

# NEXT GENERATION ▶ LEARNING



## 2016 ANNUAL MEETING

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# How I Handle Mast Cells in GI Biopsies

Dora Lam-Himlin, MD  
Mayo Clinic  
Scottsdale, AZ

Rodger C. Haggitt Gastrointestinal Pathology Society Forum  
United States and Canadian Academy of Pathologists  
Seattle, Washington, March 12, 2016

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Dr. Lam-Himlin declares she has no conflict of interest to disclose.



# Outline

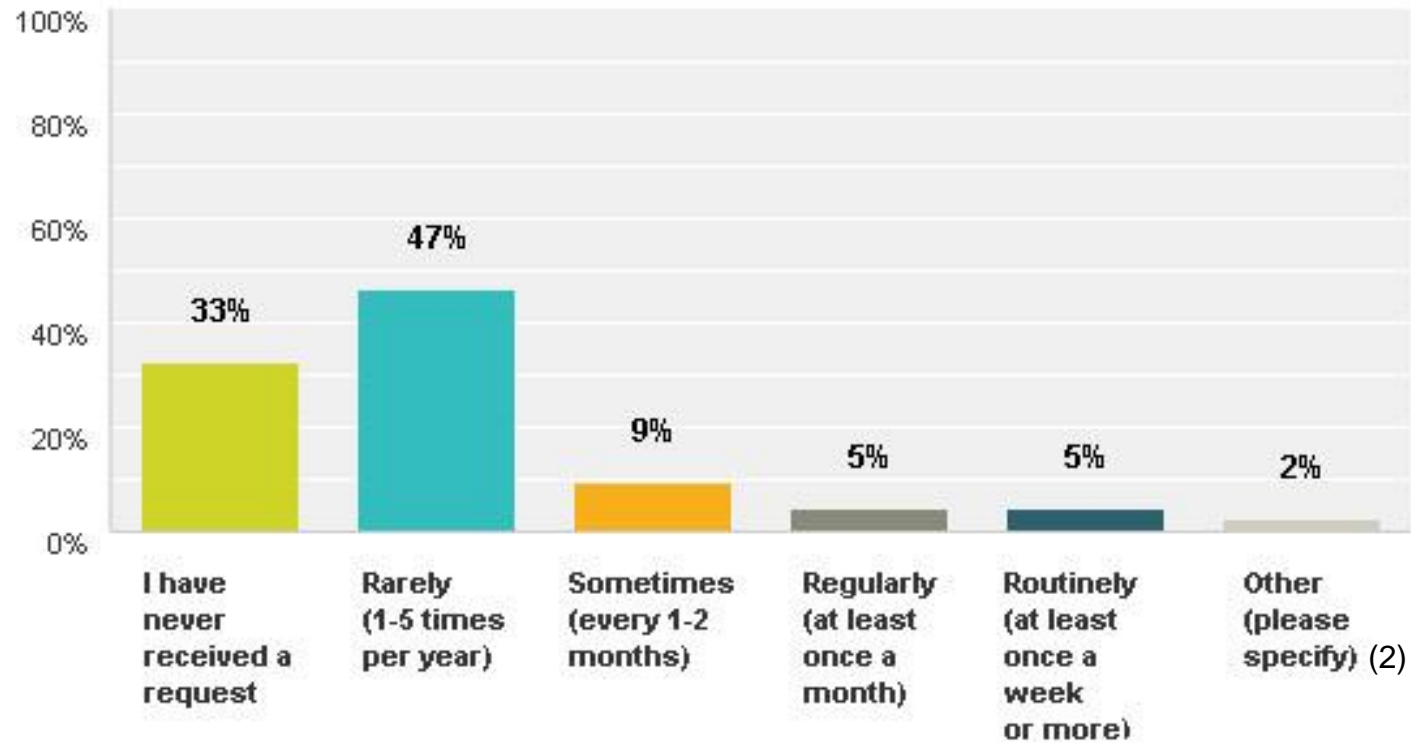
- GIPS Survey Results
- Mast Cell Disorders affecting the GI tract
  - Systemic Mastocytosis
  - Mastocytic Enterocolitis
  - Mast Cell Activation Syndrome
- My (limited) experience
- Open discussion

# Survey Results: A Focus on Mastocytic Enterocolitis

86 respondents

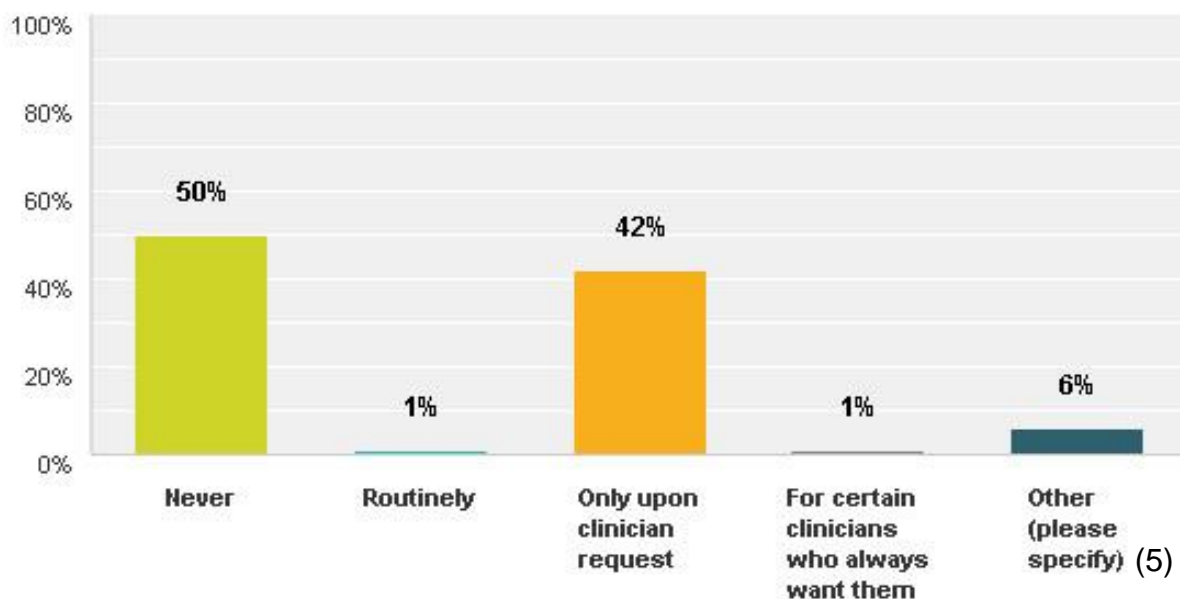
## How frequently do you receive requests for mast cell counts?

