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Triggers of Anaphylaxis in Mastocytosis Patients: Evidence of the Current Drug-Avoidance Recommendation

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Opinion statement

Mastocytosis is associated with a high risk of anaphylaxis, in part due to drug hypersensitivity reactions (DHR). Drugs associated with mast cell activation include nonsteroidal anti-inflammatory drugs (NSAIDs), drugs used in the perioperative setting, including general anesthetics, neuromuscular blocking agents (NMBAs) and opiates/opioids, radiocontrast media (RCM), vaccines, and antibiotics such as quinolones and vancomycin. To protect patients against DHR and anaphylaxis, general avoidance of potential drug triggers is common practice, which often deprives patients of important drugs at times of need and limits their options. We aimed to critically review current evidence on the indications to avoid drugs in children and adults with mastocytosis. Recent data shows that general avoidance of drugs with potential mast cell activation action is not indicated in all patients with mastocytosis, but guidelines are lacking. Drugs tolerated before and after the onset of mastocytosis should not be avoided and a personalized approach is recommended to

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address drugs inducing mast cell activation. Pre-medication (RCM, local and general anesthetics, vaccines), use of safer alternatives (opioids, NBMAs, NSAIDs in selected cases), and drug challenges (NSAIDs in most cases) are recommended to increase the safety of patients with mastocytosis when introduced to new drugs.

Introduction

The term mastocytosis comprises a heterogeneous group of diseases characterized by clonal and phenotypically aberrant mast cell (MC) accumulation in different tissues and organs, including the skin, bone marrow, and gastrointestinal (GI) tract, with or without excessive MC activation [1].

MC express a myriad of activating receptors, including the stem cell factor receptor (KIT), immunoglobulin receptors (e.g., FcεRI and FcγRI), complement receptors (e.g., C3aR and C5aR/CD88), pattern recognition receptors (e.g., Toll-like receptors [TLR]) and the Mas-related G-protein coupled receptor member X2 (MRGPRX2) [2, 3]. When activated, MC may release a full array (i.e., degranulation) or a limited amount of mediators (i.e., piecemeal-degranulation or differential release of mediators) [4]. Immunoglobulin (Ig)E-independent (and notably MRGPRX2-dependent) degranulation has different kinetics and extent of mediators release as compared to IgE-mediated activation [5].

The majority of mastocytosis are caused by activating mutations in the gene that codifies for the KIT-receptor/CD117 (i.e., *KIT*), with the KIT^{D816V} mutation being detected in over 90% of cases [6]. Such mutations are mostly sporadic and are restricted to MC and MC precursors in around two-thirds of cases [7]. Activating *KIT* mutations promote autophosphorylation and, or dimerization of the KIT receptor in a ligand-independent fashion, enhancing cell proliferation and survival [6], as well as IgE-mediated activation [8] and may lower the threshold for non-IgE-mediated MC activation [9]. Mastocytosis patients present mild to severe MC activation symptoms, which can be chronic and, or acute, including diarrhea, heartburn, urticaria, angioedema, flushing, hypotension, dizziness, brain fog, headaches, and life-threatening anaphylaxis [10].

The prevalence of anaphylaxis in mastocytosis patients is considerably higher than in the general population and may reach up to 50% [10••, 11], even though the prevalence of atopy is similar [12, 13]. According to the results found on two large case series, the percentage of allergy among mastocytosis patients ranges between 24 [14] and 28% [12, 13] in adults, and 17 [14] and 11% [15] in children. Interestingly, 67% of patients with anaphylaxis seem to be sensitized to known allergens [16]. Anaphylaxis is common among patients with systemic mastocytosis without skin lesions (typically adult males), in whom it may be present in up to 67% [12, 13]. In contrast, the frequency of anaphylaxis in mastocytosis with skin lesions (i.e., including cutaneous mastocytosis) is lower and found to be 16–19% [14, 16]. Mastocytosis patients at higher risk for anaphylaxis include those presenting without skin lesions, atopy, high total IgE, and lower serum baseline tryptase (sBT) [17], while recent data suggests a potential contribution of hereditary alpha-tryptasemia (HαT) genotypes [18–22].

