History: Elizabeth Milo is known to have dysautonomia, mast cell activation syndrome (MCAS), a connective tissue disorder (EDS), and poor GI motility. Consequently, there are several issues that need to be addressed to make the surgical experience safer.

The most important considerations in emergency situations and for surgery are:

- My reactivity and hyper-sensitivity to medications, which necessitates very low dose and slow administration (*see attached allergy list* -- **I have reacted to Morphine and Morphine derivatives with respiratory distress**).
- I HAVE NEVER HAD ANESTHESIA and cannot predict how I will respond to medications. If possible, start with Propofol *only* and at lowest dose possible.
- Maintaining my low blood pressure and low blood sugar.
- My history of idiopathic and atypical anaphylaxis with syncope.
- Avoiding vasodilators and histamine-releasing agents.
- I have craniocervical instability: Use Glidescope or fiberoptic intubation and the most conservative c-spine protocols reserved for patients with neck injuries.

Patients with mast cell disease and connective tissue disorders, such as EDS, must take into consideration possible complications of surgery, such as anaphylaxis, cardiovascular collapse, increased bleeding and even death. General anesthesia is considered a high-risk procedure in these patients and it is critical that all members of the operating team take proper precautions before, during, and after surgery to protect against potentially life-threatening mast cell reactions.

An experienced anesthesiologist is aware of medications known to cause mast cell degranulation and medications that stabilize mast cells. If the patient is satisfied that their anesthesiologist fully understands the importance of planning around mast cell disease, it will go a long way toward calming the patient, which in turn may reduce mast cell mediator release. Bear in mind that some of the most common mast cell triggers are medications, pain, stress, hormones, temperature extremes, molds, perfumes, cleaning products and detergents.

BEFORE SURGERY:

Review medication and supplement list with the surgical team. I will stop as many medications and supplements as possible at least a week in advance, in particular ones that lower blood pressure (vasodilators such as aspirin, nitroglycerin, vitamin E).

Discuss premedications. Some procedures require the patient not to take anything by mouth including medications after midnight the night before surgery. In this case, discuss administering H1- and H2-blockers intravenously prior to surgery (note: I have never had IV antihistamines: must be low dose, pushed very slowly, and monitored carefully for reactions). Premedication with corticosteroids may also be indicated.

Minimize NPO (nothing by mouth) time prior to surgery because of dysautonomia and hypoglycemia. Discuss protocol in the event of hypoglycemia during surgery (IV D5 (dextrose 5%)? -- I've never had this). Ask anesthesia team and surgeon if I am allowed to drink clear fluids before surgery and be sure to be adequately hydrated.

Discuss medications that will be used during surgery. I have mast cell activation syndrome and a history of idiopathic anaphylaxis. Anaphylactic episodes are generally treated with intravenous H1- and H2-blockers and IM epinephrine, if there is hemodynamic instability or respiratory distress. In addition, IV fluids and other support and resuscitation measures should be undertaken. Please don't use any medications that are not entirely necessary. For example, prophylactic nausea meds and local anesthetics are probably not needed.

I am unusually reactive to small amounts of medications. All medications should only be used if absolutely necessary and then used sparingly and in small doses until my response can be assessed. For example, I have had reactions to every benzodiazepine I've tried (tongue swelling, respiratory distress, migraine) and am very sensitive to even antihistamines. My doctor has warned that anesthetics can cause me autonomic nervous system issues, such as gastro-esophageal reflux, tachyarrhythmias and difficulty maintaining blood pressure. It may be prudent to perform a graded challenge procedure in the hospital under the supervision of an allergist for certain medications if there is no history of exposure to that medication (skin prick and intradermal tests).

Discuss my baseline blood pressure. I have low blood pressure normally (~85/55) and probable depleted blood volume, so extra care must be taken to ensure anesthesia doesn't cause dangerous hypotension. However, the anesthesiologist must bear in mind my normal low BP so anaphylaxis is not suspected and treated when it isn't there.

Intraoperative hypotension is one of the greatest factors associated with death related to anesthesia. Consider an intra-arterial catheter for continuous blood pressure monitoring during surgery (as opposed to a cuff). Discuss how hypotension will be treated during surgery (print study).

