

1 **Are You Missing Mold Illness?**

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2 **Scary Scary Mycotoxins**

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

3 **Mycotoxin Overview**

- What's a mycotoxin anyway?
- Negative health impacts
- Mycotoxin affinities & the body
- Other than mycotoxins

4 **STORY | Stressed Out**

- Woman, Mid-40s, CFS & "stress"
- Fatigue, sinus congestion, allergies, insomnia
- Episodic unnerving feeling of dread, Dxd panic attacks
- Incr freq, < work/travel
- "High strung" at work, exhausted when not
- Steroidal sinus spray qd-bid
- Tylenol PM hs
- Antianxiety Rx - s/e anxious/fatigue next day

- Work~historic preserv in restored Victorian mansion
- Bldg described as “musty” but had “gotten used to it”
- Hobby ~ historic sites/historic B&Bs
- Labs~ mult strains sinus fungus+hi urine mycotoxins
- Work building had an invisible mold problem
- Didn’t connect the dots that work caused her sinus issues/panic attacks bc neither happened immed
- Moved locations for work/tx for mold
- >fatigue, stress, panic attacks, allergies, sinuses, sleep
- Steroid sinus spray/Tylenol PM d/c’d over time
- Panic attacks dt mold, not an inability to handle stress
- * * *

5 What’s A Mycotoxin Anyway?

6 Mycotoxin Reminder

- Ergotism - Middle Ages St. Anthony’s Fire, Salem Witch Trials
- Ergot - mycotoxin from infected grain caused convulsions gangrene via small vessel vasculitis
- Ergotamine - used in different Rx forms for postpartum hemmorrhage, migraine, analgesia
- Alcohol - brewer’s yeast

7 Mycotoxins Of Concern

- Aflatoxin
Aspergillus flavus, A. parasiticus
- Chaetoglobosin A,C
Chaetomium globosum
- Gliotoxin
Aspergillus fumigatus
- Ochratoxin A
Aspergillus ochraseus, A. niger, Penicillium verrucosum, P. nordicum, P. chrysogenum

- Sterigmatocystin
Precursor of Aflatoxin, *A. versicolor*
- Trichothecenes (..Zearin)
Stachybotrys chartarum, *Trichoderma viridae*, *Fusarium* spp

8 **Wide Structural & Biosynthetic Diversity**

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9 **Mycotoxins**

- Produced by all fungal elements
- Vary by mold species
- *****Lipophilic***** molecules
- Secreted onto substrate & aerosolized
- Wide structural and biosynthetic diversity
- Energetically expensive
- Competitive inhibition of other microbes
- Interfere with vital cellular processes
protein & RNA/DNA synthesis
∴ most are cytotoxic

- Harmful to human health
- Inhaled, ingested & absorbed
- Commodified for oncology & weaponized

10 **Question**

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- True or False?
- You know you have a mold problem, because it stinks

11 **Answer**

- False!
- Mycotoxins, the most toxic part of mold, which seep through building materials and poison indoor air, have no scent
- Musty or moldy smells are from other mold chemicals, and need air exposure to stink. If it's trapped, you can't smell it

12 **Negative Health Impacts**

13 **Mycotoxins ~ Health Impacts**

- Immunotoxic
- Neurotoxic
- Alimentary toxic
- Dermatotoxic
- Nephrotoxic
- Hepatotoxic
- Hepatocarcinogenic
- Genotoxic
- Teratogenic
- Carcinogenic
- PMID: 26474839, 27178040, 25449202, 12221236, 26600019

14 **Mycotoxins ~ Health Impacts**

- Highly inflammatory to resp tissue
- ↓ ciliary clearance due to sm size
- Airway remodeling if persistent
- Some xBBB and reduce its integrity
- Inhalation ~ olfactory n. to hippocampus, frontal lobe
- Many cross the placenta
bioactivate in utero
- Found in breast milk
- Implicated in neuropsych, ASD pathogenesis
- PMID: 26474839, 27178040, 25449202, 12221236, 26600019, 19854819, 29880330