In mastocytosis, MC activation symptoms can be unprovoked and provoked by triggers [12]. Non-specific triggers include emotional stress/anxiety, dental eruption, fever, and the friction of mastocytosis skin lesions [23–25]. Specific triggers include drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), vaccines, opiates/opioids, neuromuscular blocking agents (NMBAs), radiocontrast media (RCM), quinolones, vancomycin, and *Hymenoptera* venoms [25, 26], which may induce MC activation through several mechanisms (Fig. 1). Due to the unpredictability of drug hypersensitivity reactions (DHR) and widespread perception of the risks associated with these drugs, mastocytosis patients are often told to empirically avoid all of these drugs. Avoidance of such drugs is

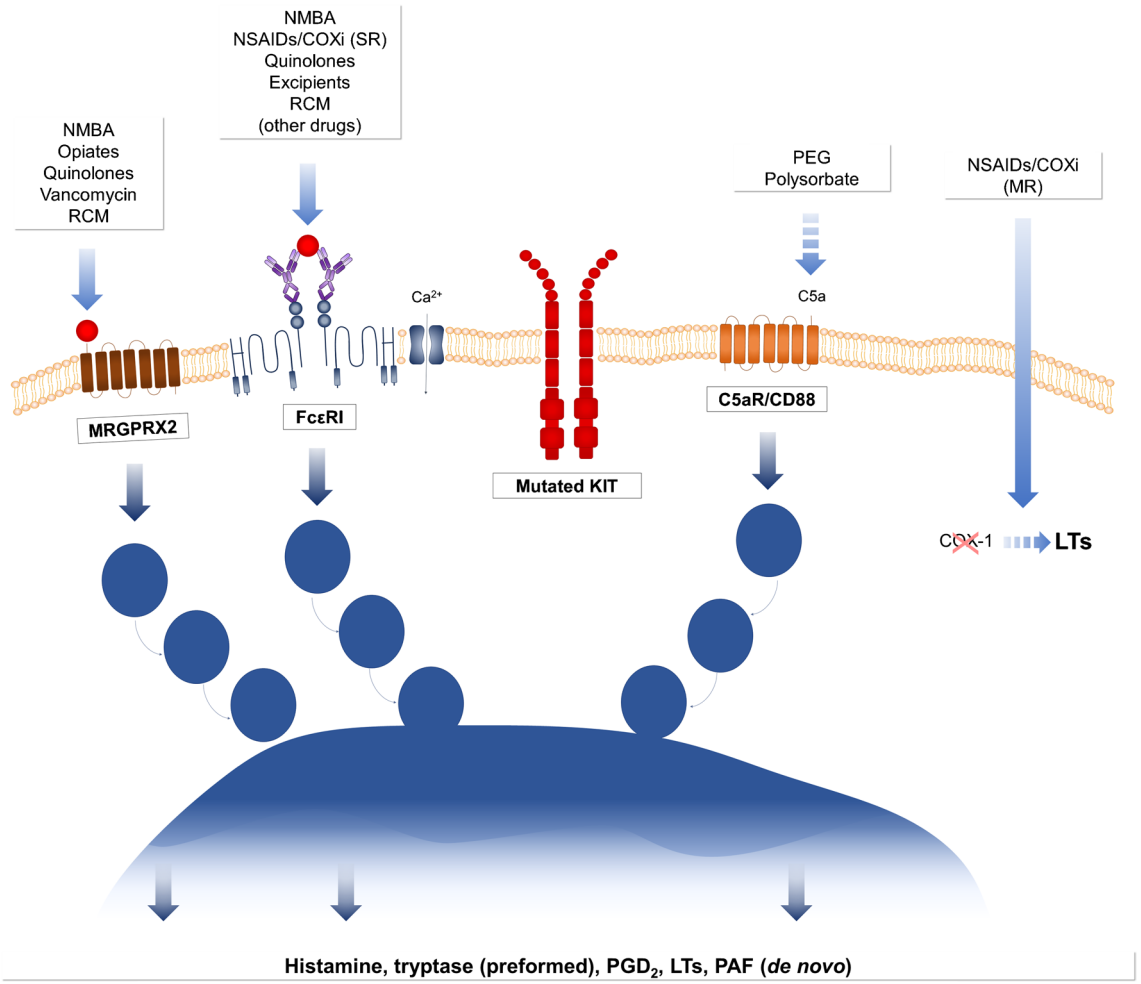

Fig. 1 Mast cell receptors potentially involved in drug hypersensitivity reactions in mastocytosis patients. Activating *KIT* mutations lead to dimerization of *KIT* which lowers the threshold for mast cell (MC) activation due to the activation of the high-affinity immunoglobulin (Ig) E receptor (FcεRI) and the mas-related G-protein-coupled receptor X2 (MRGPRX2). Both receptors lead to MC degranulation when activated. IgE-mediated activation leads to a slow-onset and prolonged release of MC mediators dependent on the calcium influx, while MRGPRX2 induces a rapid-onset and brief (even if often severe) release. The C5a receptor (C5aR/CD88) may be overexpressed in patients with mastocytosis and also leads to MC activation due to the so-called complement activation-related pseudoallergy, in which IgM/IgG antibodies against drugs (e.g., excipients found in COVID-19 polyethyleneglycol [PEG] and polysorbate) activate the classical complement pathway culminating in the release of C5a. Following activation, MC granules merge into larger ones and migrate to the membrane with which they merge, releasing their content, which includes preformed mediators (i.e., histamine, tryptase). Later, de novo release of prostaglandin (PG) D2, cysteinyl-leukotrienes (LTs), and platelet-activating factor (PAF) occurs. Cyclooxygenase (COX) 1 inhibitors (e.g., nonsteroidal anti-inflammatory drugs and paracetamol) induce the release of leukotrienes (LTs) by decreasing the release of PGE2 thereby promoting the action of leukotriene synthase.

frequently unnecessary as the associated risk of MC activation is often low and similar to the risk in the general population [10, 27, 28••, 29].

Here, we aimed to critically review current evidence on the indications to avoid drugs with mast cell activation potential in children and adults with mastocytosis.

