1 **Are You Missing Mold Illness?**

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2 **Mold ~ A Formidable Foe**

- Are You Missing Mold Illness In Your Patients?
- Dr. Jill Crista

3 **Mold ~ A Formidable Foe**

- Personality profile ~ a survivor
- Mold's Specific Carbohydrate Diet
- How mold creates harm
- Mold, biofilm, and colonization

4 **16 Mold Facts You Need To Know**

- Natural function ~ compost/recycle
- Excrete 1º and 2º metabolites ~
  inhaled, ingested, and absorbed
- 1º metabolites ~ nec for survival
  aldehydes, alcohols, odors, digestive enzymes, and structural elements
  (beta-glucans etc)
- 2º metabolites ~ competitive
  antimicrobials, mycotoxins

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7 **Tenacious**

- Moisture ~ 1º element for growth,
  2º is organic substrate
- Obvious or visible water not necessary
- High relative humidity is all that's required
- Grows on WD surface within 24-48 hours
- Difficult to kill
- Spore formation and release increases more when drying than when wet (survival of species)
- It's goal is to compost YOU

8 **Question**

-
- True or False?

- Mold is an old building problem

9 **Answer**

- False!
- Mold can grow in any building
  within 48 hours
  of the
  water damage event,
  no matter how old the structure

10 **Mold's Specific Carbohydrate Diet**

11 **Mold Types Found in WDBs**

- Penicillium chrysogenum
- Aspergillus versicolor, A. fumigatus, A. melleus,
  A. niger, A. ochraceus
- Chaetomium spp
- Acremonium spp
- Cladisporium herbarum
- Ulocladium spp
- Stachybotrys spp
- Mucor racemosus, M. spinosus
- Trichoderma spp
- Arthrinium phaeospermum
- Aureobasidium pullulans
- Study limitation: only collection plates/flood conditions
  Penicillium verrucosum, Alternaria, Fusarium missed
- PMID: 21531835, 19191921

12 **Mold Types By Material**

- Wallpaper & Gypsum (drywall) ~
  Penicillium chrysogenum
  Acremonium spp
  Ulocladium spp
  Stachybotrys spp
- Wood & “Was-Wood” ~
  (plywood/modified wood products)
  Cladosporium herbarum
  Trichoderma spp
  Arthrinium phaeospermum
  Aureobasidium pullulans
- PMID: 21531835

13 **Attic**

14 **Attic**

15 **Drywall**

16 **Drywall**

17 **Shower**

18 **Mold Types By Material**

- Concrete & Flooring Materials ~
  Aspergillus versicolor, A. fumigatus,
  A. melleus, A. niger, A. ochraceus
  Chaetomium spp
  Mucor racemosus, M. spinosus
- Other ~
  Penicillium verrucosum - ceiling tiles
  Alternaria spp - carpets, textiles, horiz surfaces
  Fusarium spp - HVAC, humidifiers
- PMID: 21531835

19 **Basement - Stachy + Chaetomium**

20 **Air Duct**

21 **Flood**

22 **Other Air Quality Considerations**

- VOCs and microbial VOCs
- Dander
- Allergens
- Rodent feces
- Gas (leaks, gas stove, sewer)
- Formaldehyde (‘new’ smell)
- Fiberglass
- Fragrances
- PCBs (candles)
- Insecticides, pesticides
- EMFs (WiFi, smart meters)
- Radon (granite, foundation cracks)
- Heavy metals (hunters/hobby, lead)
- Endotoxins

23 **How Mold Creates Harm**

24 **Respiratory System vs Mold**

- Mold
- Spores-
- Cladosporium 3-5μ
- Aspergillus 2-5μ
- Penicillium 1-5μ
- Fragments-
- 1-2μ
- Mycotoxins-
- 0.1μ

25 **Spores**

- Immune responses are highly variable ~
  From allergic to life-threatening disseminated fungal infection (IFI)
- General ROT ~
  Spores induce
  Mycotoxins suppress
  *but both deplete I/S with ongoing exposure
- Mechanisms ~
  Induce inflammatory reaction
  Reduce respiratory mucosal ciliary function
  Adhesion
  Evasion
  Invasion
- “007” analogy
- PMID: 27623953, 26600019, 29371501, 27092126, 8463496, 19527167, 19201896

26 **Spores & Airways**

- First point of contact is most likely an airway epithelial cell (AEC)
- First response by AEC is to “season it, then try to eat it”
- If that doesn’t work, AEC’s next response is to send out gene intel to I/S, then commit suicide
- Stachybotrys alters phospholipid synthesis related to surfactant ~
  Keep the lungs hyperinflated for easier invasion
- PMID: 25449202, 12221236, 26600019, 29371501, 27092126, 30589860

27 **Spore Effects**

- Inhalation of A. fumigatus extract in mice induced a dramatic rise in IgE accompanied by an increase in airway mast cells, and signs indicating an elevated systemic mast cell load.
- Analyses of potential cellular targets of IgE revealed that IgE antibodies are not required for the induction of mast cell progenitors in response to allergen but rather act by sustaining the survival of mature mast cells.