15 **Mycotoxins ~ Health Impacts**

- Induce apoptosis of intestinal epithelia
- Induce bladder wall irritation/ulceration
- Modified by multiple enzymes ~
Cyt P450s, glutathione S-transferases, UDP-glucuronosyltransferases, sulfur-transferases
- Deplete glutathione
- Cause mitochondrial damage
- Nrf2 ("oxidant thermostat") activation & depletion
- PMID: 26474839, 27178040, 25449202, 12221236, 26600019

16 **Mycotoxins ~ Health Impacts**

- Interfere with protein synthesis:
DNA/RNA, actin/myosin(muscle/cardiac), keratin/elastin, enzymes, immune globulins, hemoglobin, albumin
- Inhibit host defense
 - ↓ antibody-producing cells
 - ↓ antibody titres in blood serum
 - ↓ phagocytosis
- Relative lymphopenia, neutrophilia, eosinophilia

- PMID: 26474839, 27178040, 25449202, 12221236, 26600019, 7637687

17 **Mycotoxin Affinities & The Body**

18 **Aflatoxin**

- Hepatocellular carcinoma
esp pre-existing Hep B
- EBV-associated Burkitt's lymphoma
- Desquamative Interstitial Pneumonitis
- Immune impairment
decr lymphocytes & sIgA
- Encourages viral replication with increased inflammation
- Polymorphisms in CYP3A5 affect susceptibility
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- PMID: 27571469, 26424750, 15735246

19 **Chaetoglobosin**

- Crosses BBB
- Oncology uses provide clues:
 - CLL - induce apoptosis of leukemic cells via cytoskeleton
 - Ovarian - induces apoptosis cisplatin-resistant CA cells
 - Inhibits tumor angiogenesis via downregulation of vascular epithelial growth factor-binding hypoxia-inducible factor 1alpha.
- Mouse study: necrosis of thymus/spleen, spermatocyte degen
- PMID: 24280868, 25304379, 23695013, 713122

20 **Citrinin**

- Toxic effects on the heart, liver, kidney, intestines, reproductive
- Broad spectrum of bioactivities
- Oxidative stress + mito dysfunction
- Triggers endoplasmic reticulum (ER) stress

- Intestines ~
 - ↓ nmbv viable human intestinal cells Induced apoptotic events via:
 - mito membrane permeability
 - activates programmed cell death enzyme
 - elevated production of ROS
- Inhibits oocyte maturation and early embryo development
- PMID: 28993214, 29165056, 28404941

21 **Diacetoxyscirpenol (DAS)**

- Crosses BBB, neurotoxic
- Developmental exposure "reversibly" disrupts hippocampal neurogenesis via ~
 - Apoptosis of neural stem cells
 - Induce oxidative cellular injury
 - Suppress differentiation of granule cell lineages
- Large bowel toxicity
- Fertility ~ cytotoxic effects
 - Decr male-related fertility, direct toxic effects on the testes
- PMID: 10626642, 31836554, 31791183

22 **Enniatin**

- Crosses BBB, neurotoxic
- Apoptotic
- Brain carcinogenic ~
 - Astrocytoma cells most sensitive
 - Brain capillary endothelial cells
 - Brain microvascular endothelial
- Fertility ~ Cytotoxic effects
 - Pre- + post-implant embryos
 - Induce intracell oxidative stress and immunotoxicity in fetuses
- PMID: 29768483, 30259633

23 **Gliotoxin**

- Not specific to brain. Named after fungi.

- Disulfide bond ~ unique to other mycotoxins (affects IgG subclass III preferentially bc of it's prevalence of disulfide bonds)
- Immunosuppressive: T-lymph, PMNs, macrophages, monocytes, NK cells
- Inhibits Nf-kB (cytokines) yet incr ROS
- Mitochondria
reduced ATP
hyperpolarized membrane
- Decreases rate of protein synthesis
- Neurotoxic
- Depletes glutathione
- Inhibits histone methyltransferase (MCAS?)
- PMID: 26445050, 26258781, 23278106, 22148349, 24039048

