



Published in final edited form as:

*Am J Clin Dermatol*. 2011 August 1; 12(4): 259–270. doi:10.2165/11588890-000000000-00000.

## Guidelines for the Diagnosis and Treatment of Cutaneous Mastocytosis in Children

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### Abstract

Mastocytosis is a disease with many variants, all of which are characterized by a pathologic increase in mast cells in cutaneous tissue and extracutaneous organs such as the bone marrow, liver, spleen and lymph nodes. The disease presents in two primary age-related patterns: pediatric-onset mastocytosis and adult-onset mastocytosis, which may differ in their clinical manifestations and disease course. Pediatric-onset mastocytosis commonly is diagnosed prior to 2 years of age, and usually consists of cutaneous disease, with urticaria pigmentosa (UP) the most common pattern. The course of pediatric-onset mastocytosis is variable. This is in contrast to adult onset disease which generally presents with systemic findings and increases in extent and severity over time. Because pediatric forms of mastocytosis often differ in presentation and prognosis from adult variants, it is most important to understand pediatric mastocytosis and not rely on adult approaches as a guide on how to identify and manage disease. This is especially important in selecting therapy where antiproliferative agents have a very different set of concerns when used to treat adult mastocytosis compared to pediatric mastocytosis, especially in terms of long-term toxicity. This review is directed at providing age-specific information surrounding the care of the child with mastocytosis.

### Keywords

Mastocytosis; pediatric; urticaria pigmentosa; treatment

### Introduction

Mastocytosis is a disease with many variants, all of which are characterized by a pathologic increase in mast cells in cutaneous tissue and extracutaneous organs such as the bone marrow, liver, spleen and lymph nodes. The disease presents in two primary age-related patterns: pediatric-onset mastocytosis and adult-onset mastocytosis, which may differ in their clinical manifestations and disease course. Pediatric-onset mastocytosis commonly is diagnosed prior to 2 years of age, and usually consists of cutaneous disease, with urticaria

pigmentosa (UP) the most common pattern. The course of pediatric-onset mastocytosis is variable. This is in contrast to adult onset disease which generally presents with systemic findings and increases in extent and severity over time.

The first description of a cutaneous mast cell disease is attributed to Nettleship and Tay in 1869,<sup>[1]</sup> and was later, because of the gross appearance of the lesions, termed urticaria pigmentosa (UP) by Sangster in 1878.<sup>[2]</sup> In 1949, Ellis described an autopsy of a fatal case of UP in a one year old child. He documented mast cell infiltrations in the skin, liver, spleen, lymph nodes and bone marrow.<sup>[3]</sup> There followed many descriptions of variants of mastocytosis organized over the years into classification schemes from Degos in 1963<sup>[4]</sup> to the contemporary World Health Organization recognized classification.<sup>[5-7]</sup>

Because pediatric forms of mastocytosis often differ in presentation and prognosis from adult variants, it is most important to understand pediatric mastocytosis and not rely on adult approaches as a guide on how to identify and manage disease. This is especially important in selecting therapy where anti-proliferative agents have a very different set of concerns when used to treat adult mastocytosis compared to pediatric mastocytosis, especially in terms of long-term toxicity. This review is directed at providing age-specific information surrounding the care of the child with mastocytosis.

## Presentation of Mastocytosis in Childhood

Mastocytosis in children can present during the neonatal period, in infancy (< 6 months) or childhood (6 months to 16 years). The disease is typically characterized by the presence of increased dermal mast cells and the symptoms are due to the release of mediators and their local and/or systemic actions. Internal organ involvement is not frequent. Sixty to 80% of the patients develop lesions during the first year of life. Lesions of UP, as well as mastocytomas, can be present a birth<sup>[8;9]</sup>. Based on limited data, it is believed that males and females are equally affected and that no race is predominant. Familial cases are rare and identical twins and triplets have been described<sup>[10]</sup>. Mast cell mediator related symptoms occur in over 60% of all cases.<sup>[11]</sup>