Nonsteroidal anti-inflammatory drugs and other cyclooxygenase inhibitors

NSAIDs are part of a broad group of cyclooxygenases (COX) inhibitors (COXi) that also includes analgesics and antipyretics such as salicylates (e.g., acetylsalicylic acid [ASA]), pyrazolones and paracetamol [30]. NSAIDs and ASA exert preferential COX-1 inhibition at the peripheral and central nervous systems, enacting anti-inflammatory, antipyretic, and pain control effects [31]. In contrast, paracetamol is a weak COX-1 inhibitor with analgesic and antipyretic effects caused by central nervous system COX-2 inhibition [32].

DHR to NSAIDs or other COXi may be caused by drugs within structurally related groups, with patients reacting to a single drug or structurally related drugs [33] through an IgE-mediated mechanism or by multiple structurally unrelated drugs [10••, 34] through a COX-1-inhibition-mediated depletion of PGE_2 mechanism [35], resulting in an over-production of cysteinyl-leukotrienes [36]. Reactions can range from urticaria, angioedema, and bronchospasm to anaphylaxis [37]. Patients reacting to multiple COX-1 inhibitors typically can tolerate weak COX-1 inhibitors (e.g., paracetamol) and COX-2 preferential or selective inhibitors (i.e., nimesulide/meloxicam or coxibs) [38]. Because there are no biomarkers of NSAID hypersensitivity, drug challenges with ASA (the strongest COX-1 inhibitor) are used to exclude/confirm reactivity to multiple NSAIDs [39, 40, 41]. Still, children under 16 must avoid ASA due to potential Reye's syndrome [42].

In mastocytosis, the reported prevalence of NSAID hypersensitivity is 14% in adults and 9% in pediatric patients [10••, 43, 44•], and NSAID-induced anaphylaxis is found in 2 to 11% of adult patients [10••, 14–16, 45] and 2% of children and adolescents [10••], and has led to frequent general avoidance [10••]. Regional differences exist, with ASA being the most frequent culprit in Spain and Italy [10••, 44•] and diclofenac in Sweden [44•]. Paracetamol, coxibs, and meloxicam are tolerated by most patients [10••].

A large single-center study conducted by the Spanish Network on Mastocytosis (*Red Española de Mastocitosis* [REMA]; with 469 patients, 382 adults and 87 children/adolescents) indicated that risk factors for NSAIDS hypersensitivity included female sex, with baseline symptoms of angioedema and pruritus, a previous history of anaphylaxis other than HVA, advanced disease, higher sBT levels, and multilineage KIT^{D816V} mutation [10••]. A risk-predicting scoring model (Table 1) showed high sensitivity and requires validation in large multicenter studies.