24 **Ochratoxin A**

- Kidneys ~ nephropathy, acute renal failure, chronic interstitial nephropathy, renal carcinogenicity
- Renal fibrosis with chronic exposure
- Inhib protein synthesis + energy prod
- Depletes glutathione, incr intracell ROS
- Immune ~ cytotoxic to neutrophils
- Carcinogenic effects ~ combined direct and indirect mechanisms (genotoxicity, oxidative stress, epigenetic factors)
- Male specific neurotox → mRNA changes poss trigger for autism & its male prev
- PMID: 27384585, 27092524, 26095584, 27597255, 25597866

25 **Patulin**

- Damage to liver, kidney, spleen, intestines, I/S
- Lung and brain edema
- Retention sites - erythrocytes, blood-rich organs (spleen, kidney, lung and liver)
- Mutagenicity, teratogenicity, chromosomal aberration, DNA strand damage
- Affects the vital organs by damaging DNA
- Classified as Category 3 human carcinogen
- D/c'd past use chemo+Abs bc too toxic/carcinogenic

- Protein synthesis inhibition ~
 Binds to sulfhydryl group on AAs in proteins
 Protein cross-linking w thiol groups, esp cysteine, lysine, histadine (think MCS, viral, MCAS)
- Induces apoptosis via mitochondrial pathway
- I/S ~
 decr IFN-gamma-producing T-lymphs → Th2 dominance → allergies
 Reduces macrophage fxn → reduced innate resistance to pathogens → frequent infxns, autoimmunity, CA
- Note: add yeast to patulin foods for adsorption (apples)
- PMID: 30090541, 12112629, 26394380, 24931906

26 **Trichothecenes In General**

- Cell level ~
- Potent protein synthesis inhibitor, incl DNA/RNA; mito fxn, effects on cell division + membranes.
- GI ~
 - N/V, intestinal epithelial blunting
 - Alimentary Toxic Aleukia
- Lung Inflammation ~
 - Pulmonary Hemosiderosis
- Immune deficiency ~
 - Compromised resistance to infxn, cancer - *Glioblastoma, Melanoma?
 - Haematotoxic ~ coagulation
 - Endocrine disrupter
- PMID: 26572613, 15342083, 27198722, 22982764, 25542145

27 **Zearelanone**

- Endocrine disruptor → reproductive disorders, infertility
- Non-steroidal estrogenic mycotoxin, but still binds to/lowers albumin (risk of C.diff)
- ER binding affinity as potent as coumestrol and genistein, but ERβ is same as affinity for ERα → carcinogenic + immunotoxic

- Arrhythmic (other Fusarium myco DON)
2nd-degree AV block, atrial brady, decr total power

• PMID: 24632555, 28365492, 29868851, 27840141, 21804309

28 Other Than Mycotoxins

29 Mycophenolic Acid (MPA)

- Not technically a mycotoxin
- Part of "other chemicals" secreted by mold as part of normal metabolism
- But mycotoxins formed in competition
- ∴ where there's mold, there's MPA, but not nec mycotoxins
- Readily absorbed (w/in first few hrs)
- Excreted quickly in bile IF liver can detox
- Detox'd/excreted in Phase II as glucuronides
- PMID: 4629779, 28327659

30 Mycophenolic Acid (MPA)

- Compromises intestinal membrane integrity → GI toxicity + leaky gut
- Changes lipid-metabolizing proteins
- Affects intracellular nucleotide levels, nucleotide-dependent processes, expression of structural proteins, fatty acid and lipid metabolism
- Immunosuppressive
- Rx transplant rejection, BRCA tx
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- PMID: 4629779, 28327659

31 Endotoxins

- Bacterial byproducts found in WDBs, humidifiers,
- Highly inflam LPSs
- Change inflam mediators in airways +/- or blood ~
Eosinophils, IL-8, IL-1beta, TNFa, CRP
- Reduce neutrophil count

- SI ~↓ oxygenation enterocytes → hypermotility in attempt to reoxygenate
- GI ~ genetic reduction in replication, energy production, absorption, immunity
- Combo w mycotoxins ↑dmg to liver
- Reduction improves steatohepatitis
- PMID: 11409488, 17878567, 28477419, 26709789

32 Review

- What's a mycotoxin anyway?
- Negative health impacts
- Mycotoxin affinities & the body
- Other than mycotoxins

33 Thank You

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