The pathogenesis of cutaneous mastocytosis in children is not well understood and many children do not present mutations of c-kit, which codes for KIT, a membrane receptor for stem cell factor expressed in the surface membrane of mast cells, and which is found mutated in the majority of adult patients with systemic mastocytosis.<sup>[12]</sup> One study reported mutations in c-kit within skin biopsies from 16 out of 37 (43%) pediatric patients with cutaneous disease.<sup>[13]</sup> These include sporadic mutations at codons 816, 820 and inactivating mutations at codon 839. Missense activating mutations at codon 816 (Asp816 Val and Asp816Phe) have been found in those with UP, mastocytomas and diffuse cutaneous mastocytosis DCM. Patients with the Asp 816Phe mutation appear to acquire the disease earlier than those presenting with Asp 816 Val mutations.<sup>[14]</sup>

## Classification of Cutaneous Mastocytosis in Children

UP is the most common presentation of cutaneous mastocytosis in children and represents 70–90% of the cases. The lesions are red to brown to yellow, measure a few mm to 1–2 cm

in diameter, and present as multiple lesions in the form of macules, plaques or nodules (Figures 1, 2, 3). Erythema, swelling and blister formation after stroking or rubbing can occur, and is associated with pruritus and dermatographism. Flushing occurs in up to 36% of the patients with UP. The Darrier's sign is typically present, with wheal and flare formation after stroking one or several lesions. No scarring occurs. The affected areas include the trunk and extremities (Figure 2). Less affected are palms, soles, scalp and face, as well as sun exposed body areas. In a series of 112 patients,<sup>[15]</sup> it was reported that the lesions of UP appeared at 2.5 months as a mean, and by age 6 months, 80% of patients had lesions. After the age of 10, the mean time of onset was 26.5 years. Lesions tend to resolve by age 10<sup>[11]</sup> and if they appear after age 10, they tend to persist and remain symptomatic.<sup>[10]</sup> Diarrhea and visceral involvement are rare. Wheezing and syncope have been observed.<sup>[16]</sup> Mastocytomas or nodular lesions occur in 10–35% of the cases of cutaneous mastocytosis in children, and present as one or several lesions that resemble UP but are larger in size, up to several cms in diameter. Such lesions can vesiculate and blister (Figure 1). In a series of 112 patients,<sup>[15]</sup> solitary mastocytomas were present at birth or developed within one week. Most cases resolve by puberty but persistent lesions have been described in adults.<sup>[16]</sup> Mastocytomas rarely present with diarrhea, and association with visceral involvement or systemic disease is rare. Flushing can be present and Darrier's sign is typically positive.

DCM is rare, but can present with more severe symptoms. DCM accounts for 1–3% of the cases of cutaneous mastocytosis, and can involve the whole skin with the central region and scalp most affected. DCM can appear at birth (congenital and neonatal) or in early infancy. Blistering and bullae may be the presenting symptoms and the blisters can be hemorrhagic (Figure 1). The skin may be leathery and thickened. Hyperpigmentation may persist into adulthood and dermatographism may be prominent. The first sign may be extensive bullae, which may rupture, leaving erosions and crusts (Figure 1). This form is particularly sensitive to PUVA. There are a few reports of total or partial resolution after PUVA, but remissions generally last only a few months and retreatment is necessary in the majority of the cases. Due to the extent of the lesions and their severity, systemic symptoms can be present due to the large amount of mast cell mediators released locally and absorbed locally and systemically. Whole body flushing, pruritus, diarrhea, intestinal bleeding, hypotension, anemia, hypovolemic shock and deaths have been reported.<sup>[17]</sup> Visceral involvement with lymphadenopathy and hepatomegaly may be present. A rare complication includes pachydermia.<sup>[18]</sup>

Telangiectasia macularis eruptiva perstans (TMEP) is the least common form of cutaneous mastocytosis. It rarely presents in childhood. The lesions are characterized by red, telangiectatic macules in a tan or brown background and can co-exist with UP.

Rarely, all cutaneous forms of Mastocytosis in children can present with acute mast cell activation events, including anaphylaxis. Manifestations include whole body flushing, shortness of breath, wheezing, nausea, vomiting diarrhea and /or hypotension. A few cases are associated with cyanotic spells.

