Mast Cell Activation Syndrome 2020

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Disclosures

- Off-label use of medications:
  No FDA-approved MCAS Rx

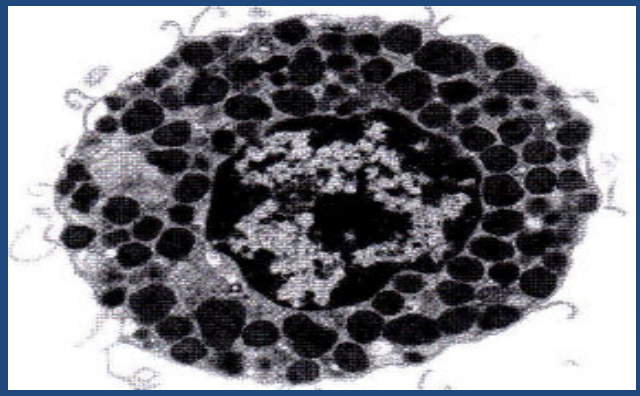
- Medical adviser: MC Science
- Speakers bureau: Salix, Takeda

Teaching points

- What is MCAS?
- Diagnostic criteria: Consensus-2 vs. Consensus-1 groups?
- How is MCAS treated?
- What makes it difficult to treat?
- How might MCAS relate to Covid-19?

Mast Cells

- Large (20 micron), round or ovoid immune cell
- Cytoplasmic granules with “messenger” substances
  ------ “**mediators**” – stored & quickly produced
- Found in all organs and tissues
- Connective tissue & mucous membranes MCs differ
- Located at interfaces with outside world:
  Mucous membranes (nose and mouth),
  Skin, Gut, Vagina, Urethra, Bladder



45 y.o. WF sick for 27 yr

19 MD's

Age 18 - flush, rash, nausea w triggers

Age 20 - bloat, constipation, rotten-egg gas

Ages 23 - 43 - orthostatic intolerance, body pain, fatigue, angioedema, “delayed pressure urticaria”

Ages 37 - 43 - no sleep, liquids, syncope w standing, BM strain, & “big box stores - Kryptonite”

Mayo - diagnosed but she *failed* over twelve POTS & MCAS meds & vascular support

Mast Cell Activation Disease

Mast Cell Leukemia

Aggressive Systemic Mastocytosis

SM assoc w heme malignancy

Indolent SM

Cutaneous Mastocytosis

MCAS

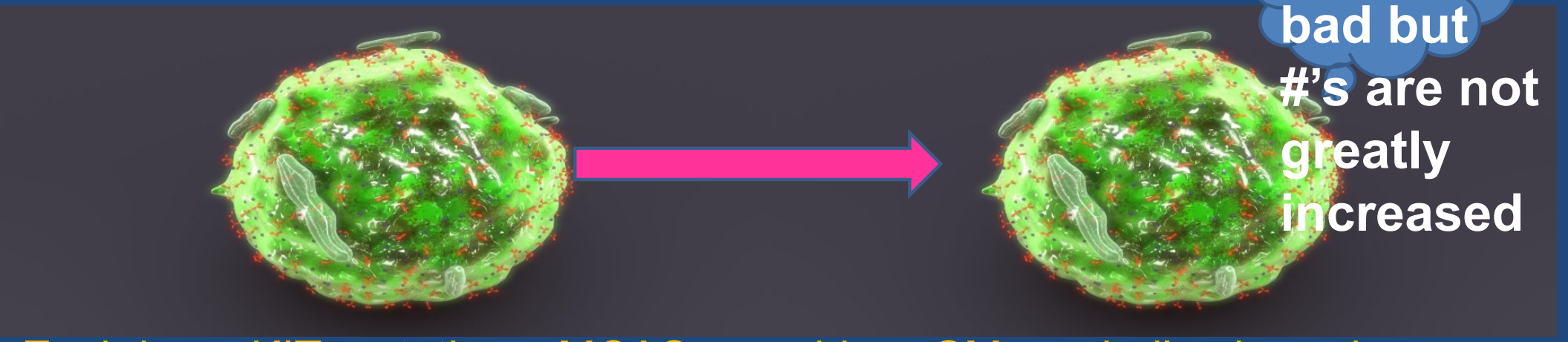
Extremely rare

↓

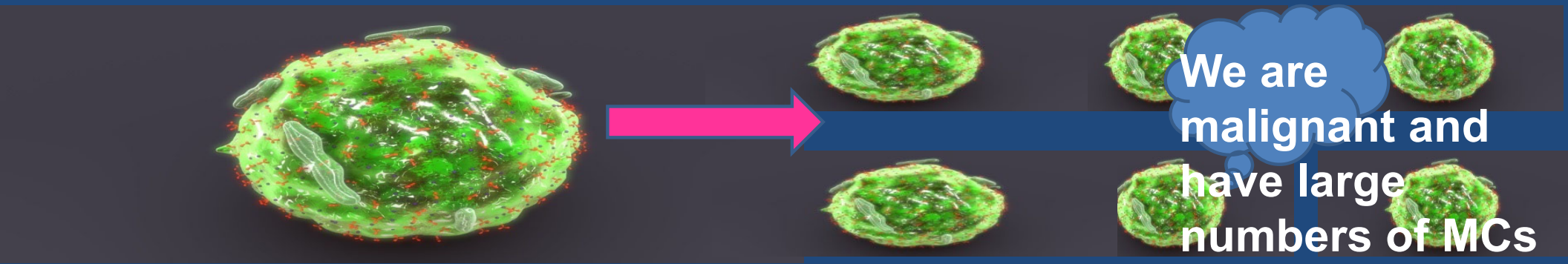
17%

per Afrin 2016

MCAS vs. Mastocytosis



Each have KIT mutations; MCAS – ovoid vs. SM – spindle shaped

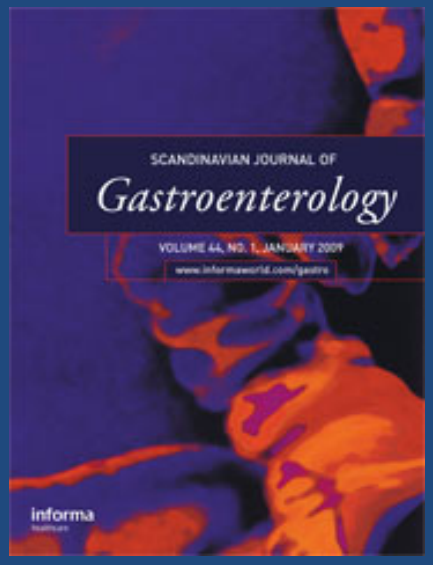


Large #'s of clonal MCs - most in bone marrow; note differences in tryptase

Gerhard J. Molderings, MD, et al.

Multiple novel alterations in *Kit* tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder.

Scandinavian Journal of Gastroenterology. 2006

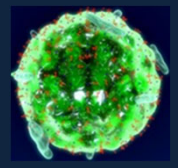


Basics of MCAS

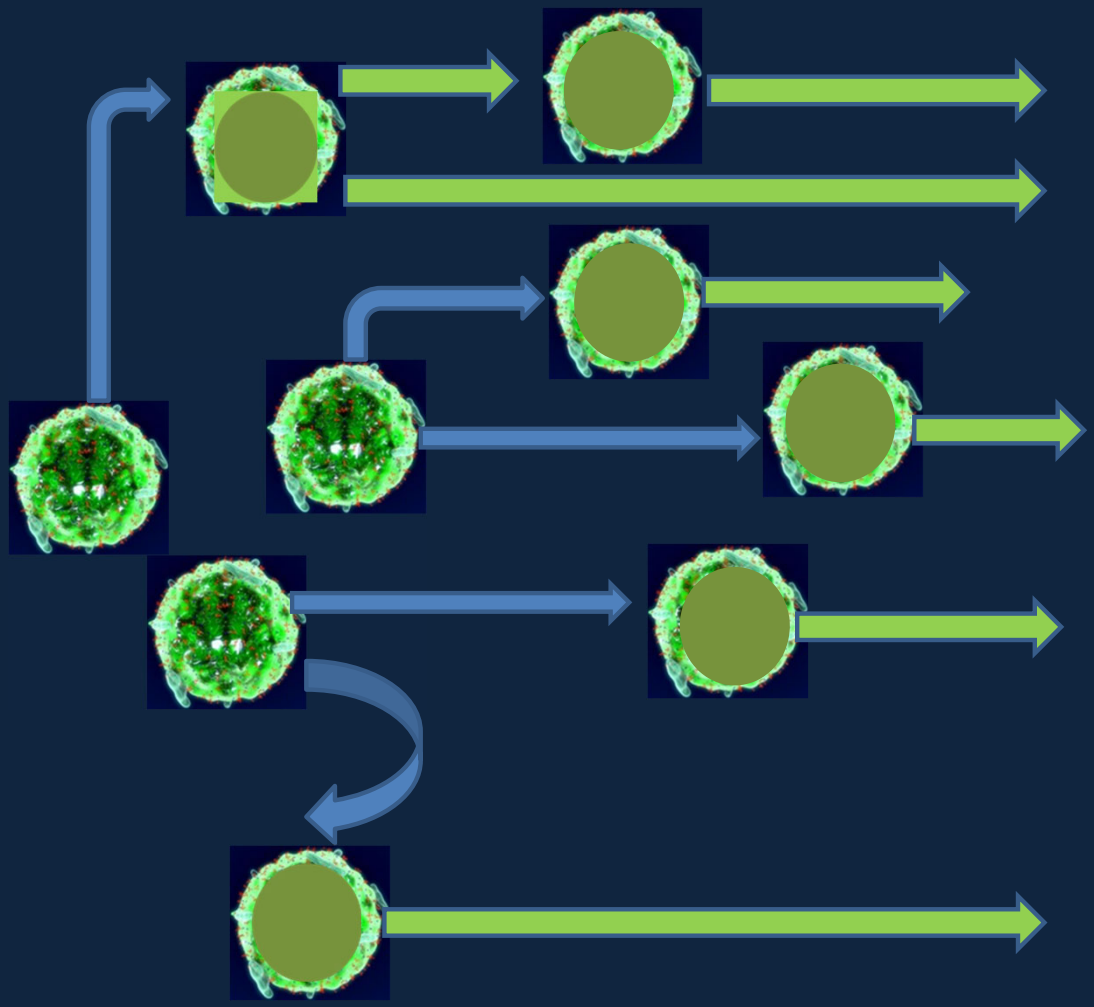
- MCAS often congenital: epigenetic disorder induces somatic mutations in some MC progenitor cells
- Aberrant MCs are few at birth & increase with age
- Rarely serious as infant/child, Sx often resolve & worsen as teen and adulthood
- Aberrant MCs are instigators of MCAS yet remain less in #
- Mediators of aberrant MCs activate healthy MCs & their mediators do the same to neighboring MCs
- Mediators of healthy MCs are main inducers of Sxs