Controlling the depth of anesthesia limits the hypotensive effects of anesthetic drugs. Deep hypnosis (BIS <45) has been associated with postoperative complications and mortality. To limit hypotension induced by intravenous drugs, anesthesia should be titrated to clinical response. To guide induction anesthesia and identify the depth of anesthesia, consider bispectral index (BIS) monitoring.

Discuss continuous IV hydration with normal saline (NS) to maintain blood pressure, however, please note that I have had reactions to IV fluids in the past due to running them too quickly or the saline being too cold. I typically run 1 liter of B. Braun *Excel* normal saline over a maximum of 4 hours, ideally warmed in a body temperature water bath (no higher than 40 degrees celsius). Lactated Ringers are not usually recommended.

Discuss pain control: No opioids or narcotics should be used. I have had reactions to Morphine and its derivatives and NSAIDS. Tramadol is a safer option, but I have never used it.

I have low cortisol and take daily low-dose hydrocortisone. Consider a 24-hour urine free cortisol level before and after surgery. A liver panel and serum cortisol should also be checked prior to any general anesthesia, if possible. I will double or triple my hydrocortisone dose before and after surgery.

Check serum electrolytes, in particular red blood cell magnesium (an intracellular test) and serum potassium and replenish if borderline or low. Low magnesium or potassium depletion could potentially lead to cardiac arrhythmias under anesthesia. Consider potassium 10 mEq, 1 tablet BID, and magnesium sulphate 50% solution, 2cc. IM 24 hours prior to surgery.

I have sleep apnea and asthma. Discuss the use of oxygen throughout procedure (make sure a disposable mask is used in case of sensitivity to disinfectants). A preoperative lung vital capacity could be helpful. (The marker for real difficulty is thought to be a VC <1.0 liter. Such a patient needs good pulmonary preparation before surgery and a plan for postoperative ventilatory support.)

Discuss possible intubation and airway difficulties. Due to EDS, a neck injury, craniocervical instability, and TMJ dysfunction, I am at increased risk of positioning-related injury (subluxation/spinal cord compression), including the potential for long-term neurological sequelae.

- Care must be taken to keep my head and neck stabilized and in a neutral position during surgery. Avoid hyperextension/hyperabduction. Discuss wearing a soft neck collar to reduce risk.
- Fiberoptic intubation or Glidescope (videolaryngoscopy) should be used and discuss intubating while patient is awake to avoid neurological damage.
- Assess the possibility of arytenoid involvement, determine the size of the glottic opening, examine TMJs to ensure that mouth opening and anterior subluxation of the mandible will permit direct laryngoscopy/intubation.

Discuss bleeding risk assessment in relation to MCAS and EDS. Pressure dressings are indicated even for minor procedures because excessive bleeding is common (even when blood counts are normal), in part due to the release of heparin during mast cell degranulation. If there is the possibility for the need of a blood transfusion during elective surgery and the patient has the ability, consider autologous donation.

EDS patients are at an increased risk of perforation from scopes and have tissues that are more fragile than the norm and can tear easily. EDS patients are also at increased risk for residual neuromuscular blockade.

The surgical team should be aware that I should not be exposed to perfume or scents at any time before, during or after the procedure.

Discuss skin reactions to tape, adhesives and ECG electrodes. If possible, use paper tape, IV3000 film dressing, and skin prep pads before placing electrodes.

Discuss post-operative recovery accommodations in the hospital, if needed -- see *After Surgery* section.

DURING SURGERY:

Constant attention from the anesthesiologist is required for the safety of a patient with mast cell disease, as some symptoms of mast cell mediator release such as flushing, hives and early signs of obstructed breathing can be masked by surgical drapes and airway tubes.

Prior to the administration of any drugs associated with surgery, it is important that an IV is running to allow immediate administration of any emergency medications that may be needed. IM/IV epinephrine and emergency resuscitation equipment should be easily accessible. In addition, there should be a minimum of noise and bustle prior to the administration of the anesthetic in order to reduce the possibility of anxiety-triggered mast cell degranulation.