## Histopathology

In UP, the number of mast cells in the papillary dermis is increased but numbers have not been standardized. Mast cells aggregate around blood vessels, and are sometimes associated with eosinophils.<sup>[19]</sup> In nodular forms of UP and mastocytomas, mast cells may infiltrate the entire dermis and extend into the subcutaneous tissues. Electron microscopy of the mast cells shows round and spindle-shaped cells that stain with both tryptase and chymase, sometimes in sheet-like distribution. The numbers of mast cells can be as high as 10 times over normal skin.<sup>[20]</sup> Mast cell numbers are higher in non-lesional skin of patients with UP and mastocytomas than in skin samples from normal controls.

## Mast Cell Mediator Related Symptoms

All forms of cutaneous mastocytosis in children can present with associated mast cell-mediator related symptoms due to the local release of mast cell mediators and their local and systemic actions. Demonstration of Darier's sign characterized by urtication and flare upon rubbing one of the lesions is associated with CM, but is not present in all patients and is thought to be due to the release of histamine, leukotrienes and prostaglandins from skin mast cells. The extent of skin involvement is not directly associated with symptoms and patients with a single mastocytoma or few UP lesions may exhibit significant local and systemic symptoms. Skin symptoms include flushing, pruritus, redness and swelling, which may occur spontaneously or be induced by triggers. Flushing spells are common (20–65%) but hypotension rarely occurs. Acute episodes of cyanosis and respiratory arrest are uncommon. Anaphylactic reactions to hymenoptera stings have been described in adolescents with UP, but the safety and efficacy of immunotherapy in this age category is not known.<sup>[21]</sup>

Gastrointestinal symptoms can be prominent, with abdominal pain and diarrhea in up to 40% of children. Hyperacidity and peptic ulcers have been reported but peptic ulcer disease is rare in children. Blistering, bullae, prolonged skin bleeding and life-threatening hypotensive episodes are common complications of DCM but are exceptional in UP and those with mastocytomas. Chondroitin sulfate was found in a hemorrhagic blister from a child with DCM,<sup>[22]</sup> implicating it as a local anti-coagulant. In addition, other products of mast cell activation, such as PAF, PGD<sub>2</sub> and histamine, have been isolated from clear blister fluid in a child with DCM.<sup>[23]</sup> Histamine metabolites have been found elevated in the urine from children with UP and mastocytomas<sup>[24]</sup> providing evidence of mast cell degranulation.

## Correlations Between Cutaneous Involvement, Bone Marrow Infiltration and Serum Tryptase Levels

The initial evaluation of the bone marrow of 17 children where 15 had UP and 2 had DCM, revealed no adult type mast cell aggregates,<sup>[8]</sup> indicating that in most cases, cutaneous mastocytosis in children does not involve internal organs which precludes the need for routine prognostic bone marrow biopsies. More recently the extent and nature of cutaneous mastocytosis has been studied to understand its association with systemic disease. In a prospective study of 19 children and 48 adult patients with cutaneous mastocytosis, UP was the most common presentation in 17 children. The extent and the density of the lesions were similar in children and adults; however, children presented higher mean and maximum diameter UP lesions as compared to adults. Three children had indolent systemic

mastocytosis (ISM), but neither the extent nor the density of UP was predictive of systemic involvement. There was no correlation between skin involvement and duration of disease or the presence of atopy. Serum tryptase was significantly elevated only in children with systemic disease.<sup>[25]</sup> It appears that neither the extent nor the nature of cutaneous mastocytosis can predict the presence of systemic disease, implying a heterogeneous disease and the need to better understand its pathogenesis.

Tryptase levels correlate with mast cells numbers in the skin; and elevations in tryptase are seen in patients with more severe disease.<sup>[26]</sup> A retrospective review of 64 patients with mastocytosis (31 children and 33 adults) correlated a severity scoring system with tryptase levels.<sup>[27]</sup> Twenty children had maculopapular cutaneous mastocytosis, 8 of which had elevated tryptase, 6 children had mastocytomas and 1 had elevated tryptase, and 3 children had DCM, 2 of which had elevated tryptase. None of the children with cutaneous mastocytosis and elevated tryptase had bone marrow findings compatible with systemic mastocytosis, but immunostaining for KIT or tryptase was not done in the majority of the cases nor were c-kit mutations investigated either within the skin lesions or bone marrow biopsies. There was a positive correlation between the extent of skin involved, the physical appearance of the lesions and the presence of associated symptoms such as pruritus, flushing, the presence of Darier's sign, bone pain and diarrhea and tryptase level. Other mediators such as histamine and N-methyl histamine have been correlated with increased mast cells numbers in the skin<sup>[24]</sup> but the levels are age dependent in children.