Molderings. Crit Rev Onc Hem. 2015.

MCAS



Mutant MCs secrete mediators in an uncontrolled manner



Normal MCs are activated by MC mediators & secrete more mediators & activate other MCs

MCAS: Etiology

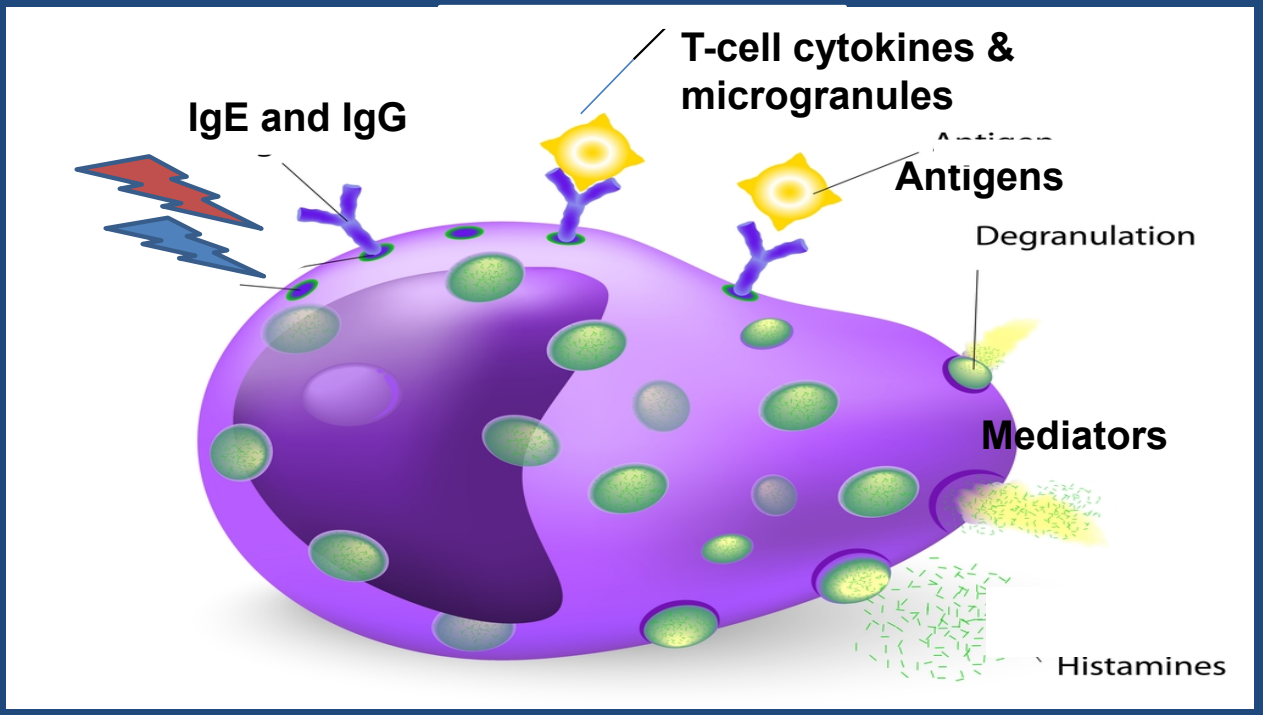
Includes at least 3 components

Step 1 Epigenetic

Step 2
- Genetic

Step 3
- Environmental

MC Activity in MCAS



- Aberrant release of mediators
- Many receptors
- T cell microparticles activates MCs

Shefler. J Immunol. 2010.
Afrin. Clin Ther. 2015.

MCAS: 1035 Mediators!

General categories

- Histamine
- Proteases (tryptase…)
- Heparin
- Pro-inflammatory cytokines (TNF-α…)
- Vascular permeability and dilators
- Leukotrienes
- Platelet aggregation factor
- Antimicrobials

MCAS Clinical Presentation

- Onset often < 20 y.o. - unrecognized for decades
- Usually multi-systemic
- Sx often “inflammatory”
- Perplexingly inconstant course:
  - Abnormalities often externally inapparent
  - Chronic, waxing/waning, or episodic
  - Different sx at different times
  - Often no obvious triggers
- Many doctors, many syndrome dx’s
- Pts commonly cease reporting sx

Molderings et al. J Hematol Oncol. 2011.

MCAS: Systemic Syndrome

- Constitutional – fatigue, fever, wt. loss/gain
- CNS – migraines/HA, brain fog, panic attacks, anxiety, depression, insomnia
- Esophagus – GERD, dysphagia, chest pain
- Stomach – nausea, dyspepsia
- LGI – bloating, abdominal pain, constipation, diarrhea
- Liver – increased enzymes
- Immune – poor healing

Afrin. Am J Med Sci. 2017.
Divoux. J Clin Endocrinol Metab. 2012.

MCAS: Systemic Syndrome

- CVS – tachycardia, chest pain
- Urinary tract – interstitial cystitis, frequency
- Ocular – conjunctivitis
- Salivary glands – swelling
- Skin – flushing, hives, rashes, swelling, itching
- Pulmonary – dyspnea, asthma, cough
- Extremities – pain, swelling, vasospasm, numbness

Afrin. Am J Med Sci. 2017. Divoux. J Clin Endocrinol Metab. 2012.

MCAS Sx (50% percentile)

- Fatigue
- Muscle pain
- Pre-syncope or syncope
- Headaches
- Itching
- Urticaria
- Nausea
- Chills
- Edema
- Eye irritation
- Dyspnea
- Heartburn

Afrin. Am J Med Sci. 2017.

Diagnosis

Important Hx Questions

- Symptoms of anaphylaxis
- Reactions to insect bites
- Sensitivity to odors … HA, nausea, faint
- Tinnitus (60%)
- Bloating: SIBO in 30%
  spontaneous bloat = mediator phenomenon
- Restless legs syndrome (40%)

Past Medical/Surgical Hx and FHx

Childhood and Puberty

Colic, reflux, eczema, asthma,
HA, GI Sx, severe menses

Surgical Hx

Ineffective surgery
Mesh

FHx

Odd, undiagnosed, chronic conditions

MCAS ROS the Easier Way

Mast Cell Mediator Release Syndrome Questionnaire

Patient name _____

Date _____

Date of birth _____

Answer all of the following symptoms/questions, even if they are only slightly bothersome, rarely occurring (for instance, not necessary present currently but in the past), or may seem not be related to your main problems.
Contact your doctor if you have difficulty completing the questionnaire.

Check (✓) inside the box if the statement applies to you.

If the statement applies to you, enter the intensity level when it was present the last time it occurred on the line next to the box. Please use the range of 1 (very mild) to 10 (unbearable) to reflect the level of your discomfort.

6 7 8 9

Applies Intensity

tigue doing everyday activities

rd to keep eyes open

taining my normal diet

aints are worsened by:
than 24 hours)..... □ **1**

..... □ **1**

wine, cheese, chocolate,

meat, left-over

..... □ **0**

may be constant:

MCMRS: 5 pg, validated, self-administered

57 questions - symptoms potential of 40 points

Additional points for labs and biopsies

≥ 14 c/w MCA

Consensus-2 Criteria for MCAS

MCAS diagnosed by:

Major criterion plus ≥1 minor criteria
and rule out other diagnoses

Molderings , Afrin 2016.; Afrin et al 2020

MCAS: Major Criteria

Constellation of complaints attributable to pathologically increased MC activity

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≥2 organ systems w typical disorders: skin, CVS, respiratory, GI, nasal, ocular, and/or anaphylaxis

≥5 organ systems in the 2013 publication

Molderings and Afrin. F1000 Res. 2016.; Molderings. PlosOne. 2013.