Answered: 86 Skipped: 0



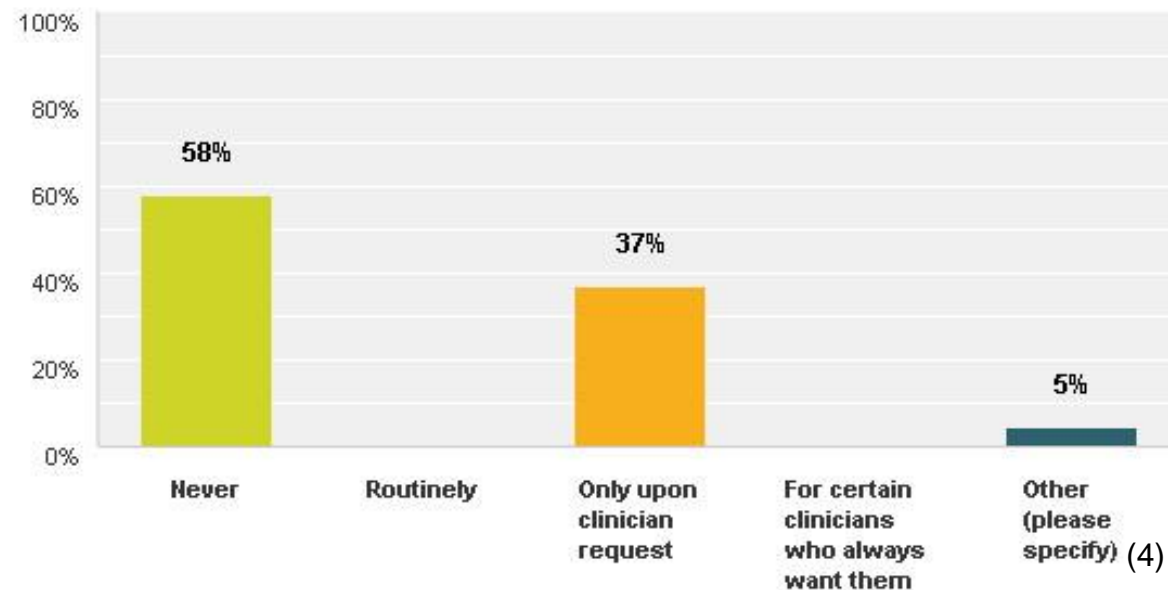
### When do you initiate an order for mast cell stains to rule out mastocytic enterocolopathy in cases of chronic diarrhea in which the COLONIC biopsies appear normal by H&E?

Answered: 86 Skipped: 0



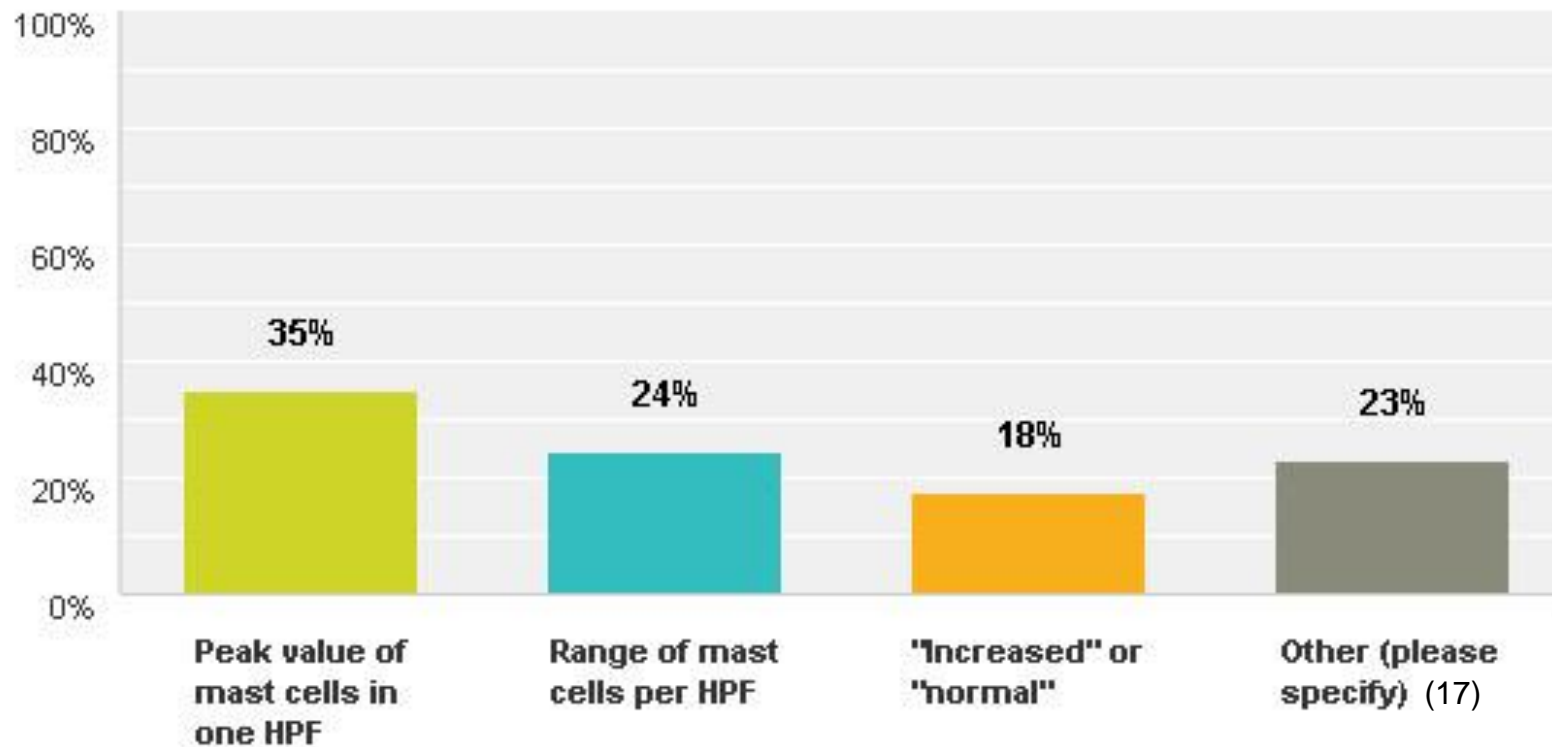
### When do you initiate an order for mast cell immunostains to rule out mastocytic enterocolopathy in cases of chronic diarrhea in which the DUODENAL biopsies appear normal by H&E?

