Special Web Call: Biofilms

Paul S. Anderson

Conflict of interest:

- None
- I have no financial connection to ANY lab, product or company mentioned
- Specific products mentioned are examples of items I use commonly in practice

Next Regularly Scheduled Webcalls:

June Blood Pressure medications – Prescribing and Tapering tips

In this webcall Dr. Anderson will describe the clinically relevant issues surrounding the choice of, dosing for and tapering off of anti-hypertensive medications. How best to do it? How to use natural medications in the process? Case examples and Q&A included.

CME Total 1.5 hours – Of that pharmacology CME is 1.5 hours

July Steroids – Prescribing and Tapering tips

In this webcall Dr. Anderson will describe the clinically relevant issues surrounding the choice of, dosing for and tapering off of steroid medications. How best to do it? How to use natural medications in the process? Case examples and Q&A included.

CME Total 1.5 hours – Of that pharmacology CME is 1.5 hours

Today's Topic Overview

BIOFILMS

- Discussion about the issues surrounding biofilm therapies
- Discussion of the safe uses of biofilm Tx with Rx:
  - Testing, dosing and follow up will be discussed.

Biofilms

Summary

Biofilms are better understood than ever before as to their medical relevance in human illness.

This portion of the session is designed to present researched and clinically verified therapies for biofilms which can be applied in chronic disease care.

Biofilm Summary by Stephen E. Fry, MD

Biofilms are considered the rule in nature rather than the exception. If you have chronic infection, biofilms may be an underlying cause. Many, if not most, microorganisms form and persist in cohesive community structures termed biofilms. These cells secrete a gelatinous intracellular substance consisting of an extracellular polysaccharide (sugar), DNA, and protein matrix. Biofilms are often found attached to living and inert stable surfaces that have a constant liquid flow that brings nutrients and removes waste products from the biofilms. Biofilms often are not composed of a single organism, but contain two or more organisms making significant contributions to the biological stability, characteristics, and behavior of the resulting biofilm.

Biofilm Summary by Stephen E. Fry, MD

Organisms found within biofilms have distinct genetic expression and functional behavior compared to individual organisms subsisting in an individual planktonic state. The establishment and life cycle of biofilms on surfaces typically proceed through four main stages:

1) Initial Attachment, 2) Irreversible Attachment, 3) Various Maturation Phases, 4) Active Dispersion or Blebbing/Fragmenting.

Many microorganisms spend most of their life cycle in a persistent biofilm state switching to free living or planktonic phases only during brief periods when environmental conditions are favorable.

Overview

- In the past three years we undertook a project to merge the older and emerging science around Biofilms in human illness with clinical practice.

- This was completed at Anderson Medical Specialty Associates with the cooperation of our patients with chronic infectious illnesses.

- These slides summarize the concepts and their successful implementation in this population.

Biofilm Overview

- “Biofilm” is generally a group of biotic organisms which have a protective matrix of metallo-mineral and organic molecule coating. This complex protects the organisms from anti-infective therapies and create a “super-biotic” organism colony.
- A biofilm can form almost anywhere where water is present.
  - The human gut
  - The bloodstream
  - Teeth. (the sticky coating on teeth after no brushing your teeth is Biofilm.)
- In most cases the biofilm matrix is able to protect the organism colony from even the highest and strongest doses of Antibiotics.

Who has biofilms?

- Everyone – but not all are clinically significant.
- Those with positive lab titers that won't clear with standard of care treatment
- Those who clear one infection only to get another or another group
- Those with chronic GI infections that are unresponsive to treatment
- Any chronically ill person
- Etc…

Can we test for biofilms?

- Let's discuss…

- Fry Labs (Scottsdale, Arizona) can run biofilm assays.

Biofilm Agents – A Spectrum:

1. Prevention:

A. Inhibit: Quorum Sensing
   I. Organism cell signaling with auto-inducers which determines gene expression, virulence, resistance, and the development of biofilms.
B. Inhibit: Initial Attachment of Biofilm Colonies
C. Inhibit: Organism Efflux Pump / Multi Drug Resistance Pump Inhibitors

2. Active therapies:

A. Bacteriostatic & ‘cidal agents
B. Direct biofilm disruption agents

Oral Biofilm Rx: Results

Phase-1 (attachment / early biofilm) Phase-2 Later Biofilm

- As compared to preventive phase-1 agents?
- As compared to other phase-2 agents?