Patients who tolerate NSAIDs before and after the onset of mastocytosis do not require testing, and avoidance is not indicated [10••, 44•, 46, 47]. For patients whose tolerance following the onset of the disease is unknown, a challenge with ibuprofen is recommended in children and adults with a negative score and with preferential/selective COX-2 inhibitors (e.g., meloxicam or coxibs) for adults with a positive score [10••]. Drug challenges need to be done by experienced providers after risk/benefit information to the patient in a shared decision process.

Table 1. Scoring model proposed by the *Red Española de Mastocitosis* to screen for hypersensitivity to multiple NSAIDs or other COXi in adult patients with mastocytosis [10••]

Variable	Score
Gender	
Female	+6
Male	−2
Manifestations	
Flushing	+4
Absense of pruritus	−3
Skin lesions	−3
Anaphylaxis not caused by NSAIDs/COXi	+5
Anaphylaxis caused by *Hymenoptera* venoms	−4
Laboratory findings	
Multilineal D816V *KIT* mutation*	+4
sBT ≥ 48 ng/mL	+6

Patients scoring seven or above should undergo drug challenges with COX-2 preferential or selective inhibitors (respectively, meloxicam and coxibs), whereas those scoring below seven may undergo challenges with ibuprofen. *If unknown, consider as negative

Vaccines

Vaccines contain adjuvants which modulate both innate and adaptive immune responses [48] and excipients to stabilize and preserve formulations (e.g., ethylenediaminetetraacetic acid [EDTA]) and as antigen carriers (e.g., polyethylene glycol [PEG] nanolipid envelope). Microbial antigens, adjuvants, and excipients may act as allergens or as pathogen-associated molecular patterns (PAMP), leading to IgE- and non-IgE-mediated activation of MC. IgE-mediated reactions have been described against excipients (e.g., gelatin, milk and egg proteins, latex, tromethamine) and microbial antigens (e.g., protein conjugates within the diphtheria and *Haemophilus influenzae* type b vaccines, and tetanus toxoid) [49–51]. SARS-Cov-2 mRNA vaccines' PEGylated nanolipid envelopes have been implicated in IgE-mediated anaphylaxic reactions, which have been more frequent in females with previous allergic reactions, including anaphylaxis to drugs and foods [52–55]. Non-IgE-mediated mechanisms, such as dose-dependent complement-mediated MC activation (complement activation-related pseudoallergy [CARPA]) [52, 56–58], have been suggested as a potential cause of DHR to COVID-19 vaccines in mastocytosis patients, as MC from patients with systemic mastocytosis overexpress the complement receptor for C5 (C5aR/CD88) [59].

Anaphylaxis to vaccines is rare in the general population, amounting to an overall rate of 1.31 per million vaccine doses [60], and is increased tenfold for SARS-COV-2 vaccines [49]. In mastocytosis, MC activation episodes related to vaccination have been reported in children and in adults [61–63]. The frequency of reactions ranges from 4 to 13% in pediatric mastocytosis

patients [61, 64, 65], with diffuse cutaneous mastocytosis (DCM) having been deemed a risk factor in a Spanish study population [63]. Although there is no correlation between lesion burden and vaccination-associated DHR, the administration of single vaccinations instead of multiple simultaneous vaccinations with pre-medications has been recommended [61], especially in patients with DCM [63, 66, 67].

Five studies with a total of 372 patients have described the safety of COVID-19 vaccination in patients with mastocytosis and other clonal and non-clonal MC activation disorders [27, 68–71]. In two studies, none out of 73 [68] and nine out of 30 [27] had a prior history of anaphylaxis. Overall, 12 hypersensitivity reactions were reported including anaphylaxis in non-pre-medicated (10%) and pre-medicated (0.6%) patients.

The data support the safe vaccination of all pediatric and adult mastocytosis patients as recommended by worldwide agencies. Pre-medication is recommended with H1 and H2 antihistamines and leukotriene receptor antagonists, but not steroids, and vaccination should be followed by a prolonged observation period of 30 min.

Drugs used in the perioperative setting and opiates/opioids

There is a perception by patients and providers that general anesthesia is a high-risk procedure for mastocytosis patients [46, 47, 72–75]. However, in a large retrospective study of patients with mastocytosis (n = 501 patients, 459 adults, and 42 children), the risk of DHR during the perioperative period was shown to be low (DHR in 2% of adults and 4% of children, and anaphylaxis in 0.4% of adults and 2% of children) [75]. Risk factors identified in the study included a prior history of anaphylaxis, major surgery, and lack of pre-medication [75]. A limited study of a pediatric population (n = 22 patients) showed that 9% of children who underwent general anesthesia presented with flushing without hemodynamic compromise [76].