Answered: 86 Skipped: 0



## If you do mast cell immunostains to rule out mastocytic enterocolopathy, how do you report them?

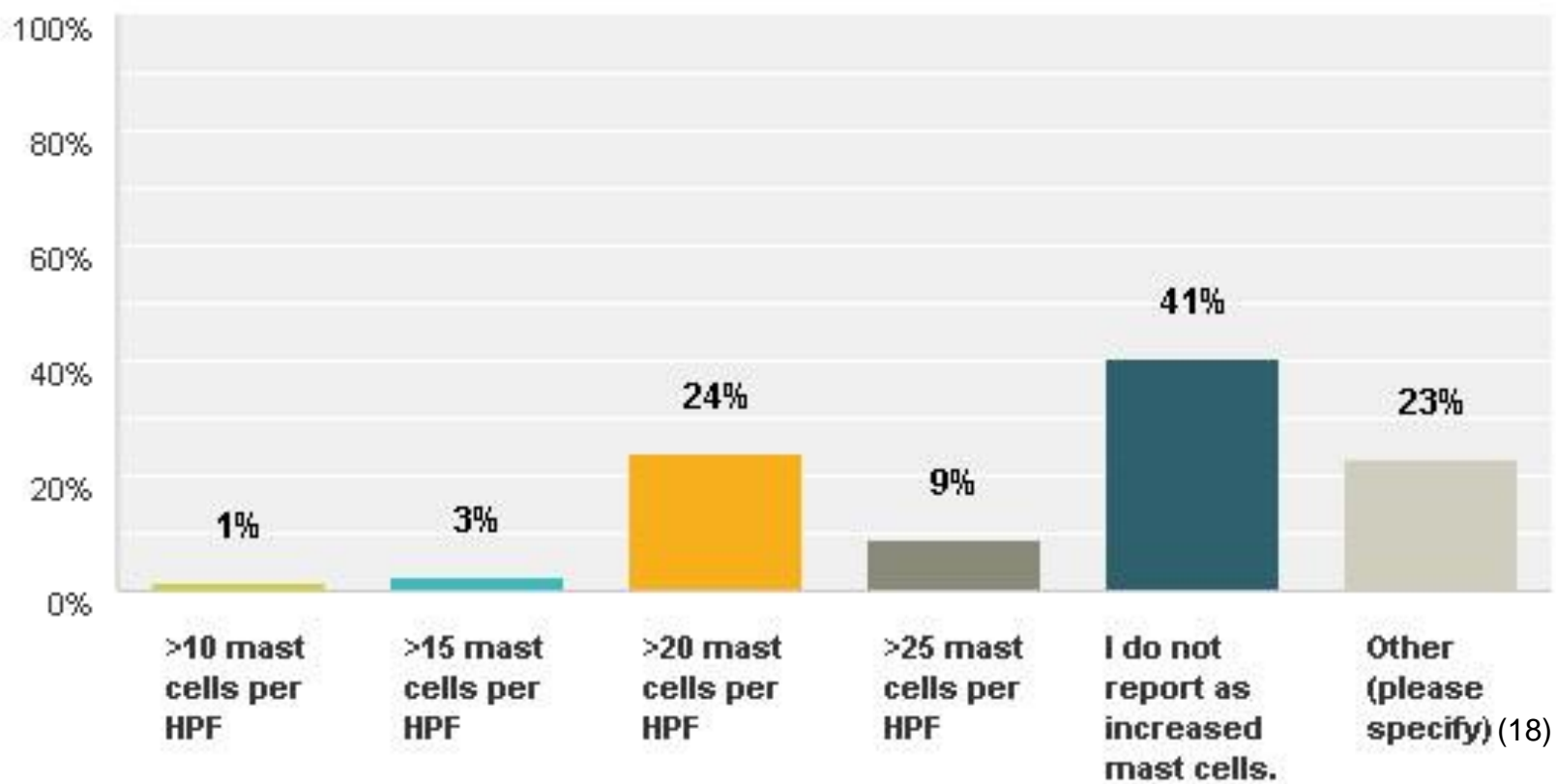
Answered: 74 Skipped: 12





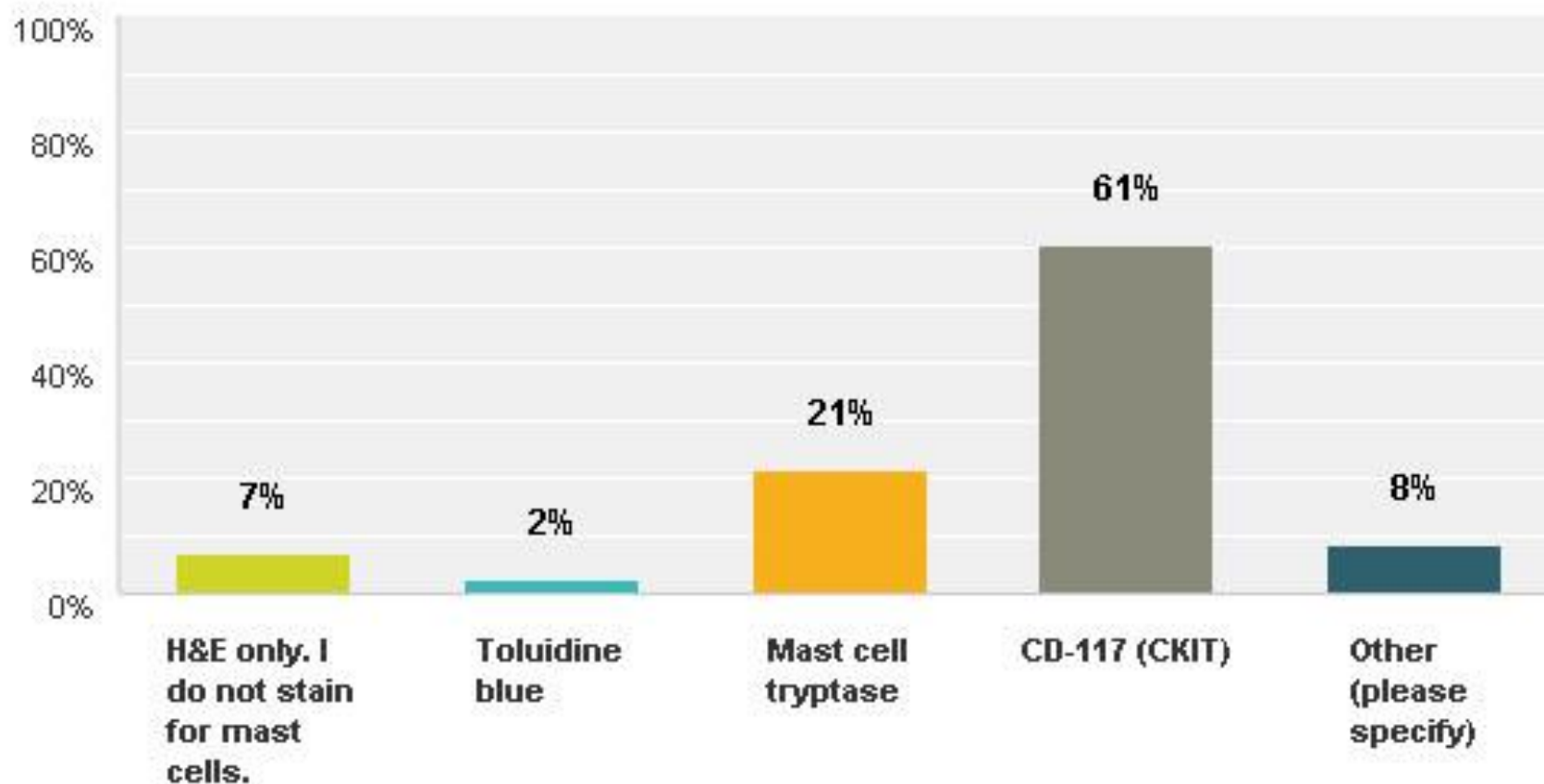
## If reporting increased mast cells, what is your threshold for upper limit of normal?

Answered: 79 Skipped: 7



## What is your preferred stain for mast cells?

Answered: 84 Skipped: 2



# Conclusions from survey

- Wide range of practice exists
- No consensus method
- GIPS members have strong opinions on this topic

# Mast cell disorders affecting the GI tract

- Systemic Mastocytosis (SM)
- Mastocytic Enterocolitis (ME)
- Mast Cell Activation Syndrome (MCAS)



# Mastocytosis

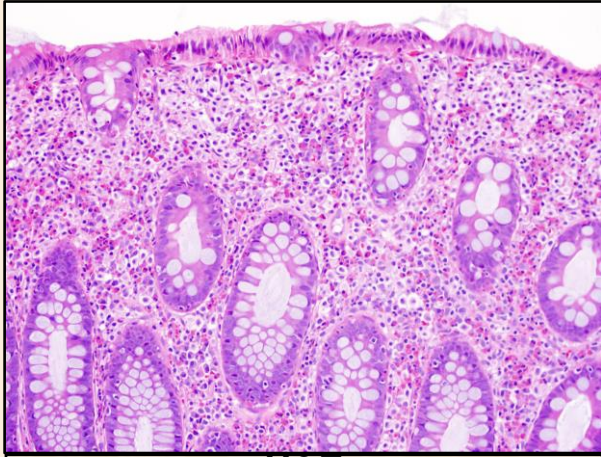
## Clonal neoplastic proliferation

- Urticaria pigmentosa
- Telangiectasia macularis eruptiva perstans
- Diffuse cutaneous mastocytosis
- Solitary mastocytoma