Be sure the patient does not become either too cold or overheated. My body temperature is typically ~97.5 degrees farenheit. Warm blankets should be used and, if possible, IV fluids should be warmed to body temperature in a water bath (never over 40 degrees celsius).

Intravenous (IV) fluids should be used to pre-hydrate patient and should be continuously running in all surgeries involving general anesthesia or conscious sedation. Dysautonomia patients usually require more fluids than typical to maintain a normal central venous pressure (CVP) and cardiac output, however too much can cause angioedema and third spacing. Hypovolemia resulting from blood loss or dehydration is a frequent cause of hypotension in the perioperative setting. Close monitoring is necessary to reduce volume shifts that will cause hypotension or tachycardia when coming out of anesthesia. Serious hypotensive should be promptly treated by IV vasopressors -- and/or antihistamines/epinephrine, in the case of anaphylaxis.

Although the diagnosis of anaphylaxis usually depends on the involvement of 2 organ systems, even if it presents with 1 organ system, such as the skin, epinephrine administration *may* be indicated. Anaphylaxis may present as an acute cardiac or respiratory event, with hypotension as the only manifestation. Should anaphylaxis occur during surgery, the drug thought to be responsible should be discontinued immediately and rescue medications should be administered (H1 and H2 antihistamines, corticosteroids, airway support with 100% oxygen, IV replacement fluids, bronchodilators). *Because of the risk of potentially lethal arrhythmias, IV epinephrine should only be administered in profoundly hypotensive patients or patients in cardio/respiratory arrest who have failed to respond to IV volume replacement and several IM doses of epinephrine.* ***I am extremely sensitive to epinephrine, so even IM epinephrine should only be used if completely necessary. I am also extremely sensitive to antihistamines, so care must be taken to use the lowest dose possible and push *very* slowly. Vigilantly monitor me for reactions to rescue medications, also.***

See anaphylaxis protocol below

It is important to keep in mind that not all hypotensive episodes during surgery are due to mast cell degranulation/anaphylaxis. It would be ideal to get blood tests during a reaction, especially tryptase (see recommended tests below).

One of the most important considerations during anesthesia is maintaining a neutral neck position. A hyperextended neck can increase spinal cord compression and this, coupled with hypotension, which decreases blood flow to the spinal cord, can have a severe effect.

- Intubation should be done by fiberoptic or Glidescope (videolaryngoscopy).
- Consider smaller ETT (endotracheal tube). Possible dysphagia following utilization of ETT or LMA (laryngeal mask airway).
- Possible increased risk of bleeding with repeated intubation attempts.
- Keep airway pressures low due to increased risk of lung injury/pneumothorax or shunt with positive pressure ventilation.

Due to EDS and osteoporosis, my head, neck, pelvis and limbs should be moved carefully (limbs kept close to my body).

AFTER SURGERY:

Patient will need post-operative fluids to maintain blood pressure and aid recovery.

Watch for post-procedure anaphylaxis or mast cell reaction. Antihistamines and Prednisone should be used prophylactically to control reactions. Refer to anaphylaxis and pre-medication protocol below.

If the patient is being admitted to the hospital, discuss what is needed for a safe recovery:

- Request a private room or a sound-proof door (versus an open curtain) and placement on a quiet ward.
- Explain any sound, light, or chemical/fragrance sensitivities and the need for scent-free nurses (a sign next to the patient's door can help remind nurses changing shifts).
- Discuss any food sensitivities.
- Discuss temperature sensitivities and the need for extra blankets or adjustment of the thermostat.
- Ask whether it's possible to minimize nighttime disruptions (for example, middle of the night blood pressure monitoring).
- Discuss the potential need for extra recovery time in hospital or for a reclining wheelchair or gurney during discharge from the hospital.
- Bring your own soap, hand sanitizer and bedding.