MCAS: Minor Criteria

- Response to MC therapy
- Increased MC mediators
- Biopsy >20 MC/hpf

(and no other disease explains symptoms)

Molderings, Afrin 2016

Consensus-1 for MCAS Dx

1. Severe, recurrent MC sx (often anaphylaxis) involving ≥ 2 organs incl. urticaria, flushing, pruritus, angioedema, nasal congestion/pruritus, wheezing, throat swelling, hoarseness, headache, hypotensive syncope, tachycardia, cramping, & diarrhea

2. Incr. mediators "preferably tryptase or incr. tryptase from baseline plus 20% + 2 during attack"; or "less specific mediators" (histamine, N-MH, PGD_2, heparin)

3. Response to MC-directed Rx

Valent et al. J All Clin Immunol Pract. 2019.

MCAS Workup: Physical

Skin examination

Orthostatic pulses

Joint hypermobility

- Beighton score
- Skin changes (elbows, heels)

MCAS Skin Changes

Flushing

Atypical acne

Ecchymosis

MCAS Vascular Changes

Hemangiomas

Flat or raised.
Usually trunk.

With attacks they can itch, burn, or multiply and after the attack they can regress.

Difficult to see on Zoom

MCAS Skin Changes

Hives

Pruritis w/o rash

Rashes

MCAS Vascular Changes

Telangiectasias

Shoulder in 56 yo – pt unaware

Chest in 28 yo – present since age 12

MCAS Growth Changes

MCAS Workup: Labs

- 50-75% yield:
  - *Chromogranin A**
  - *Histamine (plasma)**
  - *Prostaglandin D2 (plasma)**
  - Heparin (only with ultrasensitive lab – N.J. & Germany)
- 15% yield
  - Tryptase* (if ≥20 R/O SM & HAT – 7% prevalence of HAT)
  - Urine: 2,3,-dinor 11-beta-PGF2-α, N-methyl-histamine, & leukotriene E4

* Lyons. Hereditary Alpha Tryptasemia. Imm All Clin N Am. 2018.

MCAS Lab Issues

- Only 6 different classes of mediators can be tested
- Temperature sensitive
  - Cold centrifuge plasma
  - Freeze for transportation
  - Keep cold during urine collection
  - Freeze urine for transportation

- Need to be off PPI, NSAID, ASA, Vit C/D, etc. 5 d
- H1/H2 probably OK
- PG-u “unidentified interfering substance prevents testing”

MCAS Lab Issues

Tryptase

- Normal in 85% of MCAS
- Gauge of total body load of MCs (not MCAS)
- Increase of 20% plus 2 during attack
  - No data in literature
- High levels
  - Rule out systemic mastocytosis by bone marrow
  - Rule out HAT – hereditary alpha tryptasemia
    - Extra copies of *TPSAB1* [Gene by Gene]

MCAS Lab Issues

Heparin

- Standard assay: normal in nearly all pts
- Highly sensitive assay: low levels are detected of *endogenous* heparin
- 60-80% abnormal levels in MCAS
- Siemen or Chromogenix assays
- Plasma level might correlate w heparin stain in Bx

1. Vysniauskaite. Determination of Plasma Heparin Level Improves Identification of Systemic Mast Cell Activation Disease. PLoS One. 2015; 10(4): e0124912.
2. Ribatti. The Staining of Mast Cells. Int Arch Allergy Immunol Actions 2018.

MCAS Lab Issues

Chromogranin A

- High w PPI (can take ≥ 5 days off)
- CHF
- CRF
- Chronic liver disease
- Atrophic gastritis
- Neuroendocrine tumors

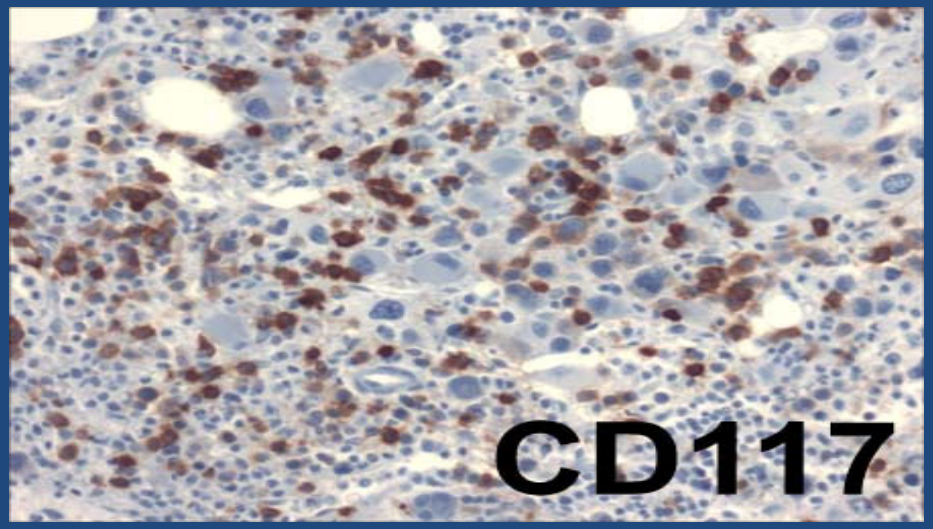
MCAS Lab Issues

Histamine

- MC activity: anaphylaxis, urticaria, opioids, heme CA, CRF, excess hist. ingest., hist. N-methyltransferase polymorphism, DAO deficiency
- Basophil activity: allergies, heme CA
- Eosinophil activity (parasitemia, eos enteritis)
- 1^{o} or MC-induced neuropsych disease

MC Detection: Biopsy

- H&E: MC granules only at 100x under oil
- CD117 stain is ideal (>20/HPF is “abnormal”)



MCAS W/U: Biopsy Issues

- Biopsies with CD117 stain – attaches to KIT protein (transmembrane tyrosine kinase) – best for # but not activity
  - MCAS – tissue speckled with MC
    - Often see 30-70/hpf; usually round

  vs.

  - Mastocytosis – cells are in aggregates and are mainly spindle shaped >100/hpf
- MCs are common in pts w GI symptoms – in MCAS the # of normal MC > aberrant MC

DDx of MCAS

Differential diagnosis and testing for disorders that are multisystemic diseases, present with some similar symptoms, or exacerbate mast cell activation

Endocrine disorders

Adrenal insufficiency
Diabetes mellitus
Endometriosis
Fabry disease
Porphyria
Thyroid disorders

DDx of MCAS

Gastrointestinal disorders

Amyloidosis
Celiac disease
Cholecystitis
Chronic bacterial infection or post-infectious autoimmune
Hepatitis
Inflammatory bowel disease
Lactose, sucrose, or fructose intolerance

DDx of MCAS

Gastrointestinal disorders – continued

Median arcuate ligament syndrome
Microscopic colitis d/t celiac disease or cryptosporidiosis
Parasitic infection
Small bowel obstruction w & w/o SIBO
Small intestinal bacterial overgrowth

DDx of MCAS

Immunological, Inflammatory and Rheumatologic diseases

Asthma and atopic diseases including chronic urticaria
Chronic fatigue syndrome
Chronic pelvic pain syndromes
Familial Mediterranean fever
Fever of unknown etiology
Fibromyalgia
Food allergy/sensitivity
Heredity alpha 1 tryptasemia

DDx of MCAS

Immunological, Inflammatory and Rheumatologic diseases (continued)

Hypereosinophilic syndrome
Hypermobile Ehlers Danlos syndrome
Hereditary angioedema
Juvenile rheumatoid arthritis
Lupus erythematosus
Sjogren's disease
Vasculitis

DDx of MCAS

Infectious diseases

Bartonella
Mold infection (CIRS)
Syphilis
Tick borne infections
Tuberculosis

DDx of MCAS

Neoplastic diseases

Carcinoid tumor
Intestinal lymphomas
Mastocytosis
Pancreatic endocrine tumors
Pheochromocytoma

DDx of MCAS

Neurologic diseases

Cyclic vomiting syndrome
Migraine
Postural orthostatic tachycardia syndrome
Small fiber peripheral neuropathy

(and others in each category…213 considerations)

Treatment

Tenets of MCAS Rx

Identify & avoid triggers

Block receptors of mediators

Inhibit mediator production

Inhibit mediator release

Molderings. Naumyn S Arch Pharm. 2016.

MCAS Step Rx

Avoidance of triggers	**1st line**	**Stress, heat, alcohol, etc.**
Diet interventions	**1st line**	**Gluten, dairy, & yeast free; Low histamine**
Histamine (H_1) blocker	**1st line**	**Cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine**
Histamine (H_2) blocker	**1st line**	**Famotidine, nizatidine cimetidine, ranitidine**

Weinstock et al. Dig Dis Sci. 2020.