### Natural History

There are a few studies available of the natural history of cutaneous mastocytosis in children and which indicate there is a tendency for spontaneous resolution before puberty.<sup>[28;29]</sup> In a retrospective study<sup>[30]</sup> of 45 children, which included 34 children with UP and 11 with mastocytomas, the first lesions appeared before the age of 6 months in 41.8% of patients, and before the age of 13 months in 78.2%. No gender differences were seen. UP predominated on the trunk and extremities. Mastocytomas were found only on the extremities. Darier's sign was positive in 89% of the patients and no differences were seen between patients with UP or mastocytomas. Associated symptoms were seen in 54% of the patients and included itching, flushing, palpitations, angioedema, hypotension and cyanosis. Bullae were frequent in the mastocytoma group. Temperature change was a frequent trigger.

A retrospective study from Mexico reviewed 71 cases of cutaneous mastocytosis of which 53 were UP, 12 had mastocytomas and 6 had DCM. Ninety four % of the patients presented a positive Darier's sign. In 92% of the cases, disease onset was recorded in the first year of life. Eighty % of patients improved or had spontaneous resolution of disease.<sup>[31]</sup> The most common presentation was with macules (46), followed by plaques (30) or papules (27), and with bullae in 16 cases. Associated symptoms and signs were absent in those with mastocytomas, except for itching. Diarrhea, was seen in 7 out of 36 cases of UP and 2 out of 5 cases of DCM.

A retrospective review of 180 pediatric patients with mastocytosis from Israel<sup>[32]</sup> identified 65% with UP, which presented a birth in 20% of the cases and 80% during the first year of life. The distribution included the trunk and extremities. Of the 117 cases of UP, 13 were

familial; and of the 5 affected families only one generation was affected. No familial history was found in mastocytomas. The patients were followed for 1 to 15 years; and 75% of those with mastocytomas and 56% of the patients with UP had complete resolution of the lesions. Associated symptoms in those with UP included asthma in 10.3%, flushing in 12.8%, fever in 1.7% and abdominal pain in 2%.

## Diagnosis

The diagnosis of mastocytosis in children (Table 1) requires a high index of suspicion in a patient with new onset skin lesions with or without mast cell mediator related symptoms. A physical examination with a positive Darier's sign, serum tryptase, blood count and differential, and a skin biopsy should be done initially. The skin biopsy should be processed and then stained using hematoxylin & eosin and giemsa; and immunostaining for tryptase and KIT. Analysis of c-kit mutations within skin mast cells is recommended. In addition to the skin biopsy, bone marrow studies are recommended if the tryptase is significantly elevated, severe systemic symptoms are present, if there is associated organomegaly or if there is no significant response to initial symptomatic therapy. Once the diagnosis of cutaneous mastocytosis is established, follow-up is scheduled every 6 to 12 months. Parents should be informed about the possibility of evolution to a systemic form in a minority of cases.

## General Concepts in the Management of Pediatric Mastocytosis

Treatment (Table 2) is aimed at suppressing skin and systemic mast cell mediator related symptoms. Symptoms are usually more severe in the first 6 to 18 months after the onset of lesions; and can appear spontaneously or after specific triggers (Table 3). In a very few cases, symptoms can be life-threatening, but satisfactory management with mast cell-mediator controller medications is frequent and is encouraging of a favorable outcome and a good long-term prognosis.

Before starting therapy, the type and extent of skin lesions should be recorded along with a baseline serum tryptase. Elevated levels of tryptase, higher than 20 ug/L, and progressively more concerning as values are found at even greater levels, indicate an increased mast cell burden and/or extensive level of degranulation and close observation, evaluation and perhaps hospitalization may sometimes be required. Because of the generally benign nature of cutaneous disease and the high rate of spontaneous regression, cytoreductive therapy is strongly discouraged except in selected cases with life-threatening aggressive variants of mastocytosis

Education of parents and care providers is essential. Individualized information, support groups for parents, and informational brochures containing the most frequent asked questions, specific protocols for specific situations and procedures such as infection with fever, vaccinations, dental work, imaging procedures and surgery, have demonstrated value and increase the quality of life of children with mastocytosis. Contact with the community is important, including alerting teachers, nurses and day care workers about the diagnosis, treatment and potential risks in children with mastocytosis. Communication with pediatricians and other doctors will protect children and help prevent life threatening

episodes during surgery, imaging procedures with dyes and dental work. It is of great importance to transmit that cutaneous mastocytosis is not a “contagious condition”.