- Systemic mastocytosis

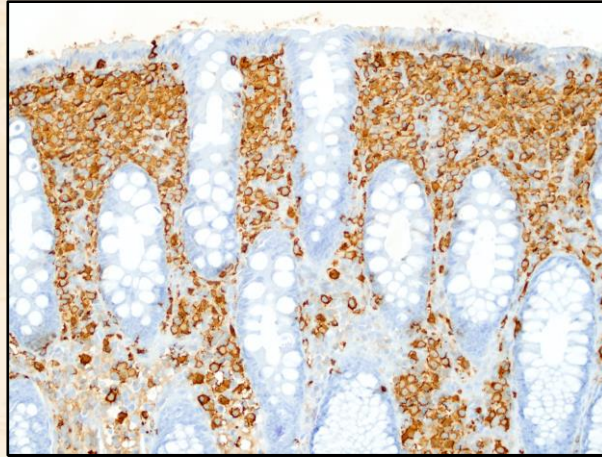
## WHO Diagnostic Criteria

Major criterion	Minor criteria
Multifocal, dense aggregates of mast cells (15 or more) detected in sections of bone marrow (preferred) or other extracutaneous organs (eg, gastrointestinal tract, lymph nodes, liver, or spleen), and confirmed by tryptase immunohistochemistry or other special stains	a. In biopsy section, more than 25% of the masts cells in the infiltrate have atypical morphology or spindle shapes; or, of all the mast cells in an aspirate smear, more than 25% are immature or atypical
	b. Mast cells co-express CD117 with CD2 and/or CD25
	c. Detection of KIT point mutation at codon 816 in bone marrow, blood, or other extracutaneous organs
	d. Serum total tryptase persistently >20 ng/ml (not a valid criteria in cases of systemic mastocytosis with associated clonal hematologic non-mast-cell lineage disease)