BOTTOM LINE: YOU CANNOT TREAT PHASE-2 BIOFILMS (which all your chronically ill folks have) WITH PHASE-1 THERAPIES.

Biofilm Agents – A Spectrum: 1-Prevention

- Enzymes
- Aromatics
- Tannins
- Phenolics
- Xylitol, Stevia
- Black cumin
- Etc…

Badet C, Furiga A, Thébaud N. Effect of xylitol on an in vitro model of oral biofilm. Oral Health Prev Dent. 2008;6(4):337-41. PMID: 19178100

Abstract

The aim of the present study was to examine whether xylitol, at different concentrations, inhibits the formation of an experimental model of oral biofilm.

Biofilms of six bacterial species (Streptococcus mutans, Streptococcus sobrinus, Lactobacillus rhamnosus, Actinomyces viscosus, Porphyromonas gingivalis and Fusobacterium nucleatum) were prepared on hydroxyapatite (HA) discs according to the Zürich Biofilm Model. Xylitol was tested at two concentrations, 1% and 3%. At the end of their designated incubation times, some HA discs were destined for confocal laser scanning microscopy (CLSM) and the others were harvested using a sterile surgical instrument. Aliquots of harvested biofilms were diluted and plated onto specific media. After a 48-h anaerobic incubation at 37 degrees C, the colony-forming units (CFUs) were counted.

CLSM images showed that only a small amount of isolated bacteria was observed on the surface of HA discs. Culture of harvested biofilms showed an inhibition in the growth of different species included in the biofilms.

Xylitol has a clear inhibitory effect on the formation of the experimental biofilms. This study shows that xylitol is not only efficient in inhibiting the acid production of cariogenic bacteria, but also in preventing the formation of a multispecies biofilm; it confirms the relevance of the use of this polyol for the prevention of oral diseases caused by dental plaque.

P. A. S. Theophilus, M. J. Victoria, K. M. Socarras, K. R. Filush, K. Gupta, D. F. Luecke, and E. Sapi. Effectiveness of Stevia Rebaudiana Whole Leaf Extract Against the Various Morphological Forms of Borrelia Burgdorferi in Vitro. Eur J Microbiol Immunol (Bp). 2015 Dec; 5(4): 268–280. Published online 2015 Nov 12. doi: 10.1556/1886.2015.00031. PMCID: PMC4681354

In this study, we evaluated the effectiveness of whole leaf Stevia extract against B. burgdorferi spirochetes, persisters, and biofilm forms in vitro. The susceptibility of the different forms was evaluated by various quantitative techniques in addition to different microscopy methods. The effectiveness of Stevia was compared to doxycycline, cefoperazone, daptomycin, and their combinations. Our results demonstrated that Stevia had significant effect in eliminating B. burgdorferi spirochetes and persisters. Subculture experiments with Stevia and antibiotics treated cells were established for 7 and 14 days yielding, no and 10% viable cells, respectively compared to the above-mentioned antibiotics and antibiotic combination. When Stevia and the three antibiotics were tested against attached biofilms, Stevia significantly reduced B. burgdorferi forms. Results from this study suggest that a natural product such as Stevia leaf extract could be considered as an effective agent against B. burgdorferi.

Fatemeh Forouzanfar, Bibi Sedigheh Fazly Bazzaz, and Hossein Hosseinzadeh. **Black cumin** (Nigella sativa) and its constituent (thymoquinone): a review on antimicrobial effects. Iran J Basic Med Sci. 2014 Dec; 17(12): 929–938. PMCID: PMC4387228

All findings discussed above indicate that N. sativa seeds have antimicrobial effects against different pathogens, including bacteria, viruses, schistosoma and fungus.

Black cumin seed in traditional medicine and in recent years for the treatment of microbial diseases has been used without any reported side effects. Therefore, this plant can provide a valuable agent for microbial diseases. However, additional studies are required to evaluate and explore the specific cellular and molecular mechanisms of the antimicrobial effects of N. sativa, alone or in combination with other drugs.