MCAS Step Rx – cont.

Leukotriene blocker	**1st line**	**Montelukast**
Rx co-morbid conditions	**1st line**	**Treat POTS, EDS**
MC stabilizer	**1st line**	**Quercetin, Luteolin**
MC stabilizer	**2nd line**	**Cromolyn**
2nd generation H_1 blocker	**3rd line**	**Ketotifen**
Monoclonal antibody	**4th line**	**Omalizumab**

MCAS Rx

Identify & Avoid Triggers

Food Elimination 3 wks – gluten, dairy, yeast, histamines

Stress
Drugs and Excipients
Odors
Electrical
Vibration
Hormonal
Atmospheric

Molderings. Naumyn S Arch Pharm. 2016.

MCAS Dietary Rx

Food Elimination (gluten, yeast, and dairy – can be important)

- FODMAP-free: 8-fold lower histamine levels after 3 wks in IBS-d pts
- Histamine-free: reduction in spontaneous urticaria (also impt in MCAS)

Good Foods and Supplements

- DAO inhibitor: reduces spontaneous urticaria & migraines
- Apples: range of flavonoids & polyphenols - reduce allergic rhinitis
- Brazil nuts: high selenium content - antioxidant that decreases histamine and PGD2
- Chamomile: Inhibits histamine release
- Fiber: Immunoregulatory effects of fiber & butyrate reduce MC activity

McKintosh. Gut. 2017., IFM Website 2020.

MCAS Dietary Rx

Good Foods and Supplements (cont.)

- Galangal (Thai ginger): Downregulates MC-derived allergic inflammatory reactions by blocking histamine release & pro-inflammatory cytokines
- Moringa: Inhibits histamines release
- Nettle: H1 receptor antihistamine & MC stabilizer
- Onions: Inhibit histamine release; stabilize MCs, & lower histamine levels. Contains quercetin
- Peaches: Inhibit MCA-derived allergic inflammation
- Turmeric: Anti-inflammatory & anti-oxidant properties. Inhibits protease-activated receptors (PAR), which play a role in inflammation and PAR-2 & -4 mediated human MC activation
- Watercress: Inhibits histamines release from MCs

MCAS Rx

Mediator Receptor Blockers

Anti-histamines

Leukotriene blockers

IgE blocker - Omalizumab

Afrin. Exp Hematol Oncol. 2013; 2: 28.
Molderings. Naumyn S Arch Pharm. 2016.

MCAS Rx

Mediator Production Inhibitors

Lipoxygenase inhibitors (zileuton)

NSAIDs (watch for anaphylaxis)

Hydroxyurea (note use in sickle cell - has inc. MCs)

Steroids (acute use only)

Afrin. Exp Hematol Oncol. 2013; 2: 28.
Molderings. Naumyn S Arch Pharm. 2016.

MCAS Rx

Mediator Release Inhibitors: Stabilize MCs

Cromolyn (oral and/or inhaled – watch for initial flare)
Pentosan (especially with interstitial cystitis)
Benzodiazepines
Cannabinoids
Low dose naltrexone
Alpha lipoic acid
N-acetylcysteine
Omalizumab
Tyrosine kinase inhibitors
JAK inhibitor (Ruxolitinib)

Molderings. Naumyn S Arch Pharm. 2016.

MCAS Rx

Mediator Release Inhibitors (cont.):

Tyrosine Kinase Inhibitors (and current FDA-IND)

Imatinib (CML, mastocytosis) ***
Tofacitinib (RA, UC) ***
Sunitinib (renal cell Ca & GIST) ***
Dasatinib (CML)

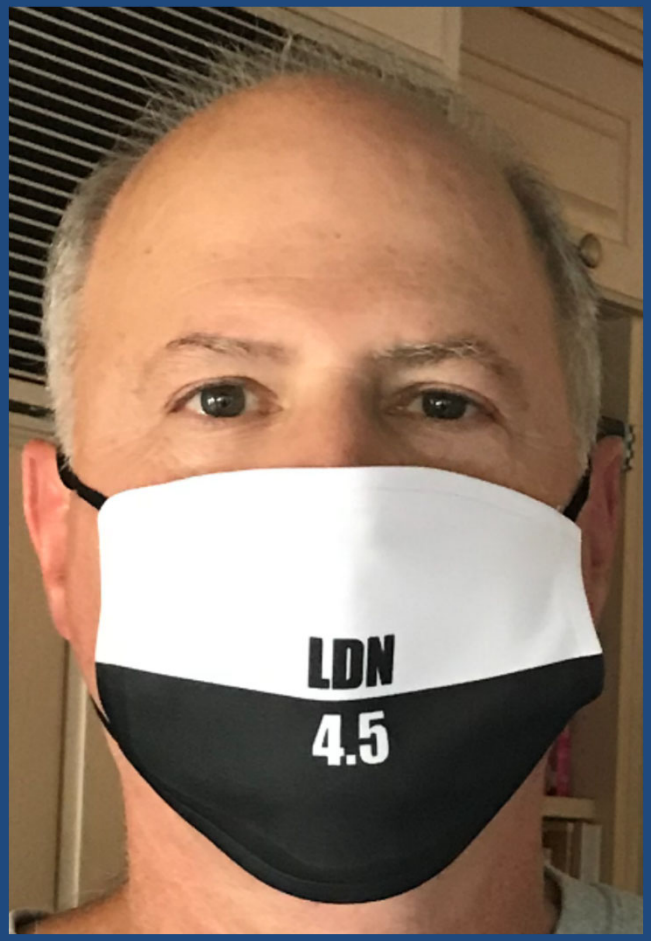
*** MCAS case reports

Afrin. Eur J Haematol. 2015.
Afrin. Eur J Haematol. 2017.

45 y.o. WF – Sick for 27 yrs

Found me via
LDNresearchTrust.org

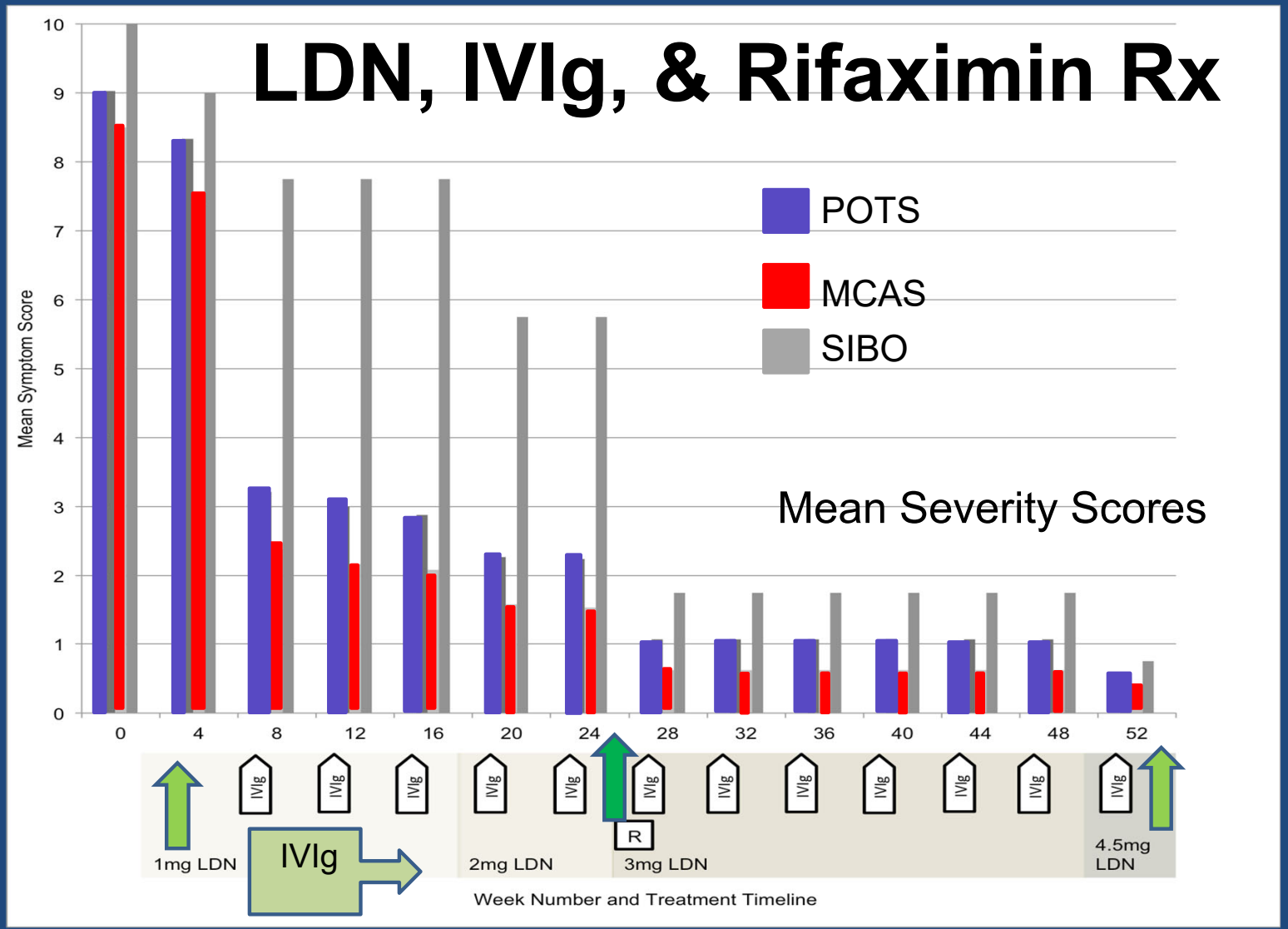
and made me
“MCAS/POTS aware”