MEDICATIONS:

Consider using (but administer with extreme caution):

- Diprivan (propofol) as the induction agent is the first choice. (However, Propofol, used alone at induction of anesthesia, promotes a significant decrease in arterial blood pressure compared with thiopentone or etomidate, even with reduced doses.)
- Versed (midazolam)
- Droperidol (an anti-nausea agent) or Aprepitant (Emend) or Ondansetron (Zofran)
- Tramadol
- Tylenol is no problem

Fentanyl should only be considered -- only if no other choice because it's a narcotic.
Ketamine or benzodiazepines, such as midazolam, may be considered (however, I have had reactions to benzos in the past).
Atarax (Hydroxyzine) should only be used in an emergency. It can cause heart palpitations and arrhythmias.
Doxepin should only be used at *very* low doses (<5mg -- I have never taken it).
A small amount of Diazamuls, a preservative-free Valium emulsion, could be considered for long surgeries where the possibility of "awareness" is a concern. This drug can also be used pre- and post-operatively for sedation, and for cramping in certain types of procedures.

Use IV preparations without preservatives or alcohol. Use B. Braun *Excel* normal saline, if possible. Do not use lactated ringers, if possible.

Oxygen should be used throughout procedure (possibly at 5 liters pre and post-operatively).

Do not use epinephrine except in life-saving situation. *But Epinephrine must be on hand during the procedure.*

Do not use medications that contain preservatives, artificial colorings, dyes, flavorings or alcohol (topical alcohol, as in alcohol prep pads, is fine, as is povidone iodine). Single-use vials are usually preservative-free.

Do not use medications that stimulate neurogenic syncope or lower blood pressure:

- No cathecholamines
- No sympathomimetics (Isoproterenol)
- No vasodilators (nitric oxide, nitroglycerin, alpha-blockers, and hypotensive agents)

I have orthostatic hypotension (OI), chronically low blood pressure and a history of vasovagal syncope. Many people with dysautonomia have low plasma volumes, low RBC mass, and venous pooling and the above drugs may cause or exacerbate these conditions.

Do not use histamine-releasing anesthetic agents:

- No Sodium Pentothal or other thiobarbituates (Thiamylal, Thiobarbital etc.)

Do not use histamine-releasing muscle relaxants:

- No muscle relaxants in the Curare family, such as Tracrium and Mevacurium.
- No Succinylcholine ((Anectine) often causes severe, generalized muscle pain, post-op.)
- No D-tubocurarine
- No Metocurine
- No Doxacurium
- No Atracurium
- No Mivacurium
- No Rocuronium

Muscle relaxants are the most likely group of the anesthetic drugs to cause anaphylaxis. If muscle relaxants must be used, the current recommendation is to start with a quarter to half the usual dose of whatever you're using. Intraoperative neuromuscular monitoring helps prevent overdose. Consider using "nondepolarizing" muscle relaxants, such as pancuronium or vercuronium.

Do not use anesthetic gasses:

- No Halothane
- No Enflurane
- No Isoflurane
- No Desflurane

These can cause problems for patients with chemical sensitivities and are highly hepatoxic. An alternative might be continuous IV infusion of a short acting anesthetic by injection or a continuous flow pump. If necessary, consider Sevoflurane.

Do not use:

- No Morphine, codeine or morphine derivatives
- No Opioids
- No Vancomycin
- No Ethanol
- No Dextran
- No Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and Toradol
- No Compazine or Reglan
- No Polymyxin B
- No Amphoteracin B
- No Quinine
- No Dextromethorphan
- No Alpha-adrenergic blockers
- No Beta-adrenergic blockers
- No Anticholinergic drugs, if possible, such as Hydroxyzine and Cimetidine
- No decongestants, cold or flu medications
- No SSRIs

Do not use local anesthetics, if possible. If needed, do not use ones with preservatives or epinephrine:

- No Procaine
- No Chloroprocaine
- No Tetracaine
- No Benzocaine

Consider using:

- Lidocaine (I have had Xylocaine-MPF 2% Methylparaben-free cutaneous injection with no reaction)
- Mepivacaine
- Prilocaine
- Bupivacaine
- Levobupivacaine
- Ropivacaine

Antibiotics are not well tolerated by mast cell patients, however, these are some that have been reported as safest by patients (use with caution):

- Clindamycin
- Cephamandole
- Azithromycin (Z-pak/Zithromycin/Zithromax)
- Keflex
- Omnicef
- Beconase AQ
- Biaxin (eg. Clarithromycin)
- Rhinocort