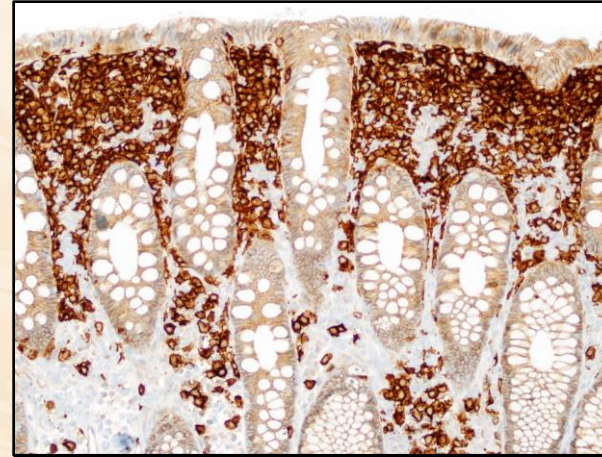
# Systemic Mastocytosis



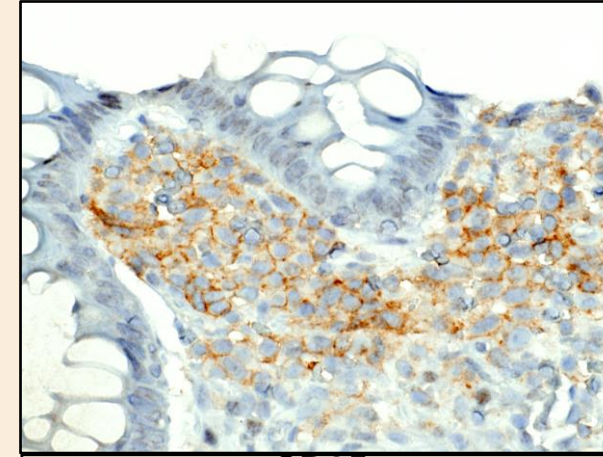
H&E



TRYPTASE



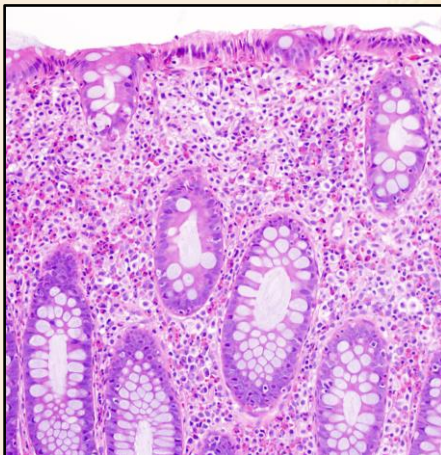
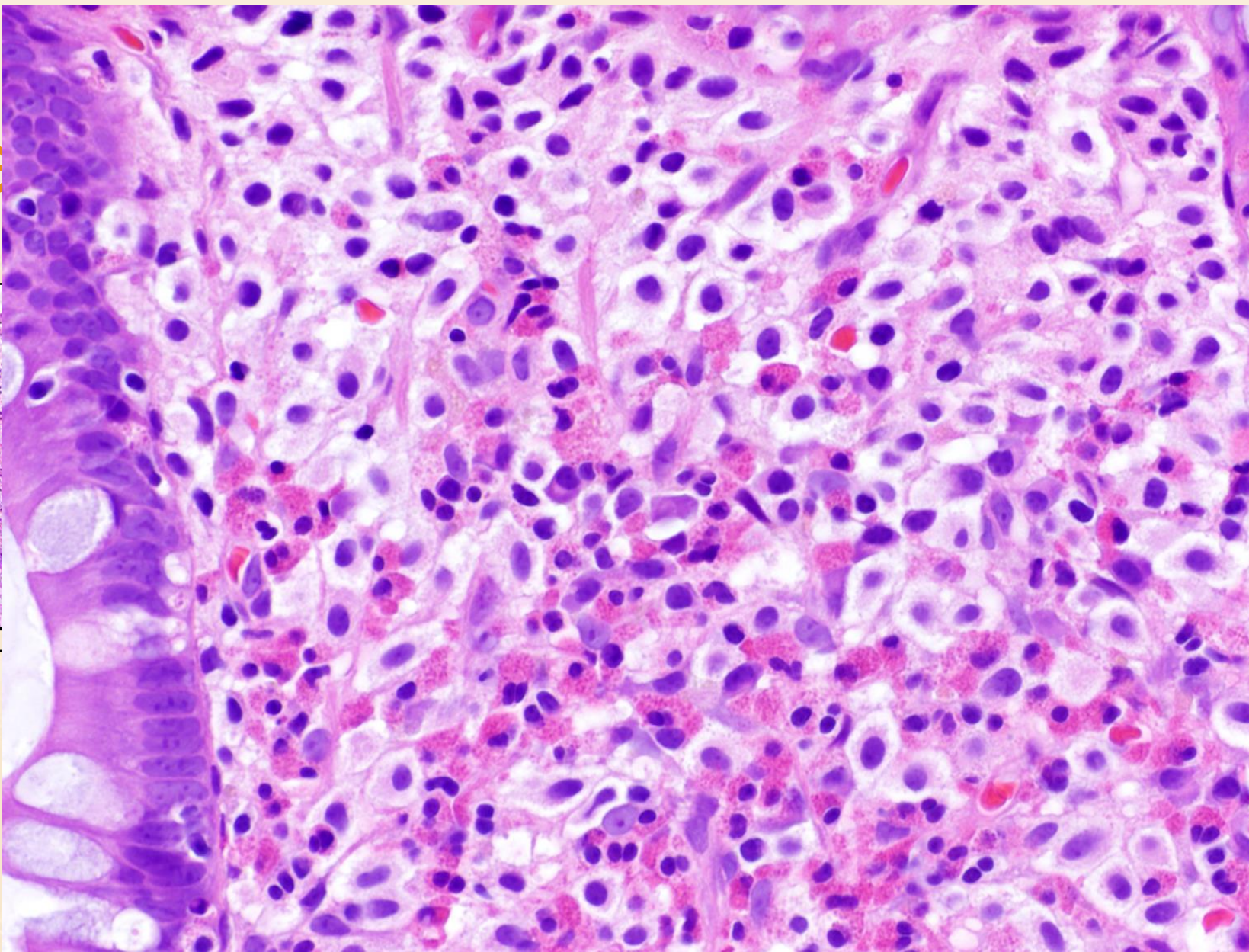
CD117