Park SR, et al. Discovery of cahuitamycins as biofilm inhibitors derived from a convergent biosynthetic pathway. Nat Commun. 2016. PMID 26880271

And – on the horizon:

Pathogenic microorganisms often have the ability to attach to a surface, building a complex matrix where they colonize to form a biofilm. This cellular superstructure can display increased resistance to antibiotics and cause serious, persistent health problems in humans. Here we describe a high-throughput in vitro screen to identify inhibitors of Acinetobacter baumannii biofilms using a library of natural product extracts derived from marine microbes. Analysis of extracts derived from Streptomyces gandocaensis results in the discovery of three peptidic metabolites (cahuitamycins A-C), with cahuitamycin C being the most effective inhibitor (IC50=14.5 µM). Biosynthesis of cahuitamycin C proceeds via a convergent biosynthetic pathway, with one of the steps apparently being catalysed by an unlinked gene encoding a 6-methylsalicylate synthase. Efforts to assess starter unit diversification through selective mutasynthesis lead to production of unnatural analogues cahuitamycins D and E of increased potency (IC50=8.4 and 10.5 µM).

Biofilm Agents – A Spectrum:
2- Active Therapy

- Antimicrobial Therapies
  - Natural (including Black Cumin)
  - Synthetic
- Direct Biofilm Disruption
  - Agents that actually disrupt and “open” the biofilm

Considerations in Active Biofilm Therapy:

- Oral Bismuth
- EDTA
- Silver nanoparticles
- Anti-infective:
  - H2O2 / HDIVC / Ge / Zn / etc…etc…
  - Anti-infective agents PO / IV
- Thiols
  - [Mono-] ALA, NAC, Glutathione
  - [Di-] DMSA, DMPS
- Oral Bismuth-Thiol Complex
  - Neither bismuth nor thiol alone but a new molecule.

Biofilm Protocols and EDTA:

- Although a topic of great length we do employ Calcium-disodium EDTA and Na2-EDTA as additive to some Immune and Antibiotic IV formulas as an augment for patients who may have Biofilm issues.

Selected EDTA-Biofilm References:
[PMID: 22941091; PMID: 18594291;
PMID: 17909983; PMID: 22029913;
PMID: 22941091; http://dx.doi.org/10.1016/j.fm.2011.07.009]

Biofilm Protocols and EDTA:

- The formula should meet the criteria for addition of EDTA, and should be given in accordance with accepted monitoring and follow up of EDTA therapies – BUT - the addition is typically much lower of a dose of Ca-EDTA than a chelation protocol.
- IF EDTA is used some minerals cannot be administered on the same day: Fe, Zn, Cu.

Biofilm Protocols and EDTA:

As to the question of “Can I just run my normal EDTA chelation protocol then do an IV of other Anti-infective / Immune therapies?”

- Sure. In most cases however the full chelation protocol used for heavy metals is not needed to achieve these effects.
- ** See the IIVNTP course “EDTA Chelation and Heavy Metal Toxicology for details on heavy metal treatment. [www.ivnutritionaltherapy.com]

Silver and Biofilms

Silver Hydrosol (i.e. 23 ppm silver hydrosol) are all I use. I do not use "colloidal" forms.

- As a matter of protocol the Silver Hydrosol IV **cannot be given on the same day** with the chelators.
  - Silver nanoparticles impede the biofilm formation by Pseudomonas aeruginosa and Staphylococcus epidermidis. Colloids Surf B Biointerfaces. 2010 Sep 1;79(2):340-4. doi: 10.1016/j.colsurfb.2010.04.014. Epub 2010 Apr 22. PMID: 20493674
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Bismuth:

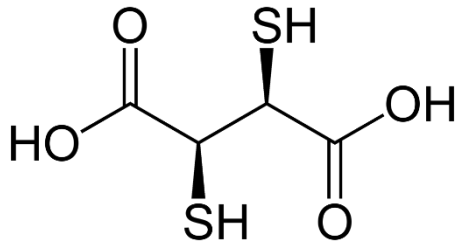
- Multiple references exist as to the synergy of bismuth with biofilm disruption.
- DO NOT USE IV BISMUTH AT THIS TIME – STICK WITH ORAL.

* NOTE - There is a physician who lost his license by killing a patient with IV Bismuth – it is not needed as an IV additive and is not ready to be used IV!