MEDICAL EMERGENCY RESPONSE PLAN for Mast Cell Activation and Anaphylaxis:

If patients presents with flushing, rash, hives, swelling, abdominal pain, nausea, vomiting, shortness of breath, wheezing or hypotension, administer:

- Benadryl (diphenhydramine, dye-free) 25mg (max 50mg) orally.
    - If unable to swallow or airway compromised, use preservative-free Benadryl IM or very slow IV push, diluted in normal saline over 2-5 minutes. Start at 25mg (max 50mg) and repeat every 4 hours, if needed.
- Solu-Medrol (methylprednisolone) 120mg (40mg for children under 12) IV/IM.
    - *Start at the lowest possible dose and monitor closely. I am sensitive to steroids and have never had them IV. My usual dose is oral Prednisone 6mg*.
- H2 antagonist, such as Famotidine IV.
    - *I have never had Famotidine or any H2 blocker by IV. I usually take oral Pepcid brand 20mg (no dye)*.
- IV fluids, run as slowly as possible for the circumstances and, ideally, warmed to body temperature.
- Consider Hydroxyzine 25 mg (12.5 mg if age 2--12), orally every 2--4 hours.
    - *I have never had Hydroxyzine and don't know how I will react.*

If the patient presents with anaphylaxis and/or acute hypotension, administer:

- Epinephrine (preservative-free) 0.3 cc/ml of 1:1000 (1mg/1ml) solution = 0.2mg--0.3mg IM (Vastus Lateralis muscle).
    - If BP < 90 systolic, can repeat up to 3 times at 5--15 minute intervals, ***however my normal BP averages 85/55, so <90 is not an accurate marker for me*.**
- Oxygen 100% by mask or nasal canula.
- Albuterol nebulization.

All mast cell patients must be monitored for biphasic (rebound) reactions.

Continuous diphenhydramine infusion (CDI) may be considered for severe mast cell activation and should be initiated at 5 mg/hour. This dose is lower than what would be expected to deliver a clinical response, but is suggested to ensure that the patient is not going to react to the brand of drug being administered (preservative-free is ideal). The dose can be escalated by 1--2 mg/hour. Titrate the infusion to the minimum dose rate which seems to provide the maximum benefit. Few patients respond to doses less than 10 mg/hour and the maximum recommended dose is 15 mg/hour in order to minimize the risk of anticholinergic toxicity.

Pre-medication for major and minor procedures:

- Prednisone 50mg orally 24 hours and 1--2 hours prior to surgery (*I've never had more than 7mg*)
- Benadryl (diphenhydramine) 25--50mg orally, 1 hour prior to surgery
- Pepcid (famotidine) 20mg (no dye) orally, 1 hour prior to surgery
- Singulair (montelukast) 10mg orally (5mg for children under 12), 1 hour prior to surgery (*I've never had Singulair and do not use this step*)

Note: my current premedication protocol is 25mg oral diphenhydramine (Benadryl brand dye-free capsules only), 150mg oral ranitidine (Zantac brand), 6mg oral Prednisone and 325mg acetaminophen (Tylenol brand). No artificial colorings in medications.*

Drugs to be avoided:

- Aspirin and non-steroidal anti-inflammatory (NSAIDS) medications
- Morphine, codeine derivatives
- Vancomycin

LABORATORY TESTS TO RUN IN THE EMERGENCY ROOM DURING AN ACUTE MAST CELL REACTION OR ANAPHYLAXIS:

1. Serum Tryptase -- upon arrival in the ER and three hours later.
2. 24 hour urines for:
    a. n-methyl histamine
    b. prostaglandin D2 (PGD2)
    c. 11-beta prostaglandin F2 alpha (BPG-F2A)
3. CMP
4. CBC with differential

Also consider:

1. Chilled plasma histamine
2. Chilled plasma prostaglandin D2 (PGD2)
3. Chilled plasma heparin
4. Serum chromogranin A
5. Serum magnesium

If possible, hourly determinations of serum tryptase, plasma PGD2 and histamine, and spot urinary PGD2 and N-methylhistamine should be pursued at baseline and over the next 2--3 hours as a reaction evolves.