Neuromuscular blocking agents are the most frequent elicitors of perioperative anaphylaxis in the general population [77, 78], which may be caused by IgE-mediated and MRGPRX2-related MC activation (for drugs containing the tetrahydroisoquinoline [THIQ] motif) [79, 80]. Non-depolarizing benzylisoquinoline NMBAs atracurium and mivacurium have been identified as having the highest potential for MC activation [79, 81] due to MRGPRX2-related activation [82]. Atracurium cause severe reactions in mastocytosis patients and its use is not recommended due to potential fatalities [73]. Succinylcholine and isoquinoline-type NMBAs, such as cisatracurium, have the lowest potential for MC activation [79, 83, 84] and are considered safe for mastocytosis patients. Succinylcholine is rarely associated with IgE-mediated reactions [26, 85]. Aminosteroid NMBAs include rocuronium which can induce IgE-mediated reactions and is not recommended in mastocytosis patients, while vecuronium, pancuronium, and rapacuronium rarely induce MC activation [79], and their use is recommended in mastocytosis patients [26, 73].

Opiates/opioids, including morphine, pethidine/meperidine, codeine, and others, are avoided by mastocytosis patients based on in vivo and in vitro

data showing direct MC activation [86, 87]. Codeine, an opiate frequently used in over-the-counter cough syrups, seems to display the strongest MC degranulation potential, followed by morphine and meperidine [88]. These effects are dose-dependent [89, 90] and thought to relate to the activation of MC δ-receptors [89], the release of histamine by free radicals [91], and MRGPRX2-mediated activation [92]. In vitro studies show that connective tissue mast cells termed MC_{TC} undergo degranulation following morphine exposure [93], whereas pulmonary, intestinal, and cardiac mucosal mast cells (i.e., MC_T) do not degranulate [94]. Buprenorphine seems to only induce degranulation of pulmonary MCs [90]. Fentanyl and other piperidine-derived synthetic opioids have been shown to be safe for mastocytosis patients, as these induce little MC activation [88, 89]. Opioids used in analgesia, including oxycodone, hydromorphone, oxymorphone, tapentadol, and tramadol (a partial opioid-receptor agonist), have been shown not to induce in vivo histamine release [92]. Even though in vivo responsiveness to morphine in mastocytosis patients (assessed by wheal size following skin prick testing) is not increased in comparison with healthy individuals and asthma patients [95], its use is not recommended, and the use of tramadol, and piperidine derivatives has been recommended instead [26, 96].

IgE-mediated DHR to hypnotics, propofol, thiopental, and ketamine are less common than reactions to NMBAs, and opiates/opioids and are not contraindicated in mastocytosis patients [97]. Propofol, thiopental, and ketamine induce the release of histamine by cutaneous and pulmonary MCs [98], whereas propofol may inhibit intestinal and cardiac MC activation [99–102]. Benzodiazepine (BZPs) IgE-mediated DHR are exceedingly rare in the general population [103], and MCs have been shown to have high affinity binding sites for BZPs [104, 105], which may inhibit MC proliferation and activation [106]. BZPs are considered safe in mastocytosis, and their use as pre-medication is recommended to reduce procedural anxiety [107]. Currently used inhaled general anesthetics seem to be devoid of MC activation potential, IgE-mediated reactions have not been described, and their use should not be avoided in mastocytosis patients [108, 109].

The prevalence of anaphylaxis in the perioperative period is higher for mastocytosis (1:250 in adults and 2:100 in children) [75] as compared to the general population (1:5000 to 1:13000) [110]. Specific and non-specific triggers include the drugs described above, procedural anxiety, temperature changes, pressure and lesional friction, and gastrointestinal organ manipulations. The role of pre-medications has not been validated in controlled studies, and the current recommendations include glucocorticoids, H1 and H2 antihistamines, leukotriene receptor antagonists and BZP [26]. Omalizumab has been shown to protect mastocytosis patients against anaphylaxis [111], and its protective effect in the perioperative period also warrants further studies.