Thiols (Mono and Di)

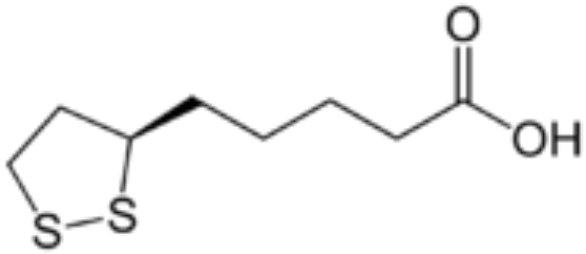
Dithiols:

- DMPS (IV and Oral use)
- DMSA (Oral use)



Monothiols:

- ALA (Oral or IV use)
- NAC (Oral or IV use)
- Glutathione (IV use)
  - Many thiol references. Some are listed above in the bismuth section.



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Biofilm Concepts:

- Stack anti-infective IV's (H2O2, HDIVC, Ge, Zn, Antibiotics etc etc…) along with the IV chelators (EDTA forms and a thiol appropriately administered).

- Give oral Bismuth-Thiol complex
  - May be given daily if desired but not at the same time as any other product or drug that is sensitive to binding.

- Many clinics use high dose enzymes, Aromatics, Xylitol… orally (between meals) day before and of the IV as well. Some do them daily.

Considerations in Biofilm Therapy: EDTA

- Oral Bismuth-Thiol complex
  - 1 – 3 capsules QD away from food
- EDTA
  - Ca-NA2 EDTA added to HDIVC or ABX IV 200-300 mg
  - NA2 EDTA added to HDIVC or ABX IV 50-100 mg
  - ** Oral CaEDTA as compounded capsule or Lipospheric preparation from Allergy Research Group or Quicksilver: 4 capsules or 2 teaspoons
- Silver
  - IV on separate day
  - Or oral 23 ppm Silver Hydrosol 15 mL QID

General Doses in Biofilm Therapy:

- Thiols
  - DMSA:
    - Orally 300-500 mg PO away from food BID day prior to and of the IV anti-infective protocol
  - DMPS:
    - 25-50 mg given in a separate bag following the IV anti-infective protocol

General Doses in Biofilm Therapy:

- Thiols
  - ALA:
    - Orally 300-500 mg BID day before and of the IV anti-infective protocol –OR- 20-100 mg given in a separate bag following the IV anti-infective protocol
  - NAC:
    - Orally 500-1000 mg BID day before and of the IV anti-infective protocol –OR- 250-500 mg given in a separate bag following the IV anti-infective protocol
  - Glutathione:
    - As tolerated, per normal IV rules. Dose of 1-4 grams.

Oral Biofilm Rx: Results

Phase-1 (attachment / early biofilm) Phase-2 Later Biofilm

- As compared to preventive phase-1 agents?
- As compared to other phase-2 agents?

BOTTOM LINE: YOU CANNOT TREAT PHASE-2 BIOFILMS (which all your chronically ill folks have) WITH PHASE-1 THERAPIES.

Oral Biofilm Rx: FAQ

- Isn’t bismuth toxic?
  - Not in this form. This is neither bismuth nor thiol. The reason a reactive form of bismuth and thiol(s) are mixed is to create a NEW molecule. The new molecule is what disrupts the biofilm.

Oral Biofilm Rx: FAQ

- Won’t it chelate my patient?
  - Same answer – no. The Dithiol is bound to the bismuth so the toxicity of bismuth and chelating ability of the thiols are negated.

Oral Biofilm Rx: FAQ

- Does the initiation of immune symptoms after starting the agent mean it is not working?
  - No. In fact it means it is working. You may need more anti-infective, endocrine, inflammatory or other support as the symptoms mean the immune system may be “seeing” the ID agents for the first time (due to opening of the biofilm).

