved the MIC up to 16-fold. This suggests adding licorice to other antibiotic regimens may help improve the clinical outcome of the infection.<sup>1</sup>

Other mouse studies have demonstrated that using topical *Glycyrrhiza* is effective at reducing lesion size and inhibiting specific genes involved in bacterial reproduction.<sup>2</sup>

<sup>1</sup> Gaur R, Gupta VK, Singh P, et al. Drug Resistance Reversal Potential of Isoliquiritigenin and Liquiritigenin Isolated from Glycyrrhiza glabra Against Methicillin-Resistant Staphylococcus aureus (MRSA). Phytother Res. 2016 Jul 8.

<sup>2</sup> Long DR, Mead J, Hendricks JM, Hardy ME, Voyich JM. 18β-Glycyrrhetinic Acid Inhibits Methicillin-Resistant Staphylococcus aureus Survival and Attenuates Virulence Gene Expression. Antimicrobial Agents and Chemotherapy. 2013;57(1):241-247.



4. *Berberine:* in-vitro studies show berberine, in a dose dependent manner, inhibits MRSA amyloid fibrils formation (aka "biofilm"). Although berberine is not directly bactericidal, it can be an effective adjunctive therapy with antibiotics.<sup>1</sup>

Although this was an in-vitro study, the dose-dependent effect would suggest higher doses would be more effective than lower doses.

<sup>1</sup> Chu M, Zhang M, Liu Y, et al. Role of Berberine in the Treatment of Methicillin-Resistant Staphylococcus aureus Infections. Scientific Reports. 2016;6:24748.



5. *Colloidal silver:* nanoparticles of silver (less than 100 nm) have demonstrated in-vitro bactericidal activity against MRSA.<sup>1</sup> The MIC was found to be 100 ug/ml and almost all of the MRSA was completely killed at 4 hours post-inoculation. The study also showed nano-Ag inhibited the development of MRSA biofilm.<sup>1</sup>

It is important to note that Ag has a long history as an antimicrobial. Caution should be exercised when using orally as it could alter normal gut flora.

<sup>1</sup> Abdel Rahim KAA, Ali Mohamed AM. Bactericidal and Antibiotic Synergistic Effect of Nanosilver Against Methicillin-Resistant Staphylococcus aureus. Jundishapur Journal of Microbiology. 2015;8(11):e25867.



#### 6. Tea tree oil (Melaleuca alternifolia):

Most in-vitro studies have shown tea tree oil has anti-microbial effects against *S. aureus*. There have only been a few clinical studies in humans comparing tea tree oil with mupirocin. While tea tree oil was effective in eradicating MRSA, it was not as effective as mupirocin.<sup>1</sup>

However, using a 4% tea tree oil nasal ointment and a 5% tea tree oil body wash compared with a 2% mupirocin nasal ointment and triclosan body wash seemed to be more effective than standard treatment.<sup>2</sup>

<sup>1</sup> Dryden MS, Dailly S, Crouch M. A randomized, controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization. J Hosp Infect. 2004 Apr;56(4):283-6.
<sup>2</sup> Caelli M, Porteous J, Carson CF, Heller R, Riley TV. Tea tree oil as an alternative topical decolonization agent for methicillin-resistant Staphylococcus aureus. J Hosp Infect. 2000 Nov;46(3):236-7.

SIBO is due to an overgrowth of bacteria in the small intestine that is still largely misunderstood. The two most common predisposing factors to SIBO are lack of gastric acid or disruptions in small bowel motility.

It is believed that SIBO arises from overgrowth of bacteria in the small bowel. However, which microbes are most to blame as obtaining small bowel flora is technically difficult, especially for anaerobes.

Lactulose breath test is the most common method of diagnosing SIBO. Lactulose makes it to the distal jejunum, so covers the entire small bowel. Glucose can be used as substrate to identify more proximal SIBO.

#### **Risk Factors**

- 1. PPI use
- 2. Pancreatitis
- 3. Non-alcoholic fatty liver disease
- 4. Hypochlorhydria
- 5. Dysmotility disorders
- 6. Diabetes
- 7. Elderly persons
- 8. Alcohol consumption
- 9. IBS
- 10. IBD/Celiac disease

#### **Naturopathic Treatment**

#### <u>Diet</u>

No specific diet has ever been studied, but many healthcare providers recommend following FODMAPs diet. These are Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols.