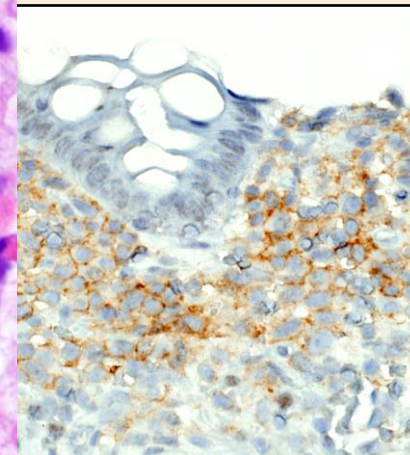
CD25



# Systemic



H&E



CD25



# Mastocytic Enterocolitis

- **New entity proposed by Jakate et al**

Arch Pathol Lab Med: Vol 130, March 2006

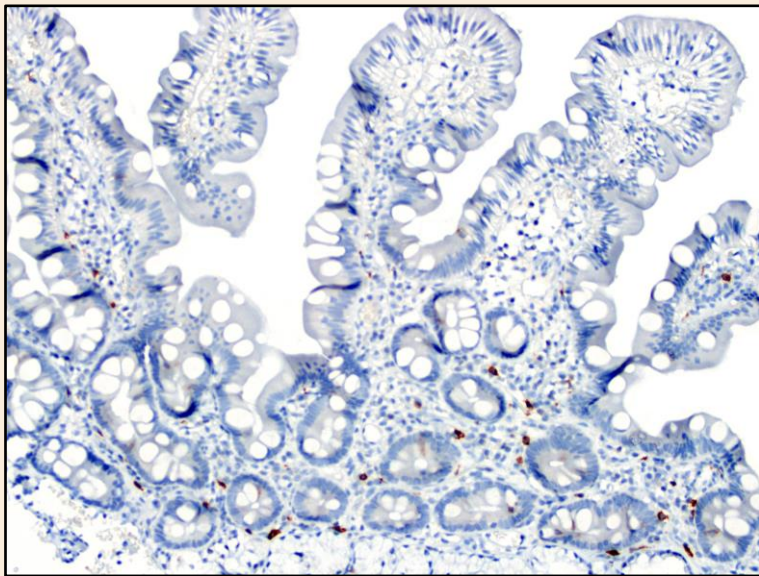
- Chronic intractable diarrhea (adults)
- >20 mast cells per HPF
- Patients respond to drugs inhibiting mast cell mediators

- **Conclusions:**

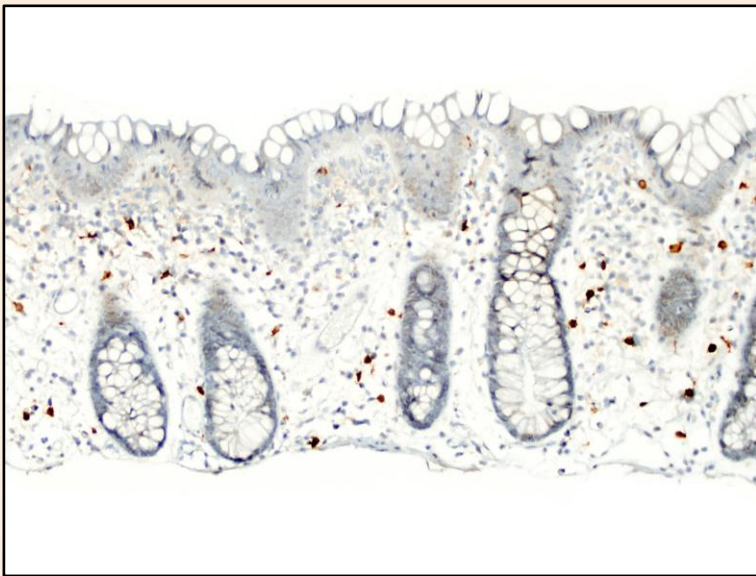
- “Increased”: >20 mast cells/hpf (>2 SD above control)
- 70% with increased mast cells
- 67% with response to drug therapy

Patient Group	Mast cell concentration Mean $\pm$ SD
<b>50 Controls</b> (adenoma screening)	13.2 $\pm$ 3.5
<b>47 Patients</b> (chronic intractable diarrhea)	25.7 $\pm$ 4.5
<b>63 Other specific diseases</b> (IBD, celiac dz, collagenous & lymphocytic colitis)	12.4 $\pm$ 2.3

