Idiopathic anaphylaxis: Diagnosis and management.

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Disclosures

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Objectives

- [x] Describe the essential pathophysiologic mechanisms of anaphylaxis
- [x] Diagnose idiopathic anaphylaxis accurately
- [x] Discuss appropriate work up strategies for anaphylaxis when cause is not obvious

INTRODUCTION TO ANAPHYLAXIS

An Overview

Introduction

- Anaphylaxis is a life-threatening syndrome triggered by wide range of antigens, involving multiple organ systems
- Reactions may be sudden, severe, even fatal
- Rapid institution of appropriate treatment essential for favourable outcome
- Epinephrine is treatment of choice

Definition

- No universally accepted definition
- Most recently proposed:
  - *"Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."*

Definition (2) – NIAID/FAAN symposium

"Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least one of the following:
   - Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   - Reduced BP or associated symptoms (e.g. hypotonia, syncope)

2. Two or more of the following that occur rapidly after exposure to a *likely* allergen for that patient:
   A) Involvement of the skin, mucosal tissue, or both
   B) Respiratory compromise
   C) Reduced BP or associated symptoms
   D) Persistent gastrointestinal symptoms (e.g. abdominal pain, vomiting)

3. Reduced blood pressure after exposure to a *known* allergen for that patient"

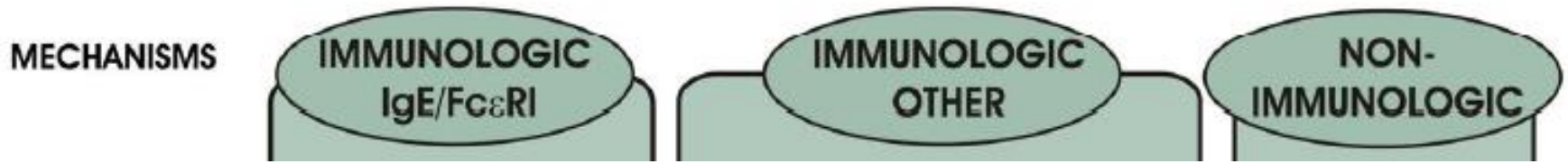
Definition - 3

- Canadian Pediatric Surveillance Program:
  - *a severe allergic reaction to any stimulus, having sudden onset, involving at least two body systems, with multiple symptoms*.