It is also advisable to have patients avoid gluten, casein and known food allergies/sensitivities.

Encourage fluids as constipation likely makes SIBO worse.

#### **Naturopathic Treatment**

- 1. Herbal therapies compared with Rifaximin<sup>TM</sup>:
- FC-Cidal<sup>TM</sup> and Dysbiocide<sup>TM</sup> (Biotics)
- Candibactin-AR<sup>TM</sup> and Candibactin-BR<sup>TM</sup> (Metagenics)

Participants with + LBT were given either 200 mg Rifaximin<sup>™</sup> tid or 2 caps of each herbal formula bid for 4 weeks. At the conclusion of the study, 46% of those taking the herbal formulas had a negative LBT compared with 34% of those taking Rifaximin<sup>™</sup>.<sup>1</sup>

The authors did not publish the differences between the two herbal protocols, so it is unclear if one protocol is better than the other.

<sup>1</sup> Chedid V, Dhalla S, Clarke JO, et al. Herbal Therapy Is Equivalent to Rifaximin for the Treatment of Small Intestinal Bacterial Overgrowth. Global Advances in Health and Medicine. 2014;3(3):16-24.

#### Table 5

Herbal Preparations for the Treatment of Small Intestine Bacterial Overgrowth

FC Cidal	Dysbiocide	Candibactin-AR	Candibactin-BR
Proprietary blend -	Proprietary Blend 950 mg per	One Capsule contains:	Two Capsules contain:
500 mg: 1 capsule	2 capsules		
Tinospora cordifolia	Dill seed	Red Thyme oil (thymus vulgaris, providing	Coptis root and rhizome extract (coptis chinensis, containing
(stem)		30%-50% thymol) 0.2 mL	berberine) 30 mg
Equisetum arvense	Stemona Sessilifolia powder	Oregano Oil (origanum vulgare, providing	Indian Barberry root extract (berberis aristata, containing
(stem)	and extract	55% to 75% carvacrol) 0.1 mL	berberine) 70 mg
Pau D'Arco (inner	Artemisia Absinthium shoots	Sage leaf 5.5:1 extract (salvia officinalis)	Berberine Sulfate 400 mg • Proprietary 4:1 Extract 300 mg:
bark)	and leaves extract,	75 mg	Coptis root and rhizome (coptis chinensis)
Thymus vulgaris	Pulsatilla Chinensis rhizome	Lemon Balm leaf 5:1 extract (melissa	Chinese Skullcap root (scutellaria baicalensis)
(aerial part)	powder and extract	officinalis) 50 mg	
Artemisia	Brucea Javanica powder and		Philodendron bark (phellodendron chinense)
dracunculus (leaf)	extract		
Sida cordifolia (aerial	Picrasma Excelsa bark extract		Ginger rhizome (zingiber officinale)
part)			
Olea europaea (leaf)	Acacia Catechu stem extract		Chinese Licorice root (glycyrrhiza uralensis)
	Hedyotis Diffusa powder and		Chinese Rhubarb root and rhizome (rheum officinale)
	extract		
	Yarrow leaf and flower extract		Chinese Rhubarb root and rhizome (rheum officinale).
	(achillea millefolium).		

C&C Infections 2/4/18: Darin Ingels, ND

#### **Naturopathic Treatment**

2. Probiotics with FOS: a small pilot study found giving probiotics (Bacillus coagulan) with FOS in addition to minocycline for 6 months (15 days minocycline and 15 days probiotics) eliminated SIBO in 93% of cases compared with only 67% using minocycline alone.<sup>1</sup>

<sup>1</sup> Khalighi AR, Khalighi MR, Behdani R, et al. Evaluating the efficacy of probiotic on treatment in patients with small intestinal bacterial overgrowth (SIBO) - A pilot study. The Indian Journal of Medical Research. 2014;140(5):604-608.