LDN
4.5

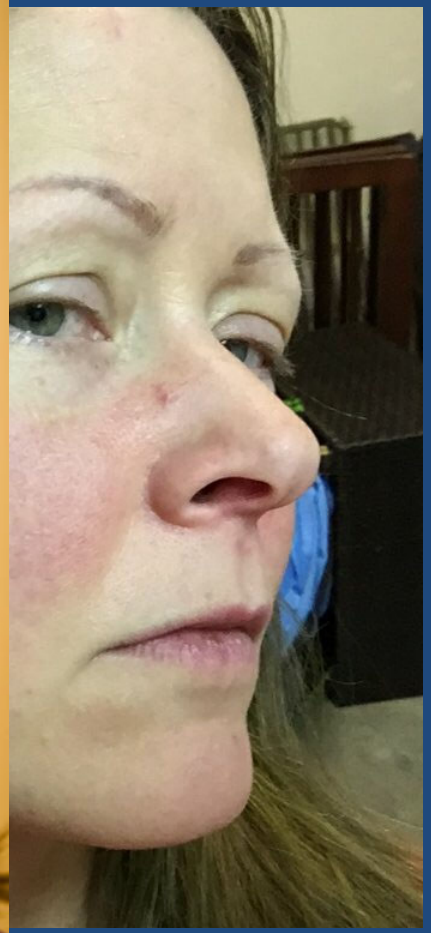
New Rx for POTS & MCAS

- IVIg
- LDN
- SIBO Rx

Weinstock, Brook, et al. Br Med J Case Reports. January 2018.


LDN, IVIg, & Rifaximin Rx
POTS
MCAS
SIBO
Mean Severity Scores
Mean Symptom Score
10
9
8
7
6
5
4
3
2
1
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
IVIg
1mg LDN
IVIg
2mg LDN
R
3mg LDN
4.5mg LDN
Week Number and Treatment Timeline

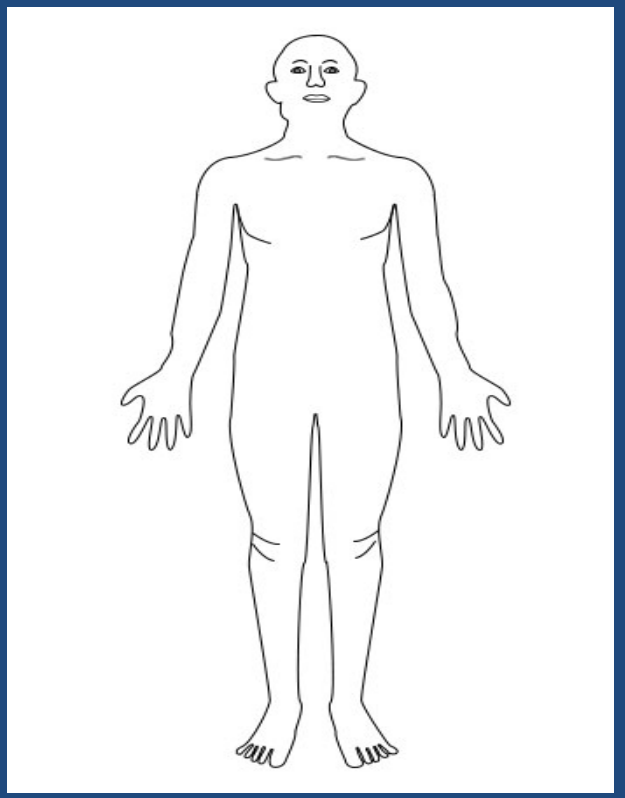
MC-Rx can be life changing



LDN for MCAS Rx

N = 116

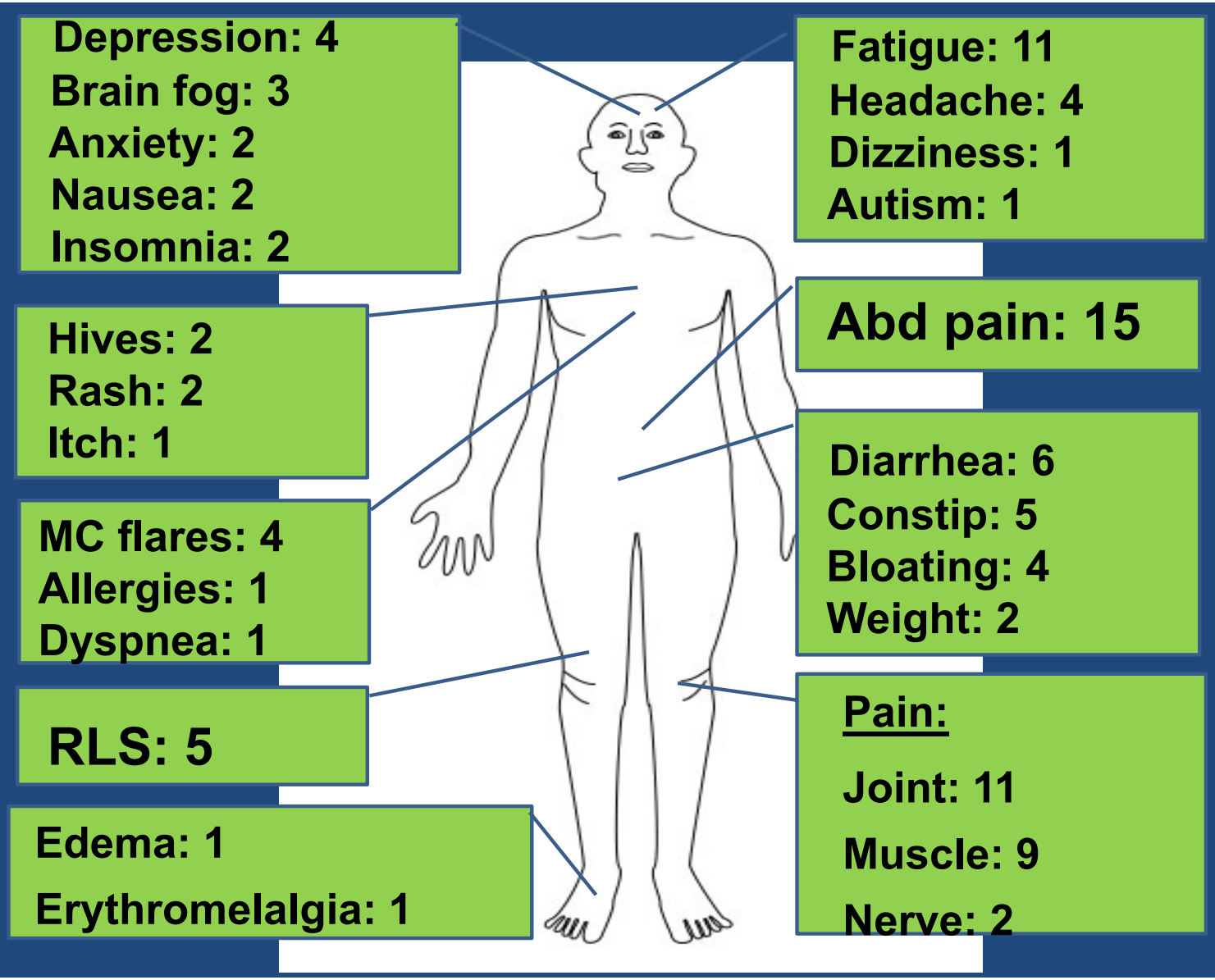
Improved: 60%
No help: 28%
AE led to DC: 22%



Weinstock. LDN and Gut Health. In the Second LDN Book. 2022.

LDN for MCAS Rx

Number of symptoms improved in 70 pts



What to do when Rx Fails?