## Treatment

Because of the benign nature of the disease, the primary objective of disease management (Table 2), is to stabilize the release of mast cell mediators and to block their effects in order to control the symptoms and signs of the disease.<sup>[33];[34];[35–41]</sup> Avoidance of triggering factors (Table 3), treatment of acute mast cell activation events, treatment of chronic mast cell activation and attempts at decreasing mast cell burden are described below and summarized in Table III.

**1. Avoidance of triggering factors**—Mast cells can be activated in some patients by hot temperatures and, in a lesser extent, by cold temperatures (Table 3). Control of temperature within a reasonable can decrease symptoms in children and, thus, a rationale use of bath, shower, swimming pool and air conditioning can decrease mediator symptoms and, the need for antihistamines. Anxiety and stress should be avoided or controlled.

**2. Systemic therapy in pediatric mastocytosis**—The need for intensive therapy in pediatric mastocytosis is exceptional. Only 10 cases among 95 children referred to one of authors (LE) Center for Mastocytosis needed treatment as in-patients and three in the Intensive Care Unit for DCM. All had a favorable outcome and no deaths were recorded. During acute mast cell activation attacks involving hypotension, wheezing or laryngeal edema, epinephrine should be administered intramuscularly in a recumbent position. Cyanotic episodes and recurrent anaphylactic attacks should be treated with epinephrine.

H1 antihistamines have been shown to be useful in decreasing pruritus, flushing, urticaria and tachycardia (Table 2).<sup>[33;42];[40;41;43;44]</sup> Both sedating and non-sedating antihistamines may be used. Diphenhydramine, hydroxyzine, and cetirizine, among other antihistamines, have proven to be useful in children (a complete review of different drugs and their dosage is presented in reference <sup>[40]</sup>). Possible adverse effects of high doses of H1 antihistamines include cardiotoxicity (reviewed in ref. <sup>[45]</sup>).

Combined treatment with H1 and H2 antihistamines has been shown to be effective in some cases for controlling severe pruritus and wheal formation.<sup>[46–48]</sup> H2 antihistamines such as ranitidine or famotidine can be used (depending on the age group) to manage gastric hypersecretion and peptic ulcer disease associated with mastocytosis.<sup>[46;49–53]</sup> If H2 antihistamines are unable to control gastrointestinal symptoms, proton pump inhibitors may be recommended <sup>[40]</sup>. Studies are underway to develop drugs that block the H3 histamine receptor.<sup>[54–57]</sup>

Oral cromolyn sodium has proven to be effective in some children to control diarrhea, abdominal pain, nausea, and vomiting.<sup>[58–61]</sup> Despite its low absorption, cromolyn sodium may be useful in some patients for the treatment of cutaneous symptoms including pruritus <sup>[61–63]</sup> and reportedly can help with cognitive symptoms in adults.<sup>[63]</sup> Progressive introduction helps reduce side effects such as headache, sleepiness, irritability, abdominal pain and diarrhea. Water-soluble sodium cromolyn cream <sup>[64]</sup> as well as aqueous-based

sodium cromolyn skin lotion [65] have proven to be effective at decreasing pruritus and flaring of lesions.

Oral methoxypsoralen therapy with long-wave psoralen plus ultraviolet A radiation (PUVA) has been reported to be effective in cases of bullous diffuse cutaneous mastocytosis in children, even in patients with life-threatening MC-mediator release episodes.<sup>[66–69]</sup> PUVA is most effective in non-hyperpigmented DCM while the response is usually poor in nodular or plaque forms.

## Peri-operative considerations

Pediatric patients with cutaneous or systemic mastocytosis may on occasion require diagnostic or therapeutic procedures that require sedation or anesthesia. Because patients with mastocytosis have an increased mast cell burden and mast cells are implicated in the pathophysiology of anaphylaxis, there is justifiable concern that adverse reactions may follow administration of pharmacologic agents administered in the peri-operative period. These concerns are re-enforced by publications listing various opioids, muscle relaxants, analgesics, and volatile anesthetics as agents that may directly or indirectly induce mast cell activation.<sup>[70;71]</sup> However, the fear of reactions to drugs used in procedures for the benefit of the patient must be evaluated, placed in perspective, and not be allowed to interfere with optimal patient care.