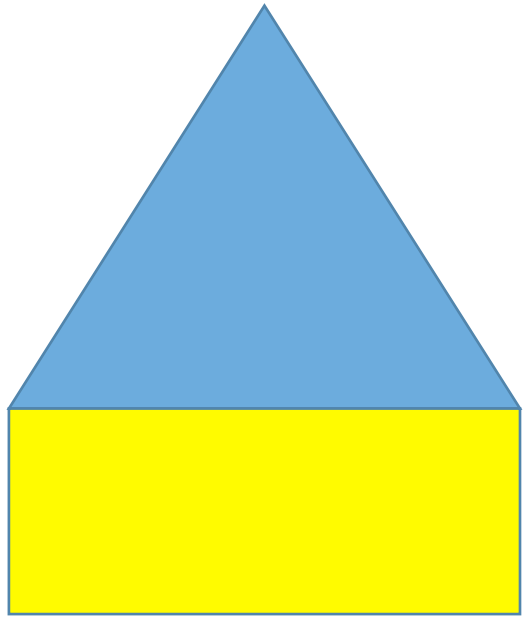
Oral Biofilm – Bismuth-Thiol Complex

- More than the sum of its parts
- Pharmacology very different from individual parts

Biofilm Rx: FAQ

- In all your research and human trial is IV administered biofilm therapy more likely to “stir up” or aggravate a patient or is oral biofilm Rx more likely?
  - In almost every case we have seen MUCH more aggravation in oral biofilm therapy. Far less with IV therapies.
  - This is likely due to the fact that biofilms are thought to start in the GI tract.