SPECIMEN HANDLING ISSUES:

The short half-lives and thermolability of many mast cell (MC) mediators require continuous specimen chilling throughout collection, storage, and transport. Particularly with regard to 24-h urine collections for MC mediator testing, patients should be carefully educated to pre-chill the collection container overnight before beginning the collection and then to keep the container continuously chilled while following an otherwise standard 24-h urine collection protocol; the container should be removed from the refrigerator or ice chest only when imminently needed and should be returned to chilling as soon as possible. Patients should also be cautioned to maintain the container in a chilled environment throughout transport. We recommend the container be placed in a bag filled with ice and sealed, with the bag then placed in an ice chest filled with ice and sealed for transport to the accessioning lab, whereupon the bag can be removed from the chest and provided to the technician with a reminder of the criticality of keeping the specimen chilled. Laboratory staff often are unfamiliar with MC mediator testing, previously a rarely undertaken endeavor. Consideration should be given by the diagnostician to sharing with laboratory personnel the ultimate clinical goal of such testing and the importance of maintaining thermal integrity of these specimens at all times, including at the time of initial accessioning as well as when packing specimens for transport to reference laboratories that may be thousands of miles distant, transits that may involve long periods sitting in unventilated cargo containers on hot tarmacs. Use of well-insulated containers, and liberal placement of cold packs in the insulated container, should be de rigueur when packing such specimens for long-distance transport.

You MUST have your allergist or primary care provider sign the bottom of this form stating that he or she will be responsible for the follow-up on the 24 hour urine collections. Otherwise, the ER physicians will be reluctant to order them since they cannot be sure of follow-up care. Remember to contact your physician for follow-up after discharge.

****

I agree to provide follow-up care for my patient, _____, and will obtain the results of the 24-hour urine collections that were initiated in the emergency room setting and will provide appropriate care based on the results.

_____

Printed Name of Physician

_____

Signature of Physician Date

Contact Address_____

_____

Phone Number_____

Fax Number_____

KOUNIS SYNDROME IN MAST CELL PATIENTS

Acute coronary syndromes can occur in allergic and anaphylactic reactions. One example, called Kounis Syndrome, is highly likely in patients with a wide variety of mast cell activation disorders and can affect patients of any age. The main triggers of Kounis syndrome are drugs, environmental exposures, and various pre-existing conditions. When patients are on a protocol exposing them to many medications, the cascade leading to anaphylaxis and Kounis syndrome can be very rapid, with the heart and coronary arteries as the primary target. Multiple mast cell mediators have direct action on coronary vessels and together result in hyperresponsiveness of mast cells, which can result in the Kounis syndrome cascade. Please note: Coronary artery spasm induced by mast cell mediators may initiate Takotsubo Syndrome or stress-induced cardiomyopathy during anaphylactic reactions.

Type 1: Normal coronary arteries, no coronary disease, no predisposing conditions; acute allergic attacks resulting in coronary vasospasms without elevations in cardiac enzymes OR coronary vasospasm with myocardial infarction with elevation of cardiac enzymes and troponins.
Treatment of the allergic episode can terminate the type 1 variant

- Corticosteroids
- H1 and H2 blockers
- Vasodilators such as calcium channel blockers and nitrates can decrease hypersensitivity induced vasospasms

Type 2: Quiescent pre-existing atheromatous disease in whom acute allergic attacks can induce either vasospastic angina or plaque erosion, or rupture manifesting acute myocardial infarction.
Treatment of acute coronary event comes first, then treat allergic attack:

- acute coronary event protocol
- Corticosteroids
- H1 and H2 blockers

Type 3: Stent thrombosis with eosinophils and mast cells identified on pathology (Giemsa, hematoxylin-eosin stain).
Treatment of stent thrombosis with allergic attack:

- Corticosteroids
- H1 and H2 blockers
- Mast cell stabilizers
- Biopsy of thrombus stained for mast cells and eosinophils. Nitroglycerin causes decreased blood pressure and increased heart rate.

Fentanyl is the opiate with the best profile for mast cell patients; administer with extreme caution.