A report of a review of the literature from 1968 to August 2006 using MeSH headings mastocytosis, anesthesia and analgesia, and anaphylaxis has revealed reports of adverse reactions in adults with mastocytosis.<sup>[72–76]</sup> In contrast to adults, no reports of anesthesia-related deaths<sup>[77–81]</sup> and few reports of anesthesia-related complications were found relating to children with mastocytosis<sup>[80;82]</sup> undergoing general anesthesia.<sup>[78;80]</sup> The paucity of information available on peri-operative management of children and adolescents with mastocytosis creates a challenge. In three single case reports, patients had uncomplicated anesthetics after pre-medication with H1 antihistamines.<sup>[77;79;81]</sup> In a fourth case report, the patient was reported to suffer a circulatory arrest.<sup>[80]</sup> One retrospective series from 1987 consisted of an analysis of 15 children with either UP or a solitary mastocytoma (N=3), who received general anesthesia in a total of 29 procedures.<sup>[78]</sup> Two patients were pre-medicated with H1 antihistamines and most anesthetics were uncomplicated, although two children had cutaneous eruptions after administration of codeine. A second retrospective series of 22 patients with pediatric mastocytosis (including CM and ISM) from 2008 examined the outcome of the routine anesthetic regimens in the 29 instances employed.<sup>[76]</sup> Preoperative drug skin testing was not performed and prophylactic antihistamines or corticosteroids not administered. Scheduled maintenance medications were continued. Routine anesthetic techniques were used. Despite the complexity of the disease, the peri-operative courses were uncomplicated and without serious adverse events. Whereas the paucity of reports of anesthesia-related deaths in children with cutaneous mastocytosis may be reassuring, the planning of anesthetics for patients with pediatric mastocytosis should be comprehensive and take into account the increased risk of anaphylaxis.



Several of the drugs used in peri-operative anesthesia (NSAIDs, opioids, sedative hypnotics, and volatile anesthetics) are reported to cause mast cell degranulation with histamine as well as other mediator release. While mast cell degranulation could have profound effects during anesthesia in patients with mastocytosis, studies documenting drug-induced histamine release from mast cells have largely been conducted *in vitro* or in animals and may not reflect the human response.<sup>[83]</sup> In limited human studies, muscle relaxants such as d-tubocurarine, tubocurarine, pancurionum and gallamine triethiodide have been reported to be associated with histamine release. However, these agents are seldom used in current anesthesia practice.<sup>[84–86]</sup> Meperidine and morphine reportedly induce increases in histamine levels in humans more frequently than fentanyl and sufentanyl.<sup>[86]</sup> In the 2008 report, the physicians used fentanyl, morphine and meperidine and observed no evidence of hemodynamic lability. The authors are aware of a lethal idiosyncratic reaction to ketorolac in one adult with mastocytosis (unpublished data) and therefore recommend avoidance of ketorolac in adults and children with mastocytosis. Given the potential for drug-induced mast cell degranulation during anesthesia, an understanding of the nature of reported patients' allergies is a necessity and will guide selection of appropriate agents to administer.

Understanding the general nature of pediatric mastocytosis is also important for care in peri-operative management. In all variants of mastocytosis, skin pressure may provoke local erythema and edema. Non-immunologic stimuli such as wide variations in temperature, stress, or application of tactile pressure may trigger flushing or itching. In patients with DCM, mechanical pressure can sometimes lead to blister formation.<sup>[87]</sup> Special attention to position and to protection of pressure points thus has to be given to patients with mastocytosis during anesthesia.

Patients may have medication-controlled symptoms of GERD. It is thus prudent to consider the need for rapid sequence induction. Consideration should also be given to evaluating the coagulation profile, as mast cells contain heparin. Consequently, in children with mastocytosis, prothrombin (PT) and partial thromboplastin times (PTT) may be slightly prolonged. Although there were no reports of unexpected bleeding during surgical procedures in patients with mild abnormalities in coagulation profile,<sup>[76]</sup> measurements of baseline PT and PTT should be considered prior to invasive procedures where blood loss can be expected.