28 **Spore Effects**

- Allergic recruitment induction ~
  Influence mast cell homeostasis to enhance survival
  Induce pulmonary mast cell degranulation even in the absence of antigen-specific IgE
  Increased allergic responses to other respirable antigens
  (dust, grass, pollen, pet dander, exhaust)
- Inflammation/irritation/degradation of respiratory mucosal linings over time (+gut/bladder)
- Spore invasion/infection due to LT immune depletion
- PMID: 27623953, 26600019, 29371501, 27092126, 8463496, 19527167, 19201896

29 **Spore Effects**

- "We used two in vivo models induced by exposure to Aspergillus fumigatus (Af) and Alternaria alternata (Aa), as well as an Af-exposed in vitro system. We also checked NLRP3 expression in lung tissues from patients with allergic bronchopulmonary aspergillosis (ABPA)."
- What's the key question of this study?
  "Phosphoinositide 3-kinase (PI3K)-δ isoform has been shown as an important mediator of allergic lung inflammation, including the fungi-induced form; however, a role of PI3K-δ in the modulation of innate immune response against fungal allergens has not been reported. "

30 **Spore Effects**

- A: bronchoalveolar lavage D: lung tissue (DAPI stain=nuclear localisation)
- Af-exposed mice: ↑NLRP3 expression (a limiting factor in NLRP3 inflammasome activation)
- "NLRP3 is increased in lung tissues from patients with ABPA (allergic bronchopulmonary aspergillosis)"
- "Elevation of NLRP3 inflammasome assembly/activation was also observed in Af-stimulated murine and human EpCs."
- "NLRP3 inflammasome is implicated in Af-induced allergic lung inflammation"
- "These data indicate that Af exposure may be related to the NLRP3 inflammasome activation in human lung disorder..."

31 **Spore Effects**

- Af-exposed mice: ↑IL-1β
- "NLRP3 inflammasome has been known to be implicated in allergic inflammatory processes as well as antifungal defence through IL-1β."
- "Notably, selective inhibition of NLRP3 inflammasome led to the decrease of IL-1β in the lung of Af-exposed mice,..."
- "...and neutralisation of IL-1β improved numerous features of Af-induced allergic lung inflammation."
-

32 **Spore Effects**

- Af-exposed mice: ↑PI3K-δ
- With admin of a selective inhibitor of PI3K-δ (IC87114, alpelisib & ..lisib Rx family)↓NLRP3
- "PI3K-δ (phosphoinositide 3-kinase) plays a key role in regulation of immune processes through activating immune cells and trafficking inflammatory cells."
- "PI3K-δ is also activated in response to fungal exposure and plays a role in the regulation of ER stress, thereby being crucially implicated in fungal allergic inflammation."
- "Inhibition of PI3K-δ improves Af-induced allergic lung inflammation through regulation of NLRP3 inflammasome assembly/activation."

33 **Spore Effects**

- "These findings demonstrate that fungi-induced assembly/activation of NLRP3 inflammasome in airway epithelium may be modulated by PI3K-δ, which is mediated partly through the regulation of mtROS generation."
- "Inhibition of PI3K-δ may have potential for treating fungi-induced severe allergic lung inflammation."
-

34 **Spore Effects**

- "Oxidative stress has been shown to be strongly associated with most of the features of asthma and leads to accumulation of phosphatidyl inositol (3,4) bis-phosphate, which in turn activates PI3K pathway and contributes to oxidative stress."
- "Thus, there exists a vicious loop between oxidative stress and lipid phosphatase signaling."
- "These results suggest a novel mechanism of action of resveratrol in attenuating asthma phenotype by downregulating PI3K-Akt pathway via upregulating INPP4A."