Check for triggers

Look for a different disease

MCAS Rx Problem #1

Excipient Reactions

Dyes

- Common problem with ranitidine
  (also dyes with white pills)

Preservatives

- Inc. intravenous diphenhydramine

Fillers

- Inc. methylcellulose in those with tree allergies

MCAS Rx Problem #2

- Pseudo-allergies via MC-specific receptor MRGPRX2
  - Fluoroquinolones
- Matching high mediators to specific Rx not predictable
  - High histamine level pts may need more than just H-R blockers
  - High PGD2 level pts may not respond to aspirin (note – common allergy)

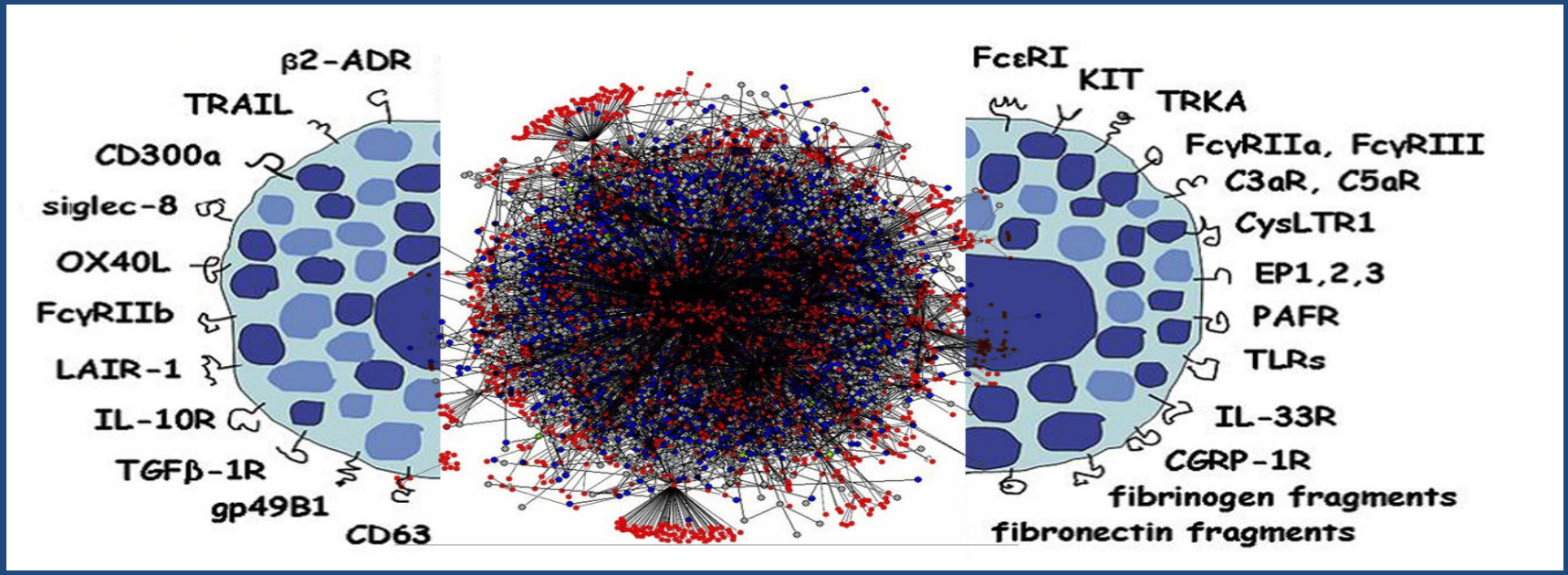
MCAS Rx Problem #3: MCs & Reduced Apoptosis

- Chronic activation of both aberrant & healthy MCs prevents natural apoptosis
- Leads to ongoing accumulation and longevity with individually different activities

MCAS Rx Problem #4: 200 Receptors

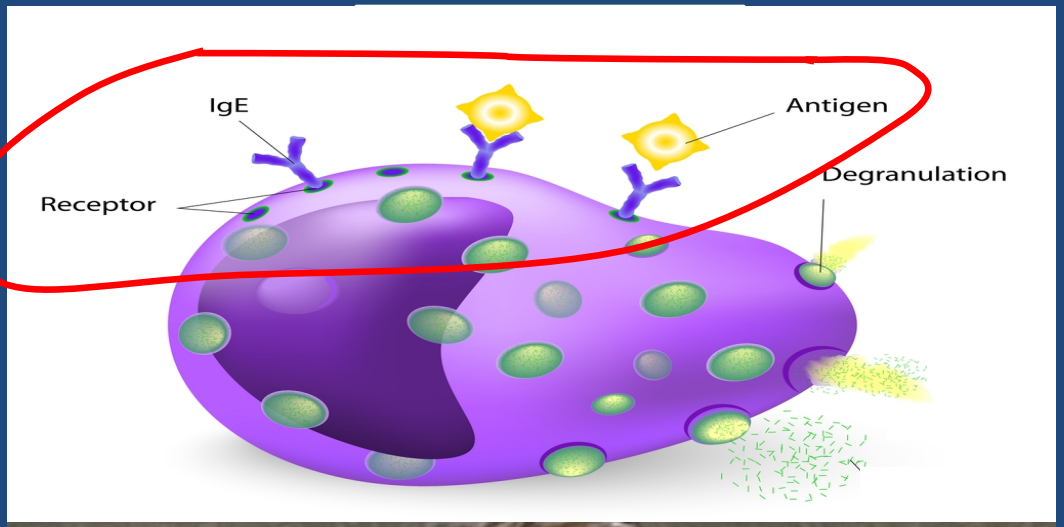
Selected inhibitory recognition sites

Selected activating recognition sites



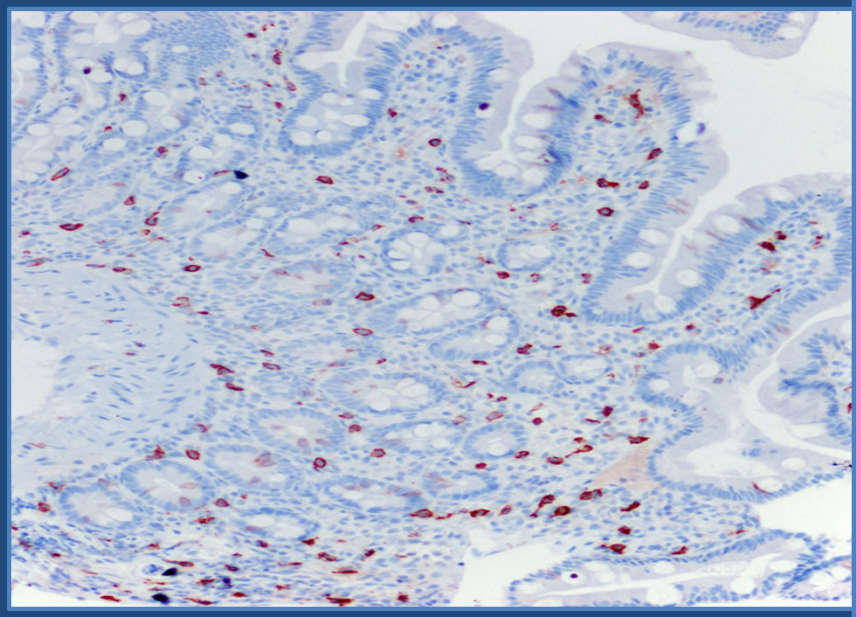
Complete inhibition of MC activity via single receptors cannot be achieved because induced inhibitory effects are compensated by redundant pathways

MCAS Rx Problem #5: Triggers



MCAS Triggers

Additional mutations



- **Diet**
- **Infections – mold, EBV, tick-borne, etc.**
- **Dysbiosis (antibiotics)**
- **SIBO**
- **Stress**
- **Hormones & pregnancy**
- **Heavy metals**
- **Chemicals**
- **Electrical & environmental stimuli**
- **Autoimmune - vaccines**

POTS and hEDS

Note: virtually all MCAS is 1°

Molderings et al. 2014.

Diet as MCAS Trigger

- 38 y.o. WM - spicy food & coffee lead to sudden attacks of pain with marked bloating – multiple ER visits by ambulance – neg GI w/u
- Abdominal pain as baby; nodules age 18
- ROS: fatigue, myalgia, weight gain, incont. w diarrhea, sweats, palpitations
- PE: nodules, moles, hemangioma

Mold as a MCAS Trigger (G-paresis and Pseudo-obstruction)

63 y.o. WM property manager w frequent vomiting Three admits for ileus vs. SBO. Last led to exploratory surgery. Operative report: dilated small intestine w/o transition point or adhesions.