Local anesthetics (LAs) are divided into ester-type LAs (e.g., benzocaine, procaine), which are associated with immediate DHR [112], and amide LAs which rarely cause immediate DHR or anaphylaxis [113, 114]. Preservatives and antioxidants contained in LAs formulations, or LAs/vasoconstrictor association formulations, including parabens, metabisulfite, and latex [112, 115–117], have rarely been identified as reaction culprits. Skin tests' predictive values are not well defined since false positive tests followed by negative

subcutaneous challenges have been reported [118]. Non-immune-mediated reactions such as syncope resulting from parasympathetic hyperstimulation or hyperexcitability of peripheral nerves have been described [119]. The prevalence of DHR to LAs has been described as 0.8% in mastocytosis adults [75], and ester-type LAs are not recommended [26, 46, 96]. Pre-medication may be recommended prior to procedures requiring local anesthesia—usually, a non-sedative H1 antihistamine 1 h before the procedure.

Radiocontrast media

RCM are an uncommon cause of DHR and anaphylaxis in the general population [120, 121] and in mastocytosis patients [14, 16, 46, 122]. In the general population, hyperosmolar/ionic RCM have been associated with a higher frequency of severe DHR [120]. The prevalence of DHR to non-ionic/hyposmolar RCM is much lower at 0.1% in a large cohort, including 299,413 patients who underwent contrast tomography [121]. Still, RCM osmolarity does not seem to correlate with histamine release [123]. In vitro studies indicate that hyposmolar non-ionic RCM (e.g., iohexol) do not induce direct MC activation [124]. Reactions to RCM are thought to be IgE- [125] or MRGPRX2-mediated [126, 127], and the role of excipients, notably tromethamine, has not been defined.

Literature reports on DHR associated with hyperosmolar or hyposmolar RCM in mastocytosis patients are scarce, and, based on in vitro data indicating MC activation with hyperosmolar RCM [128], the use of hyperosmolar/ionic RCM has been contraindicated [129]. DHR reports in mastocytosis patients include iohexol [130], non-disclosed angiography contrast media [131], non-disclosed non-ionic ICM [122], and otherwise unspecified contrast media [15, 122, 132–134]. Some of the reports indicate that patients were able to tolerate RCM with pre-medication [122, 130]. Pre-medications prior to RCM are recommended, but no controlled studies exist to provide outcomes [26, 46, 47, 122, 134]. Evaluation of mastocytosis patients with suspected DHR to RCM may include skin testing and drug challenge testing [46]. In the unusual event of DHR to multiple RCM, tromethamine hypersensitivity should be investigated. Paramagnetic contrasts (e.g., gadolinium derivatives) may be used as alternatives to RCM, but gadobutrol should be avoided for those allergic to tromethamine [50].

Antibacterials

Quinolones (e.g., ciprofloxacin, levofloxacin, moxifloxacin) are broad-spectrum antibiotics involved in immediate DHR both through IgE-dependent and MRGPRX2 activation [135]. Quinolones' safety [136] and resistance [137] profiles have made their use mostly limited to multiresistant bacteria (e.g., *Pseudomonas aeruginosa*). The prevalence of immediate DHR to

fluoroquinolones is as high as 1 out of 1100 treatments [138]. In mastocytosis, only one case of DHR has been reported to date [139]—curiously, in a patient with bone marrow mastocytosis with Hymenoptera venom anaphylaxis, a disease subvariant that seems less prone to DHR [29]. Recommendations to avoid quinolones in patients with mastocytosis have been based on the high rate and severity of the reactions [140].

Vancomycin is a glycopeptide used to treat bacterial gram$^+$ infections (e.g., methicillin-resistant *Staphylococcus aureus*, *Enterococci*) and a weak MRGPRX2 agonist [141]. Vancomycin infusions can induce histamine release in healthy volunteers related to the infusion rate (formerly, red man syndrome) [142]. There is no evidence that slow-rate infusions may be associated with MC activation in patients with mastocytosis, but vancomycin should be avoided in these patients based on its MC activation properties.