35 **Spore Fragments**

- 500:1 Fragment:spore
- Usu occurs when dead/dried mold is disrupted
- Become ultrafine particulate in permanent suspension, even in lungs
- Highly inflammatory to sinus & lung tissue ~
  More potent than spores at inducing proinflam cytokines
  Asp/Pen - enhance TLR2-dependent expression and release of IL-6 + IL-8 in human bronchial epithelial cells
- Airway remodeling if persistent exposure

- “Mold-othelioma” - mesothelioma-type LU condition related to mold fragment exposure vs asbestos:
  Shortness of breath, cough, pain in the chest or abdomen, fatigue, fever or night sweats, respiratory complications, muscle weakness, nausea or bloating
- PMID: 30917597, 31116698

36 **Spore Effects**

- ”Human bronchial epithelial cells were exposed to X-ray treated spores and hyphal fragments from pure cultures of Aspergillus fumigatus, Penicillum chrysogenum, Aspergillus versicolor and Stachybotrys chartarum.”
- “Hyphal fragments of A. fumigatus and P. chrysogenum induced expression and release of the pro-inflammatory cytokines, while none of the other hyphal preparations had effects.”
- [*Is this how the more toxigenic species like Stachy persist? By evading allergic detection?]
- “Untreated A. fumigatus spores formed hyphae and triggered expression of pro-inflammatory genes with similarities to the effects of hyphal fragments.”

37 **Mycotoxin Immune Overview**

- Immunosuppressive via:
  Direct action on immune cells
  Epigenetic alterations to the immune response
  Direct genetic alterations
- Inhibit host defense via:
  NK cell hypofunction
  T-/B-cell deficiency
  LT exposure - Ig subclass def (false neg allergy/infection labs)
- Leukopenia w relative lymphopenia, neutrophilia & eosinophilia
- TGF-β1↑
  ↑ impairs T-reg fxn → immune overactivation/asthma
- Disordered GALT, affects nutrient absorption, intestinal apoptosis
- PMID: 26474839, 27178040, 25449202, 12221236, 26600019

38 **Spore Effects**

- “Our results are the first to suggest that AFB1 promotes Swine Influenza Virus (SIV) replication and SIV-related lung damage by activating the TLR4-NFκB pathway.

- This finding is supported by previous studies demonstrating that TLR4 antagonists or TLR4 knockout can prevent lethal influenza infection (20, 42). Therefore, we infer that AFB1 might promote TLR4 overexpression and excessive inflammatory responses and reduce tolerance (43), thereby promoting SIV replication."

39 **Spore Effects**

- Swine Influenza Virus (SIV) replication correlates to increasing concentrations of AFB1.
- "Taken together, our results suggest that AFB1 exposure promotes SIV replication in vitro."
-

40 **Spore Effects**

- "In addition, the inflammatory response was quantified by the release of TNF-α and IL-10, and the results showed that AFB1 at doses of 10 to 40 μg/kg markedly increased TNF-α release but significantly decreased IL-10 release in sera (Figures 5D,E)."

41 **Spore Effects**

- "To further verify the in vitro results, lung tissues were taken from SIV-infected mice exposed to AFB1 to assess viral replication...and histological damage.
- The areas of hemorrhage are denoted with the blue arrows.
- SIV-infected mice exhibited decreased weight gain, but enhanced... inflammatory cell infiltration compared with mice from the blank group, and these changes were aggravated following exposure to 10–40 μg/kg AFB1.
- AFB1 promotes SIV replication and lung damage in mice."

42 **Spore Effects**

- "...given the differences in morbidity and mortality following SIV infection, we hypothesize that AFB1 promotes SIV infection.

43 **Spore Effects**

- "...macrophages are the first line of defense against viral infection,...critical for the defense against influenza virus infection.
- M1 macrophages produce proinflammatory cytokines, thus contributing to host defense against pathogens and tissue injury;
- M2 macrophages produce anti-inflammatory cytokines, thus promoting tissue repair.
- The phenomenon of the existence of the two contrasting M1/M2 phenotypes is referred to as 'macrophage polarization'.

- Macrophage polarization can occur at any point in an inflammatory process;
- multiple phenotypic markers, cytokines and growth factors, such as nitric oxide synthase (iNOS), TNF-α and IL-10, interact to determine the final polarization state.
- Previous studies indicated that AFB was immunotoxic to porcine alveolar macrophages (PAMs) and that AFB leads to time- and dose-dependent decreases in the viability and phagocytic activity of PAMs;
- furthermore, AFB decreases proinflammatory cytokine levels and increases anti-inflammatory cytokine levels in macrophages. "

44 **Spore Effects**

- "Inflammatory cell infiltration, inflammatory cells in the bronchial lumen and areas of hemorrhage are denoted with the black, yellow and blue arrows, respectively.