Simons FE et al. Case definitions: Anaphylaxis. CPSP Protocols 1999

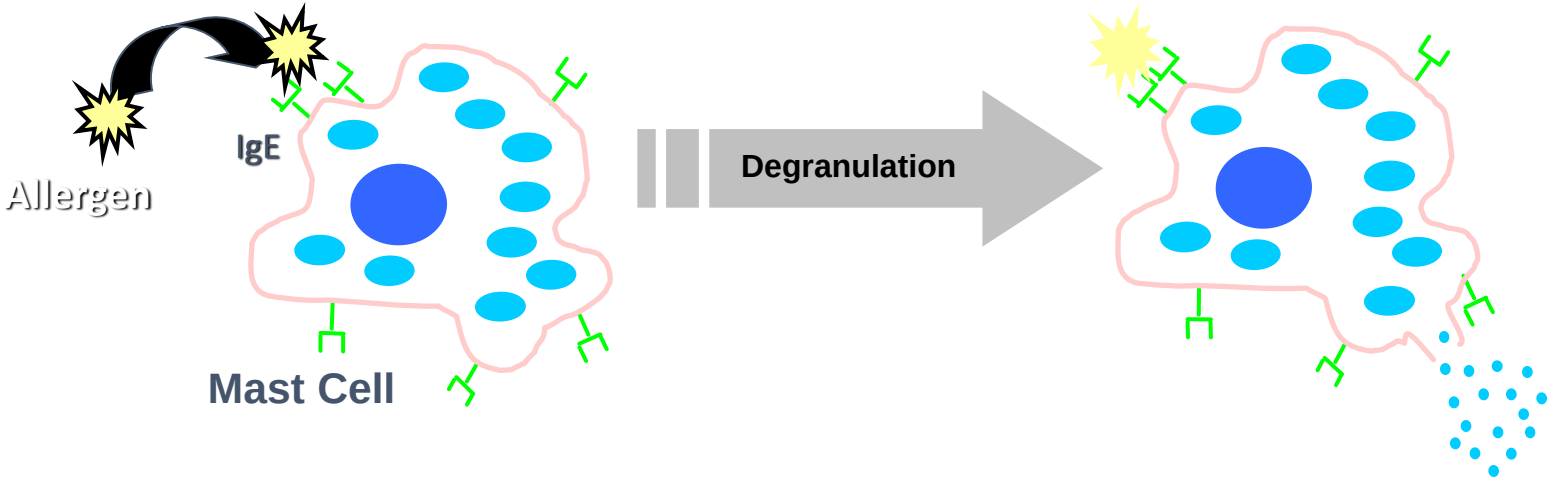
Classification

- Immunologic
  - IgE-mediated
  - Non-IgE-mediated
- Non-Immunologic



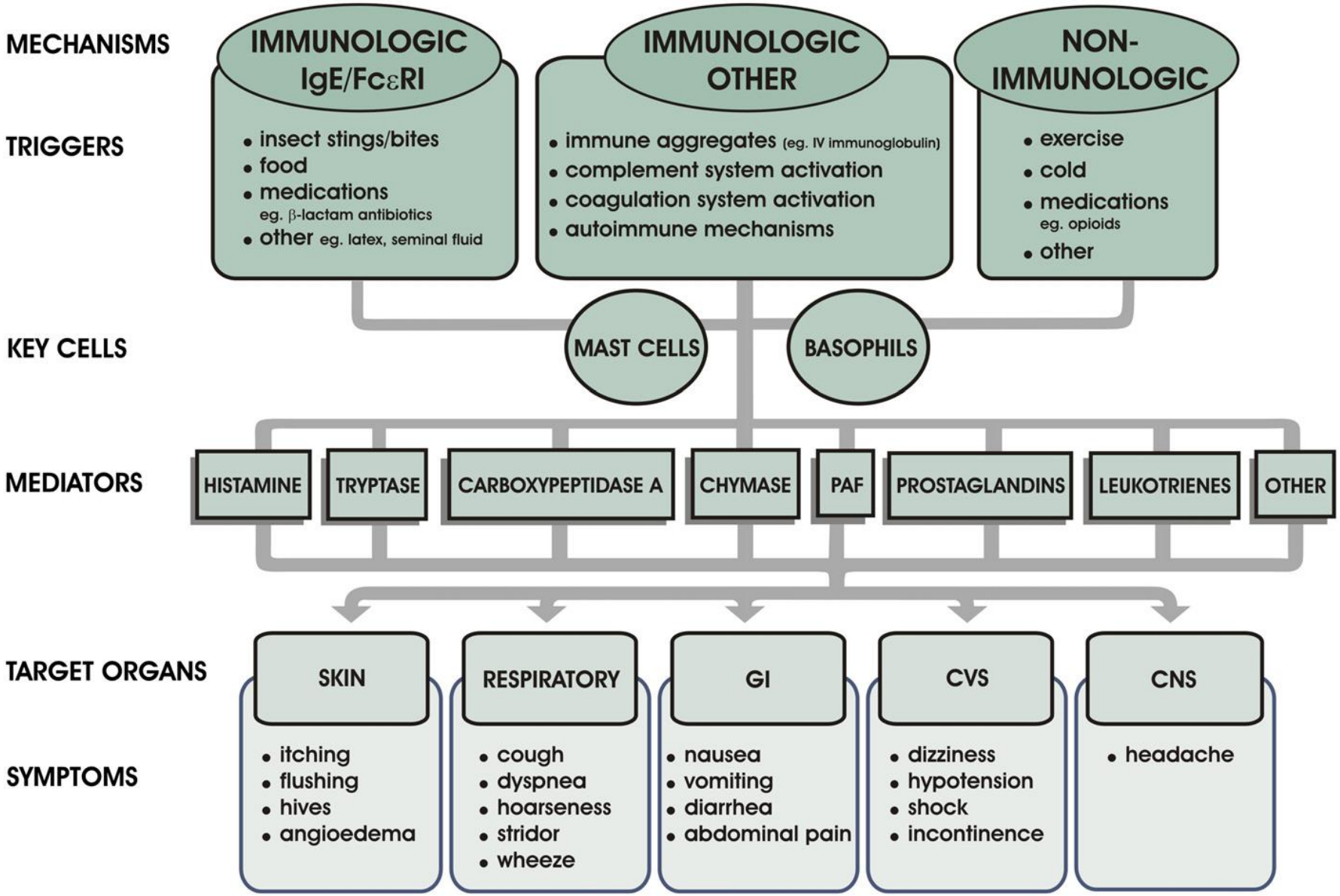
Pathophysiology – IgE mediated

- Results from interaction of allergen with specific IgE antibodies, in a previously sensitized person
- IgE antibodies bind to receptors on mast cells and basophils
- On re-exposure, antigen binds and cross-links the IgE antibodies on these cells.
- Leads to degranulation of the mast cell and/or basophil, and release of preformed mediators (including histamine)



Pathophysiology

- Mast cells found in especially large numbers beneath mucosal and cutaneous surfaces
- Release of histamine and other mediators (PAF, leukotrienes, prostaglandins) results in:
  - smooth muscle spasm
  - ↑ vascular permeability
  - vasodilation
  - myocardial depression
  - activation of vagal effector pathways

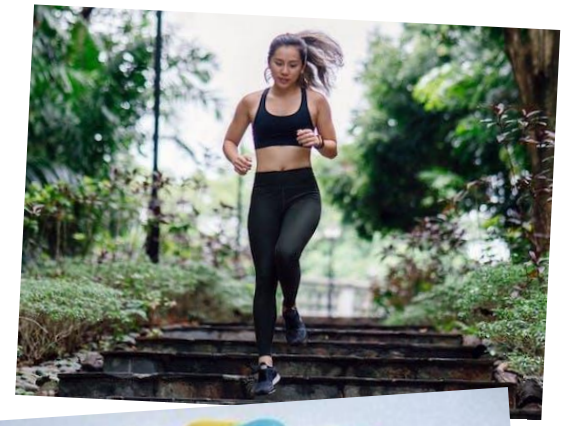

MECHANISMS
TRIGGERS
KEY CELLS
MEDIATORS