Serum tryptase is constitutively expressed in patients with mastocytosis and is a reflection of extent of mast cell burden. During anaphylaxis, an elevation in serum tryptase level over baseline may be observed within 15 minutes of its onset and last for 2–4 hours. In one study, elevated serum tryptase at baseline did not predict the occurrence of adverse events. However, it is recommended to obtain baseline serum tryptase levels in all patients prior to surgery, as an increase in tryptase levels associated with an adverse event would suggest mast cell activation; helpful for diagnostic purposes.

Routine skin testing to anesthetic drugs, muscle relaxants or opioids prior to anesthetics is an option, but data may be difficult to interpret. According to reports in the literature, skin test results are not reliable predictors of adverse reactions to drugs because some drugs can directly degranulate mast cells *in vivo*.<sup>[88]</sup> Moreover, intradermal testing has not been

validated in patients without a history of reaction to given drugs, and a positive skin test has not been shown to be 100% predictive of adverse reactions.<sup>[88]</sup>

Although the spectrum of clinical manifestations of mastocytosis, increased mast cell numbers, and perceived drug sensitivity makes the approach to anesthetic management in these patients more challenging, routine anesthetics may be safely administered to children with pediatric mastocytosis. This approach calls for a thorough understanding of mastocytosis and its manifestations and appropriate use of routine anesthetic techniques in those patients without a previous history of adverse events. Given the nature of pediatric mastocytosis and the potential for anaphylaxis, the authors advocate the administration of incremental, rather than single boluses of needed drugs (opioids, muscle relaxants) known to activate mast cells, and meticulous preparation to treat, albeit rare, possible adverse events during anesthetics. We suggest medically indicated drugs (opioids, muscle relaxants) should not be eliminated from therapeutic consideration in the perioperative period, unless there is a clear prior history of sensitivity. When questions arise over the use of critical drugs, we advise careful a careful challenge be performed ahead of the scheduled procedure beginning with small amounts of agent. Further, when anesthetizing a patient with pediatric mastocytosis, appropriate personnel and resuscitative therapy for emergent use in the event of anaphylaxis must be readily available.

## Research needs

Because pediatric mastocytosis in both a rare and sporadic disease, data has been slow to accumulate relating to pathogenesis, natural history, prognostic features, diagnosis and treatment. What is known has been reviewed in this article. To approach these questions, funding of centers of excellence is needed so as to allow the recruitment and study of sufficient patients with various patterns of disease. Prospective studies then need to be implemented to follow these children as they grow to adulthood to allow and understanding of the prognosis of mastocytosis disease variants. Is the classification of mastocytosis in adults applicable to children; what is the meaning of genetic findings of abnormalities in KIT and other critical genes regulating human mast cell growth? What is the experience with sensitivity of drugs used to manage pain and induce anesthesia? Should cytoreductive therapy be instituted and when?

However, this approach takes time, support, and patience. Until such clinical studies are funded and carried forward, individual centers should be encouraged to approach these research issues as best possible. Case reports and small series are to be encouraged, but results should not be generalized because of the complexity and varying patterns of pediatric disease involving mast cells. Aggressive therapy applied to the control of pediatric mastocytosis should be approached with much caution, as the natural history for the majority of children affected is one of continued improvement.

## Acknowledgments

This work was in part supported by the Division of Intramural Research, NIAID/NIH.

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Bullous Mastocytosis in a 3 month  
African American child



Boullous Mastocytosis in a Caucasian  
child

**FIGURE 1.**



Urticaria Pigmentosa in infant

FIGURE 2.