#### **Naturopathic Treatment**

3. Probiotics without FOS: short-term probiotic use may be effective at eliminating SIBO in patients with chronic liver disease. A combination of *Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus rhamnosus*, and *Streptococcus thermophilus* given for 4 weeks helped reduce symptoms of SIBO, but had no effect on liver disease.<sup>1</sup>

<sup>1</sup>Kwak DS, Jun DW, Seo JG, et al. Short-term probiotic therapy alleviates small intestinal bacterial overgrowth, but does not improve intestinal permeability in chronic liver disease. Eur J Gastroenterol Hepatol. 2014 Dec;26(12):1353-9.

#### **Naturopathic Treatment**

- 4. Guar gum:. Giving 5g/day of guar gum with 1200 mg of Rifaximin<sup>™</sup> for 10 days was more effective in eradicating SIBO than by just giving Rifaximin<sup>™</sup> alone, by 87% and 62%, respectively. <sup>1</sup>
- It is unknown whether guar gum by itself would provide any benefit.

<sup>1</sup> Furnari, M., Parodi, A., Gemignani, L., et al. Clinical trial: the combination of rifaximin with partially hydrolysed guar gum is more effective than rifaximin alone in eradicating small intestinal bacterial overgrowth. Alimentary Pharmacology & Therapeutics, 2010;32: 1000–1006.

#### **Naturopathic Treatment**

#### 5. Digestive enzymes:

There is no research on the use of digestive enzymes of HCL in the treatment of SIBO, but if we believe that part of the problem is the inability to break down food products and dysfunctional digestion and/or fermentation, digestive enzymes may help provide symptomatic relief.

I recommend using digestive enzymes containing pancreatin and DPP-IV for those with gluten or casein intolerance.

#### **Naturopathic Treatment**

#### When its not SIBO...

There is some new evidence that patients who have SIBO-like symptoms and have a negative hydrogen and methane breath test may suffer from sucralase deficiency. This was previously believed to be a geentically inheirited condition, but it may affect some individuals who do not necessarily carry the gene.

You can test by doing a sucrose hydrogen breath test.

Sucraid<sup>®</sup> is an enzyme developed to help those who have this deficiency.

Clostridium difficile: Gram positive, anaerobic, spore forming and toxin producing (some strains) bacteria that can be infectious (fecal-oral route) or simply overgrow due to antibiotic use or other perturbations of the GI tract.

24% of HC workers had C. difficile spores on their hands after working with C. diff patients (0% for unexposed HC workers). <u>http://www.ncbi.nlm.nih.gov/pubmed/24334792</u>.

About 60% of young children carry C. diff asymptomatically. Only 3-5% of healthy adults carry C. diff.

Sensitivity of the EIA test for detection of C. diff toxin in stool is low (only about 50%), so the PCR test is replacing the EIA test.

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Clostridia by themselves are generally harmless. The toxin produced by *Clostridium difficile* is what triggers symptoms.

By aware that testing for the toxin can be difficult as the toxins (A and B) are heat labile and breakdown easily if not kept at a cool temperature once outside of the body. Stability of toxin at room temperature is only 4 hours and up to 72 hours if refrigerated.

If you are going to have patient collect sample, make sure they refrigerate the sample immediately and take to lab on ice or cold pack to ensure the toxin remains intact if present.

#### **Naturopathic Treatment**

#### Diet

One study found patients with CDI has low RBC levels of  $\Omega$ -3 Fatty acids and higher levels of RBC  $\Omega$ -6 fatty acids.<sup>1</sup> While this was not an interventional study, other research has shown that  $\Omega$ -3 fatty acids have anti-inflammatory effects. Adding  $\Omega$ -3 FA's may help reduce inflammation associated with CDI.

Avoid known food allergies/sensitivities/intolerances.

<sup>1</sup> Czepiel J, Gdula-Argasińska J, Garlicki A. n-3 and n-6 Fatty Acid Changes in the Erythrocyte Membranes of Patients with 658240251 Clostridium difficile Infection. Folia Biol (Krakow). 2016;64(1):3-10.

#### Naturopathic Treatment

1. **Probiotics:** Evidence suggests taking probiotics can help prevent and treat active CDI. While several strains have been studies, a 2011 review found that probiotics that contained Saccharomyces boulardii and Lactobacillus species were most effective.<sup>1</sup>

Another meta-analysis found that probiotics reduced CDI by 66%.<sup>2</sup>

I have had good success using VSL#3<sup>®</sup>. It is a combination of *Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii* subsp.Bulgaricus. Each capsule delivers 150 billion organisms. Give 2-4 caps bid-tid with food.