45 **Spore Effects**

- Low levels of AFB promote SIV infection, inflammatory responses, immune organ damage, induce a switch in alveolar macrophage polarization from M1 to M2, and confer poorer outcomes in SIV-infected in mice.

46 **Mold Wins**

- Breathing changes ~
  Shallow, airway constriction
- Chronic inflammation ~
  All resp passages
  Nasal, sinus, lung
- Airway remodeling ~
  Lower lobes of lungs
  Scarring
- Immune deficiency ~
  Mucosal lining
  NK cell dysfunction
  T- and B-cell disorder
- Neuroinflammation
- Parallel GI tract inflammation
- PMID: 23710148

47 **Recognized Human Impacts**

- Allergic (IgE-mediated) ~
  Allergic rhinitis
  Hypersensitivity Pneumonitis
  Asthma
- Non-allergic (non IgE-mediated) ~
  Non-IgE mediated asthma exacerbation
- Infection ~
  Aspergillosis
- PMID: 24368325

48 **Mold: Mis*sed*Diagnoses**

- Seasonal Allergies
- Chronic Sinusitis
- Interstitial Lung Disease
- Anxiety/Depression
- Tinnitus
- Sarcoidosis
- T-cell Abnormality
- Acquired Immunodeficiency
- Chronic Fatigue Syndrome
- Interstitial Cystitis
- Nephritis
- Insomnia/Sleep Apnea
- Dysautonomia/Neuropathies
- Mast Cell Activation Syndrome
- Cancer
- PMID: 26738372, 25616361, 25745963, 22253638

49 **STORY | Carpet Mushrooms**

- College friend invitation to see her carpet mushrooms
- Three species of mushroom crops sprouting up through her carpet

- Repurposed barn to a cottage
- Initial ~ acne and fatigue
- Next ~ nausea and decreased appetite
- Cyclical vomiting syndrome
- In 3 months, developed kidney disease
- Too sick to go to school or work
- No explanation for why this previously fit, healthy 20-yo woman was falling apart so quickly
- A few weeks out of the cottage, she started to feel a little better
- Her chiropractor asked about her living environment and made connection
- More than a building issue, it was literally killing her
- Took years to recover kidney function
- * * *

50 **Mold, Colonization & Biofilm**

51 **Colonization**

- Different than infection (Aspergillosis)
- Sinuses of normal controls ~
  fungus, bacteria normal findings
- So what's the big deal?
- Only sick people's fungal colonies behave badly
  form mycotoxins
- Colonization
  sinuses (>90%), lungs, GI tract
- PMID: 24368325, 23710148

52 **Colonization, biofilm, or both?**

- Mycotoxins ~ competitive survival tactic
- Other microbes in sinus to compete?
- Culprits ~ MARCoNS, Pseudomonas, Klebsiella

- Chronic rhinosinusitis patients
  endoscopic sinus surgery
  those w biofilm ~
  more severe disease preoperatively
  persistence of postoperative sxs
  ongoing mucosal inflammation
  increase infections
- PMID: 20537281, 24368325, 23710148

53 **My Theory**

- Persistence despite Avoidance?
- Normal controls: +fungus, -mycotoxins
  Sick pts: +fungus, +mycotoxins
- WDB exp is the key ∴ mycotoxins the trigger
- If susceptible and/or sufficient exposure duration:
  Mycotoxins trigger protective mechanism
  Conversion of healthy microbiome to pathogenic biofilm
  Fungal overburden
- Once recovered, mycotoxins can re-trigger old pattern
- Theory explains persistence and flares
- Rationale for effectiveness of antifungals w/o infection Dx

54 **Biofilm**

- In nature, is more the rule than the exception
- Slime layer
- Mixed microbial inhabitants
- Matrix-like compound
  Protects & adheres inhabitants
- Quorum sensing
  Share survival information
  Collectively survey host immunity
  Determine when to reproduce
- Assist and compete (Mad Max)

- Study | “microbiology of sinusitis is influenced by prev antimicrobial therapy, vaccinations & the presence of normal flora capable of interfering w growth of pathogens.”
- PMID: 27086363

55 **The Key Is . . .**

- Exposure to a water-damaged building

56 **Review**

- Personality profile ~ a survivor
- Mold’s Specific Carbohydrate Diet
- How mold creates harm
- Mold, biofilm, and colonization

57 **Thank You**

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-
- Dr. Jill Crista
- Naturopathic Doctor
- support@drcrista.com