Macronodular Mastocytosis in child



Plaque Mastocytosis in Child



Diffuse plaque Mastocytosis in child



Child after treatment with mast cells mediator controller medications

**FIGURE 3.**

**Table 1**

## Diagnostic Approach in Pediatric Mastocytosis

**For suspected cutaneous mastocytosis (multiple or single lesions)**

**Skin biopsy** (3 mm punch): histology, mutational studies if possible

Compatible with diagnosis: aggregates of >20 mast cells +/- abnormal morphology, +D816V c-kit

If single lesion: mastocytoma, no further studies required

**If UP, TEMP or other forms diagnosed, need:**

**Selected laboratory tests:** peripheral blood count, differential and platelet count; routine biochemistries as required; baseline serum tryptase

Studies can be repeated every 6 to 8 months. If severe MC-mediator related symptoms are present, analytical studies may be repeated more frequently

**Abdominal ultrasound if organomegaly suspected or with:**

Severe systemic mast cell-mediators related symptoms:

GI, flushing, syncope or pre-syncope, cyanotic spells

Persistence of skin lesions after puberty

Clinical changes suggestive of systemic involvement

**Bone marrow biopsy and aspirate if:**

Severe recurrent systemic mast cell-mediators related symptoms:

GI, flushing, syncope or pre-syncope, cyanotic spells

Organomegaly or significant lymphadenopathy

Persistence of skin lesions after puberty

Clinical changes suggestive of systemic involvement

**Table 2****Treatment of Pediatric Mastocytosis****A. Avoidance of Triggers**

Specific foods, medications, allergens; and general triggers (Table 3)

Physical measures

Avoid sudden changes of temperature.

Avoid extreme temperatures in bath/shower, swimming pool, air conditioned.

Avoid dryness of skin

Avoid rubbing

Local care of skin

Take steps to avoid drying of skin and use skin moisturizer

Water-soluble sodium cromolyn cream

Apply two to four times a day for urticaria, pruritus, vesicles or bullae. Do not use on denuded lesions (consider topical antibiotics)

Topical corticosteroid cream

In diffuse lesions apply bath or sterile gauze with zinc sulfate

**1. Solitary mastocytoma**

Water-soluble sodium cromolyn cream:

Corticosteroid cream.

Avoid friction and pressure

Consider surgical excision (flexures, soles, palms, scalp)

**2. UP and other forms**Trigger (s)-related symptoms

Avoidance of triggers

H1 antihistamines

H2 antihistamines

Continuous moderate symptoms

Scheduled non-sedating H1 antihistamines; if necessary add sedating H1 antihistamines at demand

Scheduled or at demand H2 antihistamines

Oral disodium cromolyn in case of persistence of symptoms

Severe symptoms

Scheduled non-sedating H1 antihistamines

Scheduled sedating H1 antihistamines

Scheduled H2 antihistamines

Oral disodium cromolyn

Add antileukotrienes in refractory cases

**3. Diffuse forms with life-threatening mast cell-mediator related symptoms, bullae and blistering**

Treatment may require hospitalization and, in some cases, at the Pediatric Intensive Care Unit.

Local therapy

Sterile conditions

Topic sodium cromolyn

Topic corticosteroids

Zinc sulfate

Antibiotics in denude areas

Systemic therapy

Epinephrine if necessary

Adequate sedation if necessary

Scheduled non-sedating H1 antihistamines

Scheduled sedating H1 antihistamines

Scheduled H2 antihistamines

Oral disodium cromolyn

Corticosteroids mainly in cases with associated angioedema or abdominal pain (with or without diarrhea) unresponsive to sodium cromolyn

Add antileukotrienes in refractory cases

Consider PUVA as an exceptional alternative in cases with persistent episodes of diffuse bullae and blistering unresponsive to anti-mediator therapy

**Table 3****Triggering Factors in Pediatric Mastocytosis**


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<b>Physical stimuli</b>
Frequent
Heat
Sudden changes of temperature
Rubbing/pressure of skin lesions
Scalp trauma (children with scalp involvement)
Infrequent
Cold
Sunlight
<b>Emotional factors</b>
Stress,
Anxiety
Sleep deprivation
<b>Infectious diseases with fever</b>
Viral (Esp. respiratory and gastrointestinal)
Bacterial (bronchitis, pneumonia)
<b>Drugs*</b>
Non-steroidal anti-inflammatory drugs
Morphine and derivatives
Cough medication: dextromethorphan
<b>Miscellaneous</b>
Dental procedures
Vaccinations
Surgery
<b>Associated allergic diseases**</b>

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1. Responses greatly vary from patient to patient. 2. Patients with known sensitivities must wear a Medic alert bracelet or necklace.

\* If patients have not taken these drugs before, provocation test may be performed under close medical supervision.

\*\* Foods, environmental allergens and other factors may exacerbate or precipitate mast cell activation in mastocytosis patients.