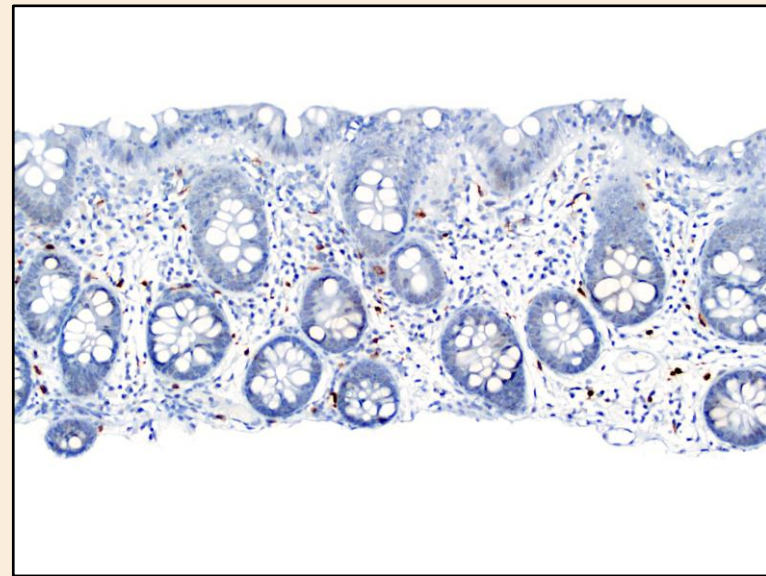




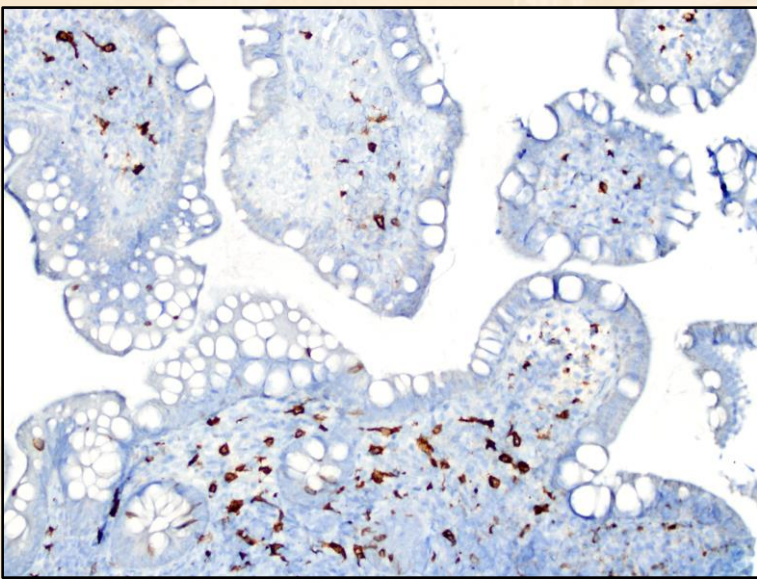
Normal Duodenum CD117



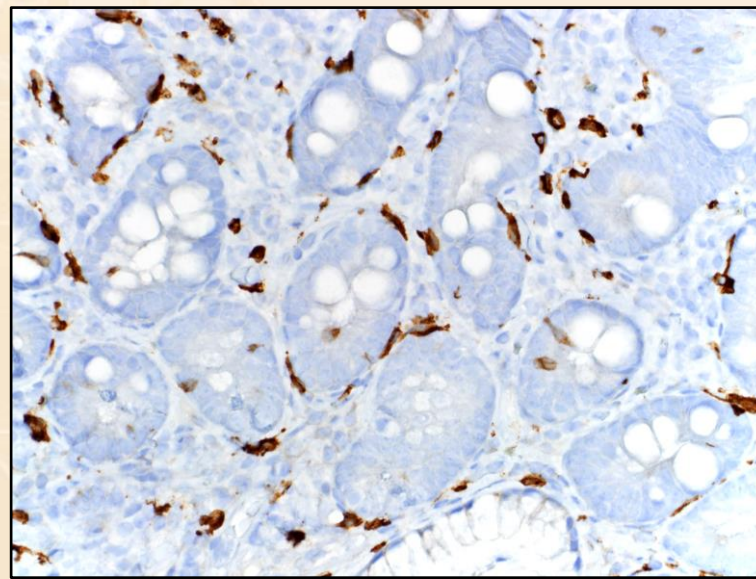
Normal Colon CD117



Lymphocytic Colitis CD117



Mastocytic Duodenitis CD117



Mastocytic colitis CD117

# Requests for Mast Cell Counts Increased

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# Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD,<sup>a</sup> Jason L. Hornick, MD, PhD,<sup>b</sup> Cem Akin, MD, PhD,<sup>a</sup> Mariana C. Castells, MD, PhD,<sup>a</sup>  
and Norton J. Greenberger, MD<sup>a</sup> *Boston, Mass*

J Allergy Clin Immunol. 2011 Jul;128(1):147-152

- Pts have at least 4 signs and symptoms of mast cell degranulation:
  - Abdominal pain
  - Diarrhea
  - Flushing
  - Dermatographism
  - Memory and concentration difficulties
  - Headache
- Laboratory tests showing increased mast cell mediators:
  - Serum tryptase
  - Serum mature tryptase
  - Urine Histamine
  - Serum/plasma PGD<sub>2</sub>
- Response to medications targeting mast cell mediators
- Pts do not meet WHO criteria for SM or clonal disorder (MMCAS)

# Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

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- Pts have at least 4 signs and symptoms of mast cell degranulation:

- Abdominal pain
- Diarrhea
- Flushing
- Dermatographism
- Memory and concentration difficulties
- Headache

TABLE IV. Mean number of MCs at each site

Site of biopsy	No. of patients	Mean/hpf (normal)*	Range (normal)*
Stomach	7	17 (13)	14-28 (5-21)
Duodenum	7	23 (27)	18-26 (4-51)
Left colon	5	20 (21)	15-27 (10-31)
Right colon	4	17 (21)	12-18 (10-31)

\*Data from Hahn and Hornick.<sup>18</sup>

- Laboratory tests showing increased mast cell mediators

- Serum tryptase
- Serum mature tryptase
- Urine Histamine
- Serum/plasma PGD<sub>2</sub>

- Response to medications targeting

- Pts do not meet WHO criteria for SM or clonal disorder (MMCAS)

## Conclusions:

1. Histology of MCAS is normal
2. No difference in mast cell counts between MCAS and reference standard



**A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients.**

Doyle LA<sup>1</sup>, Sepehr GJ, Hamilton MJ, Akin C, Castells MC, Hornick JL.