<sup>1</sup> Na X, Kelly C. Probiotics in clostridium difficile infection. J Clin Gastroenterol. 2011 Nov;45 Suppl:S154-8.

<sup>2</sup> Johnston BC, Ma SS, Goldenberg JZ, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Ann Intern Med. 2012 Dec 18;157(12):878-88.

#### **Naturopathic Treatment**

#### 2. Fecal microbiota transplant:

A recent meta-analysis showed that FMT was more effective at resolving CDI than antibiotics alone. More than 80% of patients with CDI improved with FMT, whereas only 31% of those with CDI improved with antibiotic therapy.<sup>1</sup>

However, FMT continues to have difficulties with adverse events. AE's were significantly higher in those who received transplants through upper GI methods (43.6%), compared with those who received their transplant through lower GI methods (17.7%).<sup>2</sup>

<sup>1</sup> Drekonja D, Reich J, Gezahegn S, et al. Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review. Ann Intern Med. 2015 May 5;162(9):630-8.

<sup>2</sup> Wang S, Xu M, Wang W, et al. Systematic Review: Adverse Events of Fecal Microbiota Transplantation. Grivennikov S, ed. PLoS ONE. 2016;11(8):e0161174.

### **Naturopathic Treatment**

#### 3. Indole-3-carbinol:

A recent mouse study found that adding I3C to the diet helped reduce severity of CDI. The I3C appears to help upregulate  $T_{reg}$  cells, other T cells and neutrophils without increasing inflamation.<sup>1</sup>

Although there are no human studies for CDI, I3C has been used in clinical trials for prevention of cancer, particularly breast cancer.

<sup>1</sup> Julliard W, De Wolfe TJ, Fechner JH, Safdar N, Agni R, Mezrich JD. Amelioration of Clostridium difficile Infection in Mice by Dietary Supplementation With Indole-3-carbinol. Ann Surg. 2016 Jun 8.

#### **Naturopathic Treatment**

4. *Vitamin A:* research suggests vitamin A has immune enhancing effects. It is known to help reduce some diarrhea, HIV, measles, malaria and other infections in preschool children.<sup>1</sup> However, it is not clear by what mechanism it works.

It is also know that children with higher fecal SIgA are less likely to develop CDI compared with those who have lower SIgA levels.<sup>2</sup>

It is reasonable to try using high-dose vitamin A therapy (50,000 IU-200,000 IU) in CDI. Watch for vitamin A toxicity, including headaches, joint pain, muscle aches, fatigue and dry skin.

<sup>1</sup> Villamor E, Fawzi WW. Effects of vitamin a supplementation on immune responses and correlation with clinical outcomes. Clin Microbiol Rev. 2005 Jul;18(3):446-64.

<sup>2</sup> Bridgman SL, Konya T, Azad MB, et al. High fecal IgA is associated with reduced Clostridium difficile colonization in infants. Microbes Infect. 2016 Sep;18(9):543-9.

### **Naturopathic Treatment**

5. *Vitamin D:* vitamin D deficiency has been associated with CDI. People with lower vitamin D (25-OH) levels were 60% more likely to develop CDI than those with sufficient vitamin D levels.<sup>1</sup>

Vitamin D also has a protective effect on the intestinal barrier and may help reduce intestinal permeability.<sup>2</sup>

Give enough vitamin D3 to restore serum levels to sufficient status (> 30 ng/ml). I try to get levels between 60-100 ng/ml.

<sup>1</sup> Furuya-Kanamori L, Wangdi K, Yakob L, et al. 25-Hydroxyvitamin D Concentrations and Clostridium difficile Infection: A Meta-Analysis. JPEN J Parenter Enteral Nutr. 2015 Dec 23.

<sup>2</sup> De Santis S, Cavalcanti E, Mastronardi M, Jirillo E, Chieppa M. Nutritional Keys for Intestinal Barrier Modulation. Frontiers in Immunology. 2015;6:612.

### For More Information

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Lyme Disease 9/30/17: Darin Ingels, ND

### The End!

Questions?

C&C Infections 2/4/18: Darin Ingels, ND