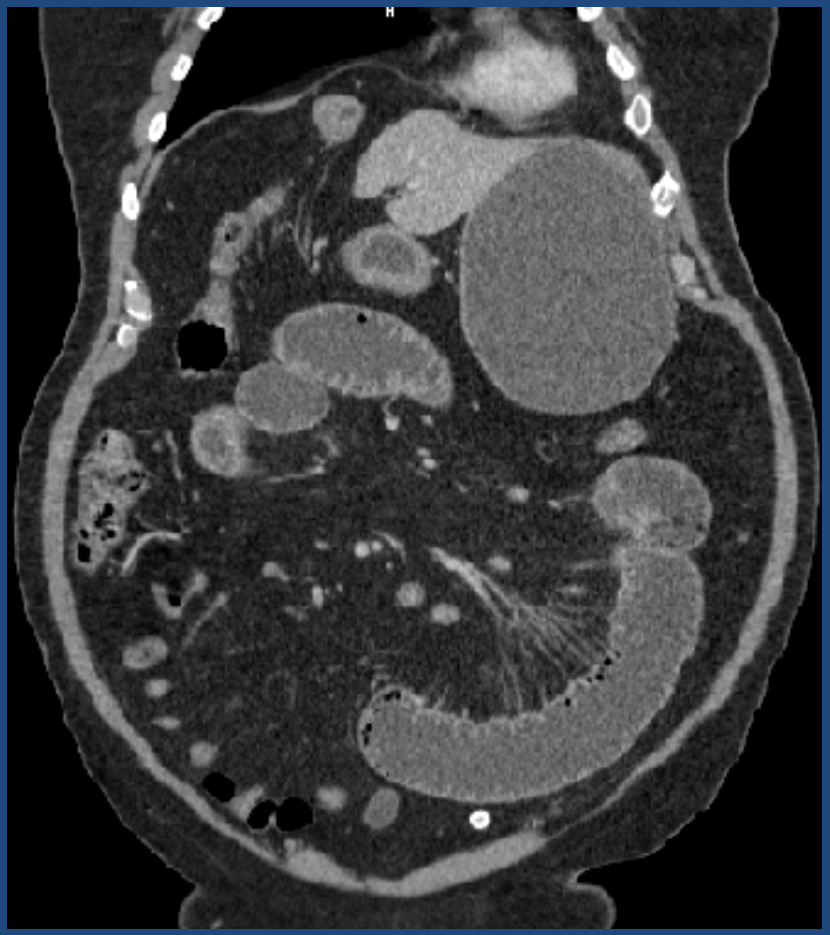
More Hx: attacks going into homes with mold.

Chronic problems: constip., dyspnea, fatigue, chest pain, near fainting, RLS.

Childhood & teens: severe headaches

W/U: histamine 3.9

MC Rx: helping (except w severe mold)



Mold as a MCAS Trigger

31 y.o. WF with “cyclic” nausea & vomiting
Oct 2017: move to old apartment; June 2018: onset nausea
Sept 2019: LW MCAS Dx, Rx failed. Any mold? “No”
2018-2020: 71 ER visits & 11 admissions
Feb 2020: Wernicke-Korsakoff syndrome

Microbiome as MCAS Trigger

- Dysbiosis reduces SCFA (butyrate) which increases MC degranulation & TNF-α

- Increased intestinal permeability leads to MC hyperplasia … role for SIBO … increase infl. & MC activity

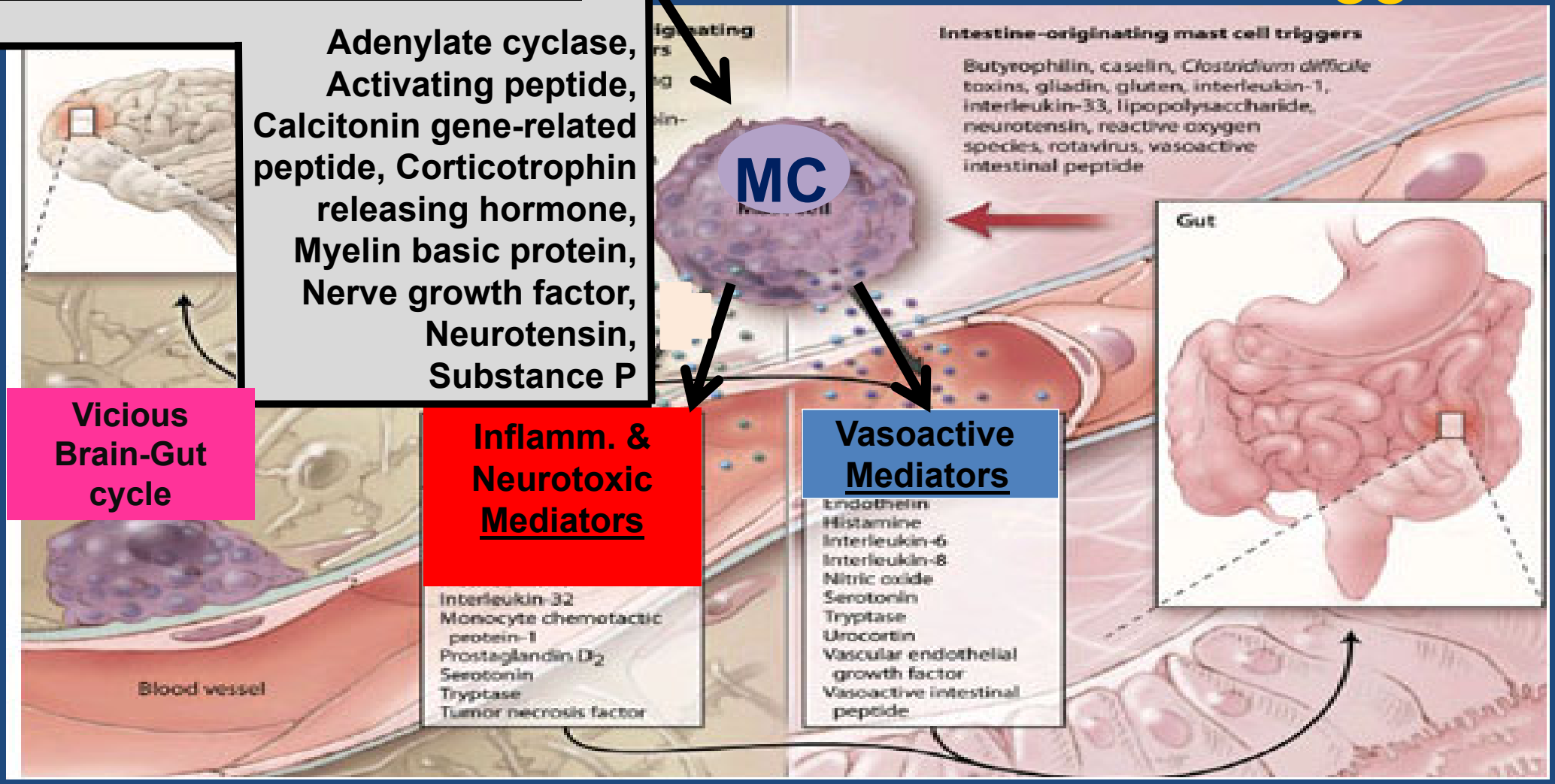
Afrin, Khoruts. Clin Ther. 2015.

Stress as MCAS Trigger

CNS Proteins Activate MCs

Adenylate cyclase, Activating peptide, Calcitonin gene-related peptide, Corticotrophin releasing hormone, Myelin basic protein, Nerve growth factor, Neurotensin, Substance P

Vicious Brain-Gut cycle



Inflamm. & Neurotoxic Mediators

Interleukin-32
Monocyte chemotactic protein-1
Prostaglandin D_2
Serotonin
Tryptase
Tumor necrosis factor

Vasoactive Mediators

Endothelin
Histamine
Interleukin-6
Interleukin-8
Nitric oxide
Serotonin
Tryptase
Urocortin
Vascular endothelial growth factor
Vasoactive intestinal peptide

Heavy Metals as MCAS Trigger

- 69 y.o. w MS as teen
- Nose bleeds, bruises, & RLS as child
- Post op bleeding as adult

- Amalgam extraction w poor technique led to high mercury levels, flushing, hives, rash, & bloating (negative LBT)

MCAS & COVID-19 Infection as a Trigger

&

MCAS as a Risk Factor for Severe Infection and PCIS

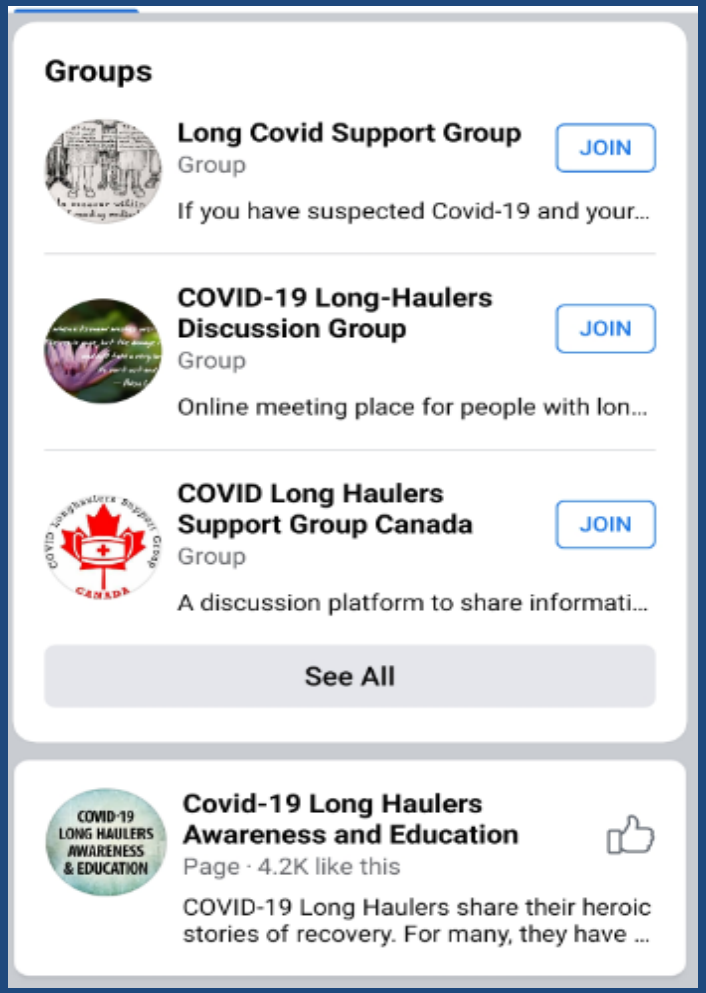
Dermatographism in Post-COVID-19

COVID-19 Hyper-inflammation & POST-COVID-19 Illness May Be Rooted in MCAS

- Cytokine storm is cause for severity of acute infection
- MC activation occurs in COVID-19 infection
- MC orchestrates inflammatory response and releases cytokines
- Three U's: Uncontrolled MCs of Undiagnosed, Untreated MCAS patients may react strongly in response to COVID-19 which then activates normal MCs leading to further cytokines

Afrin, Weinstock, Molderings. Int J Inf Dis 2020. *In press*.