Conclusion

Mastocytosis has been associated with an increased risk of DHR to a wide array of drugs, including NSAIDs, drugs used in the perioperative setting, opiates and opioids, vaccines, RCM, antibiotics such as quinolones, and vancomycin and identifying patients at risk is paramount to prevent unnecessary avoidance of critical drugs. The proportion of patients with DHR depends on the drug and the disease with adult patients presenting higher incidence than children (Table 2). Avoidance should be restricted to specific drugs to which there is a history of reactions. Drugs with the best safety

Table 2. Frequencies for drug hypersensitivity reactions of drugs frequently avoided in mastocytosis patients

Drug group	Frequency of hypersensitivity in mastocytosis	References
NSAIDs/COXi	Children: up to 9% Adults: up to 14%	[10••, 43, 44•]
RCM	Children: unknown (rare) Adults: rare	[122]
Drugs used in the perioperative		
General anesthesia	Children: 2–18% Adults: 0.4%	[75, 76]
Local anesthesia	Children: unknown (rare) Adults: 0.8%	[75]
Vaccines	Children: 4–13% Adults: 3% (COVID-19 vaccines)	[61, 65] [27, 68, 69, 70, 71]
Quinolones	Unknown	-
Vancomycin	Unknown	-

COXi cyclooxygenase inhibitors, *NSAIDs* nonsteroidal anti-inflammatory drugs, *RCM* radiocontrast media

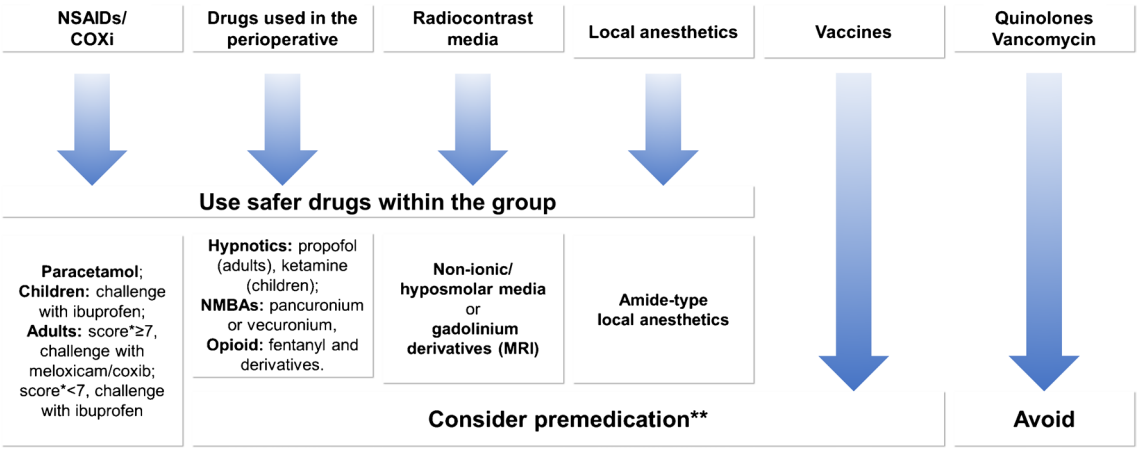

Fig. 2 Drugs that are frequently avoided in patients with mastocytosis and suggested approach. COXi, cyclooxygenase inhibitors; MRI, magnetic resonance imaging; NMBA, neuromuscular blocking agents; NSAIDs, nonsteroidal anti-inflammatory drugs; RCM, radiocontrast media. * see Table 1. Asterisk (**) indicates prednisolone 0.5 to 1 mg/Kg (or equivalent) 12 and 1 h before, and cetirizine 10 mg (or other non-sedating H1 antihistamine on equivalent dose), famotidine 20 mg and montelukast 10 mg 1 h before major surgery and procedures in patients with previous reactions/same dosing of glucocorticoids 13, 7 and 1 h before RCM infusion. Cetirizine 10 mg (or other non-sedating H1 antihistamine on equivalent dose) and famotidine 20 mg for vaccination and minor procedures. Omalizumab may be used in patients with multiple reactions to multiple drugs who have failed other pre-medications.

profile should be preferred over those known to elicit MC activation and drug challenges for less preferred drugs should be done at times of need by experienced providers. Patients should not be labeled as allergic to drugs to which they have not been exposed before. Delabeling patients with allergy labels not sustained by objective data should be done to improve the quality of life of mastocytosis patients. Pre-medications should be used judiciously before tests and procedures known to induce reactions (Fig. 2). Pre-emptive and empirical avoidance of drugs is not recommended in children with mastocytosis who have not presented previous reactions or have not been exposed to the drug. Further clinical and basic research and the generation of data bases will help understand DHR in mastocytosis and guide treatments and procedures, improving safety.

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Compliance with Ethical Standards

Conflict of Interest
The authors declare no competing interests.

Human and Animal Rights and Informed Consent
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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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