Aims of study:

1. Determine utility of GI biopsies in diagnosis of SM
2. Characterize clinical, histologic, and immunohistochemical features of SM in GI tract
3. Determine mast cell density in normal colonic mucosa
4. Compare findings with diarrhea predominant IBS

## A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients.

Doyle LA<sup>1</sup>, Sepehr GJ, Hamilton MJ, Akin C, Castells MC, Hornick JL.

Patient Group	Mean mast cell count in 5 contiguous HPF (range)
100 asymptomatic (adenoma screening)	26 (11-55)
100 IBS, diarrhea predominant	30 (13-59)

### • Conclusions

- Mast cell density in asymptomatic patients is highly variable
- IBS patients slightly higher, but overlap in range with control is too great to be clinically useful

## Performing colonic mast cell counts in patients with chronic diarrhea of unknown etiology has limited diagnostic use.

Sethi A<sup>1</sup>, Jain D, Roland BC, Kinzel J, Gibson J, Schrader R, Hanson JA.

### • Conclusions

- Mast cell counts are uninterpretable on random Bx
- Mast cell counts are increased in the left colon in CDUE
- Wide overlapping range with normal colon results in nondiscriminatory cutoff value

Patient Group	Mean highest mast cell count in 1 HPF (±SD)	Right Colon Mean (±SD)	Left Colon Mean (±SD)
89 asymptomatic (adenoma screening)	24.1 (±8.7)	25.4 (±9.0)	22.2 (±8.6)
76 Chronic diarrhea of unknown etiology (CDUE)	30.7 (±10.5)	28.2 (±11.0)	31.0 (±15.9)



# What do my clinicians think about this?

- Number of requests for “r/o mast cells” has decreased dramatically
- Some allergy/immunology clinicians still request, but recognize the data do not support counting mast cells.
- Neurologists have shown interest
  - Autonomic dysfunction (e.g. postural orthostatic tachycardia syndrome/POTS)
  - Ehlers-Danlos syndrome
- High interest in developing markers for gut mast cell mediators

# What I do

## Any of the following histologic features:

- ↑ visible mast cells
- ↑ density eosinophils
- Unexplained lamina propria pallor
- Unclassifiable cells with pale cytoplasm

OR

Request from clinician to “r/o mast cells”

Perform  
CD117 & CD25  
immunostains

CD117+ CD25+

CD117+ CD25-

“Up front”  
CD117

## Systemic Mastocytosis

NOTE: Biopsies show confluent sheets of CD117+ mast cells with atypical spindled morphology and aberrant co-expression of CD25. The presence of abnormal mast cell clusters in an extracutaneous site fulfills diagnostic criteria for systemic mastocytosis (World Health Organization: one major and one minor criterion.)

## Single Scattered Mast Cells

NOTE: CD117 immunostain highlights single scattered mast cells without confluence and without aberrant co-expression of CD25. These findings provide no evidence of systemic mastocytosis.

## Single Scattered Mast Cells

NOTE: At the request of the clinician \_\_\_\_, CD117 immunostain highlights \_\_ # mast cells per high powered field. The cells are single and scattered, without confluence.



# Discussion

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	Jakate et al 2006	Hamilton et al 2011	Doyle et al 2014	Sethi et al 2015
Patient group	Chronic intractable diarrhea (AGA w/u)	Evidence of mast cell degranulation ( <i>symptoms/labs</i> )	Diarrhea predominant IBS ( <i>clinical dx</i> )	Chronic diarrhea of unknown etiology (AGA w/u and nl bx)

Mast cell stain

Counting method

Conclusion

	Jakate et al 2006	Hamilton et al 2011	Doyle et al 2014	Sethi et al 2015
Patient group	Chronic intractable diarrhea (AGA w/u)	Evidence of mast cell degranulation ( <i>symptoms/labs</i> )	Diarrhea predominant IBS ( <i>clinical dx</i> )	Chronic diarrhea of unknown etiology (AGA w/u and nl bx)
Mast cell stain	Mast Cell Tryptase and Toluidine Blue <ul style="list-style-type: none"> <li>Found that Toluidine Blue highlighted 30-60% fewer mast cells</li> </ul>	Mast Cell Tryptase and CD117	CD117 <ul style="list-style-type: none"> <li>Found that tryptase was negative in a subset of neoplastic mast cells</li> </ul>	CD117
Counting method				
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Counting method	Average of 10 HPFs across at least 2 tissue fragments	Average of 10 contiguous HPF's (Hahn and Hornick 2007)	Average in 5 contiguous HPF's in highest density area	Single HPF in highest density area
Conclusion				



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Patient group	Chronic intractable diarrhea (AGA w/u)	Evidence of mast cell degranulation ( <i>symptoms/labs</i> )	Diarrhea predominant IBS ( <i>clinical dx</i> )	Chronic diarrhea of unknown etiology (AGA w/u and nl bx)
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Counting method	Average of 10 HPFs across at least 2 tissue fragments	Average of 10 contiguous HPF's (Hahn and Hornick 2007)	Average in 5 contiguous HPF's in highest density area	Single HPF in highest density area
Conclusion	67% of these patients who also have >20 mast cells/HPF will show symptomatic improvement with treatment	Patients with MCAS benefit from treatment, but not a histologic diagnosis	IBS patients have slightly higher mast cell counts, but the overlap with normal range is too great to be clinically useful	Mast cell counts slightly higher than compared to normal, but no discriminatory cutoff value exists

Lamhimlin.Dora@Mayo.edu



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