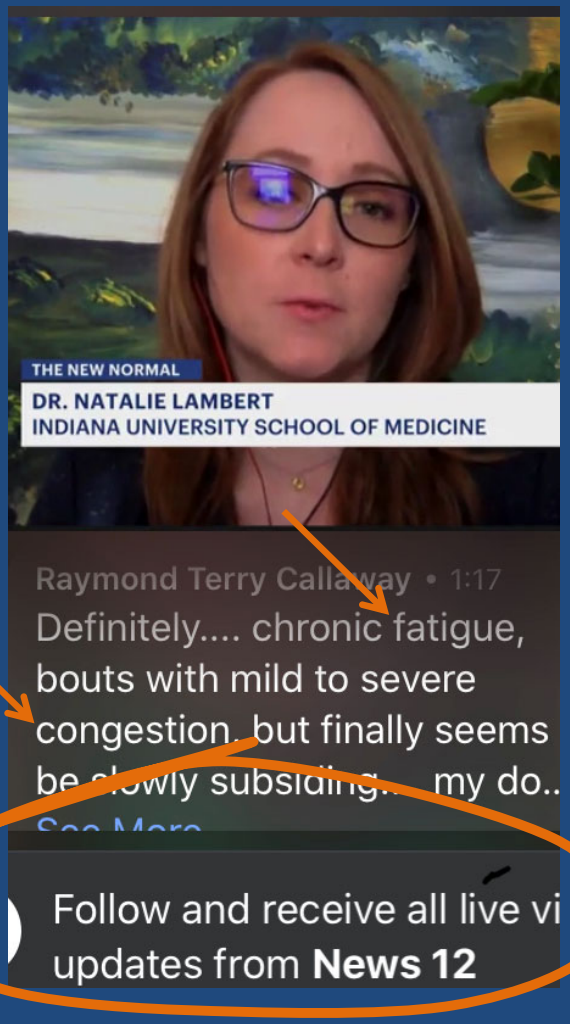
Post-COVID-19 Inflammatory Syndromes



One FB group has 15K members as of 8/20/20 … 20K as of 9/6/20

COVID Long-Haulers
or
Long COVID

Webster Definition:
Long haul =
a long period of time



Post-COVID-19 Symptoms

N=143 pts; 37% F; mean age 57 yrs (range, 19-84 yrs)

73% had interstitial pneumonia; LOS 14 ±10 days;
5% received invasive ventilation

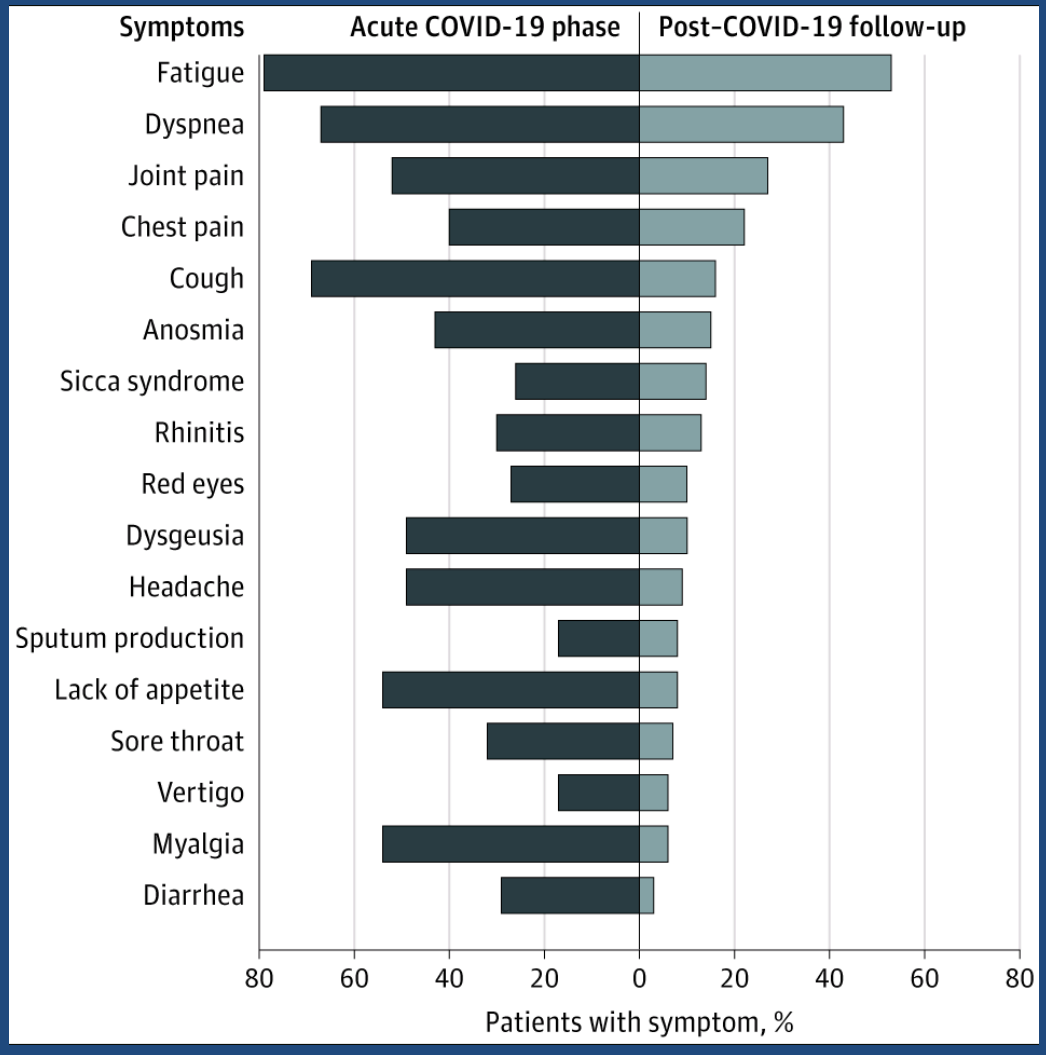
Pts assessed a mean of 60 ±14 days after onset of
1st COVID-19 symptom

At the time of evaluation, only 13% completely free of any symptom

32% had 1 or 2 symptoms and 55% had 3 or more

Carfi. JAMA. 2020.

Post-COVID-19 Symptoms



Carfi. JAMA. 2020.

Post-COVID-19 & MCAS Common Conditions

Table 1.	Organ and system involvement in MCAS. Conditions underlined are also seen in Acute COVID-19 infection and chronic COVID-19 Inflammatory syndrome
Organ / System	Symptom / Finding
Constitutional	Fatigue, Fevers, Chills, Weight loss, Weight gain
Ears, Nose, Throat	Conjunctivitis, Rhinitis, Sinusitis, Dysosmia/Anosmia, Tinnitus, Hearing loss, Dysgeusia/Ageusia, Sore throat
Neurologic	Headaches, Migraines, Brain Fog, Anxiety, Depression, RLS, Insomnia, Seizures
Cardiovascular	Chest pain, Palpitations, Hypotension
Pulmonary	Cough, Dyspnea, Wheezing
Urogenital	Frequency, Urgency, Dysuria, Pelvic pain
Esophageal	Heartburn, Dysphagia, Globus, Chest pain

RLS for both?

Post-COVID-19 and MCAS Common Conditions

Table 1. **Continued**	**Organ and system involvement in MCAS. Conditions underlined are also seen in Acute COVID-19 infection and chronic COVID-19 Inflammatory syndrome**
Stomach	Dyspepsia, Nausea, Vomiting
Small intestine / colon	Bloating, Food intolerance, Abdominal pain, Diarrhea, Constipation
Hepatic	Elevated transaminases, Hepatomegaly
Salivary Glands	Swelling
Lymphatics	Lymphadenopathy
Dermatologic	Flushing, Pruritis, Urticaria, Hemangiomas, Nodules, Rashes, Alopecia
Musculoskeletal	Myalgias, Arthralgias, Edema

Summary

- Missing link to many diagnostic dilemmas & “syndromes”
- More diagnosed with Consensus 2 vs. 1 criteria
- Patience in Rx often works
- Look for triggers to be successful

Do You Believe in MCAS Now?

(not me)