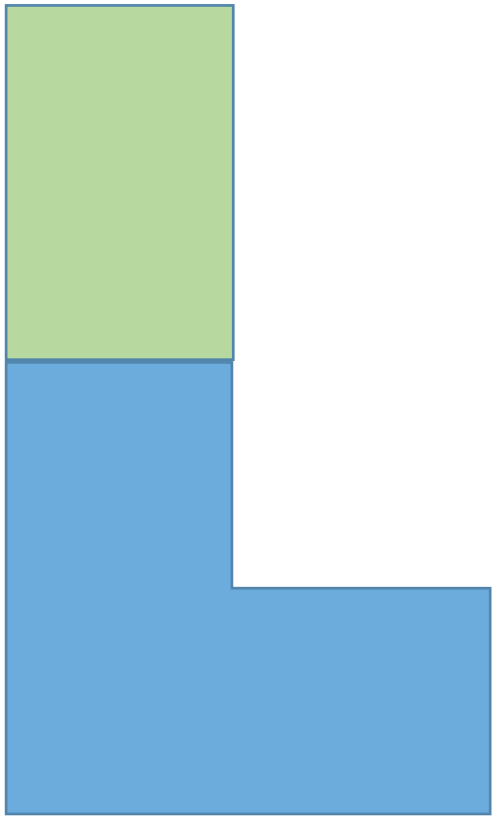
Free Bismuth



Metallo-attractive Portion

Toxic metal / Reactive Portion

Free Thiol

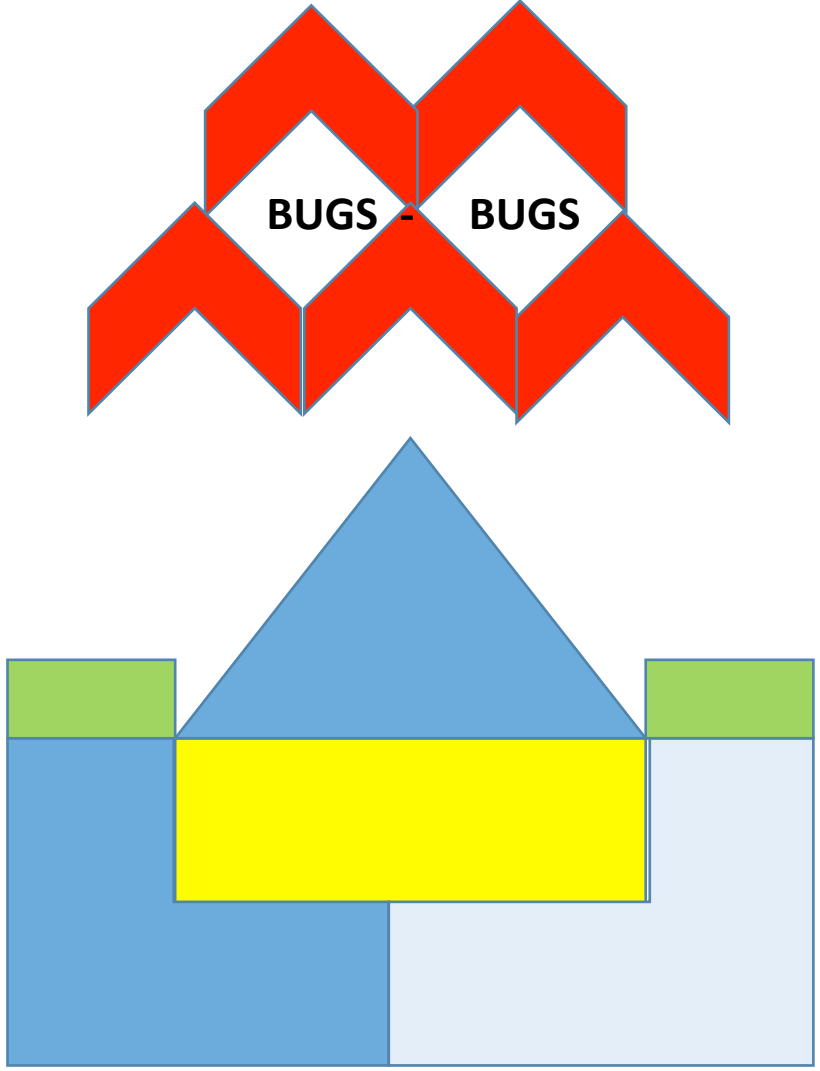


Stable

Portion

Chelating

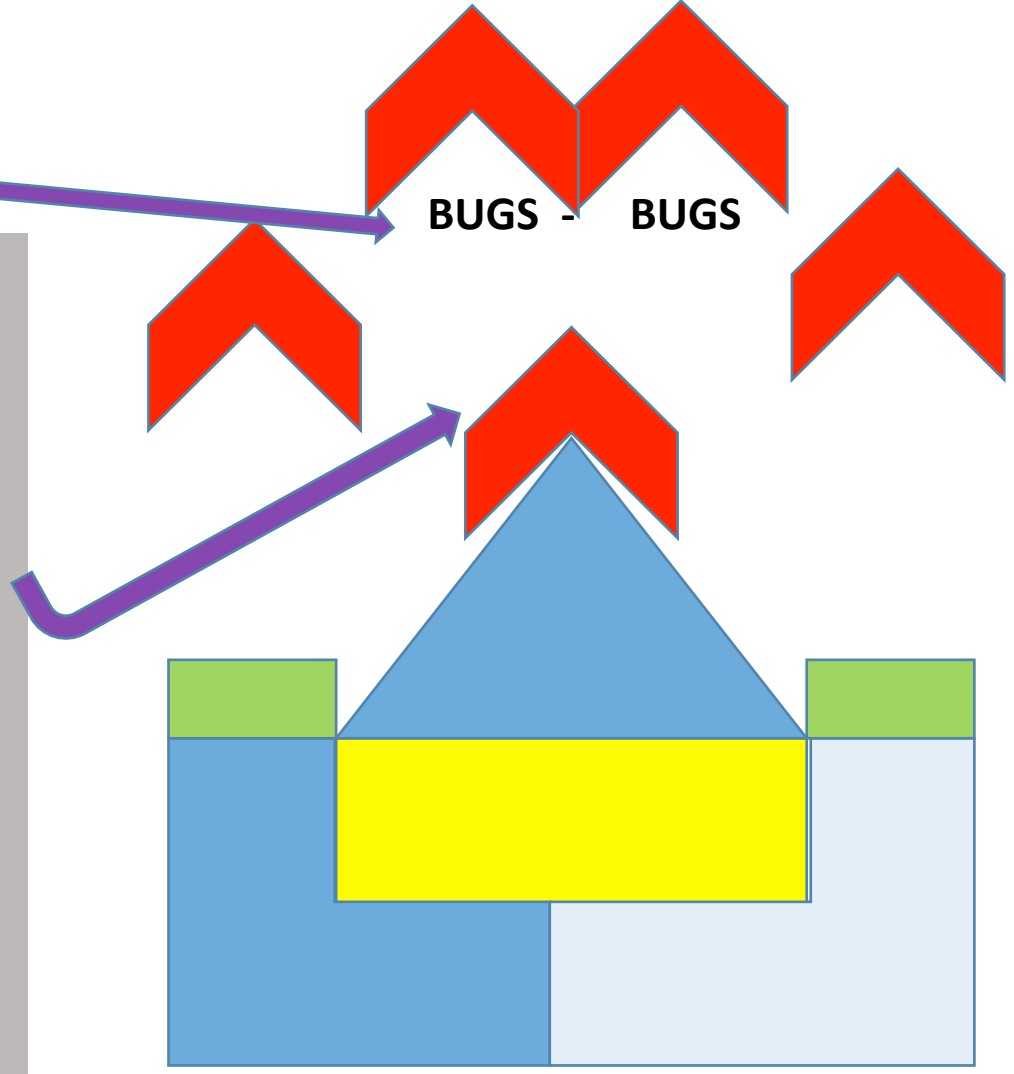
Portion



Bismuth-Thiol Complex

Non-toxic and non chelating portions are on the “outside” and aim into the biofilm matrix via bismuth moiety attraction – create a “wedge effect”.

Bismuth-Thiol Complex



So - “suddenly” the immune system “sees” the BUGS!

Anti-infective substances and immune activity begin the fight they didn’t know was needed before.

Non-toxic and non chelating portions are on the “outside” and aim into the biofilm matrix via bismuth moiety attraction – create a “wedge effect”.

Oral Biofilm Rx:

- I have worked with Imprimis pharmacy (US) to make “Biosolve-PA” capsules based on the strongest ingredients available in the studies mentioned.
  - Initial testing on humans shows very good tolerance.
- Formula:
  - DMPS 25mg/ Alpha Lipoic Acid 100mg/ Bismuth Subnitrate 200mg per Capsule
  - Ideally no substitutions
  - DMSA 100 mg can sub for DMPS
  - Bismuth Subcitrate can sub for Subnitrate (will make product weaker)

Oral Biofilm Rx:

- "Biosolve-PA" [I make no money from the manufacture or sale of this agent] dosing:
  - Approximates the most potent – most researched biofilm drugs
  - Uses the most (available) forms and combinations of medication chemistry
- DOSE:
  - 1 cap QD away from food, 3X a week for one week as a test dose
  - 1-4 caps QD to BID away from food 3-5X a week
  - Extra doses (on the "off days") are helpful in dermatologic flares during therapy for dermatologic and 'Herx' type reactions
  - Once an immunologic reaction is reached the dose may need to be decreased as needed

Oral Biofilm Rx:

- Normal trial is for 60 – 120 days during other anti-infective therapy
  - May be used much longer if clinically indicated
- Usual trajectory of therapy:
  - First 30-60 days may have no change
  - Eventually (when the biofilm Rx breaks the biofilm open) the patient will typically exhibit signs of an immune reaction. This can be any cytokine based reaction.
  - This is the time when a balance must be struck:

Oral Biofilm Rx:

- The balance is between allowing the immune reaction and the anti-infective therapies to work and not having the patient be too uncomfortable.
- The issue is enough support without suppressing the immune system so it can react fully.

Biofilm Rx Support:

- This “balance is gained typically by allowing the biofilm Rx to continue and modulating anti-infective Rx along with enough Adrenal (and occasionally Thyroid) support.
- If the patient is on non-Rx adrenal support they may need 5-10X the dose for a time.
- If they are on low dose hydrocortisone and adrenal support they often will need more hydrocortisone (sometimes 2-4X for a time).

What is next?

Phase-1 (attachment / early biofilm) Phase-2 Later Biofilm

- After you have broken through the biofilm and therapy is progressing (which may take 3-12 months) then you can phase in the “phase-1” agents to clean up the biofilms that are most clinically significant – AND – keep them from re-forming.

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General Information - WebCalls

- Every third Tuesday of the month (Regular webcalls)
- Pacific time: 5:30 – 7:00 or whenever we finish
- Calls will be recorded and available to subscribers any time after processing (usually the day following).
- PowerPoint files will be available after todays presentation

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11. IV and Injection Q&A
12. Sulfation Pathways
13. Antidepressant Rx and Taper
14. Pediatric Rx and dose adjustment
15. Renal Rx and Dose adjustments

CME Certificate

This is to attest that:

Dr. _____

Attended the webinar “Safe Uses of Biofilm Therapies” given online live or via recording on or after 05-31-2016.

Duration: 1.5 clock hours

Pharmacology 1.0 hours

This event discussed diagnosis, treatment and management of biofilms and therapies associated with them.

Faculty: Paul S. Anderson, ND