TARGET ORGANS
SYMPTOMS
IMMUNOLOGIC IgE/FcεRI
• insect stings/bites
• food
• medications
eg. β-lactam antibiotics
• other eg. latex, seminal fluid
IMMUNOLOGIC OTHER
• immune aggregates (eg. IV immunoglobulin)
• complement system activation
• coagulation system activation
• autoimmune mechanisms
NON-IMMUNOLOGIC
• exercise
• cold
• medications
eg. opioids
• other
MAST CELLS
BASOPHILS
HISTAMINE
TRYPTASE
CARBOXYPEPTIDASE A
CHYMASE
PAF
PROSTAGLANDINS
LEUKOTRIENES
OTHER
SKIN
• itching
• flushing
• hives
• angioedema
RESPIRATORY
• cough
• dyspnea
• hoarseness
• stridor
• wheeze
GI
• nausea
• vomiting
• diarrhea
• abdominal pain
CVS
• dizziness
• hypotension
• shock
• incontinence
CNS
• headache

Etiology

- IgE-Mediated:
  - Foods
  - Hymenoptera (stinging insects)
  - Drugs
  - Latex
- Immunologic – Other
  - Immune aggregates (*e.g*. IVIG)
  - Complement system activation

Etiology

- Non-Immunologic
  - Exercise-Induced Anaphylaxis
  - Medications
  - Cold-induced
- Idiopathic Anaphylaxis



So What about this “idiopathic” ANAPHYLAXIS?

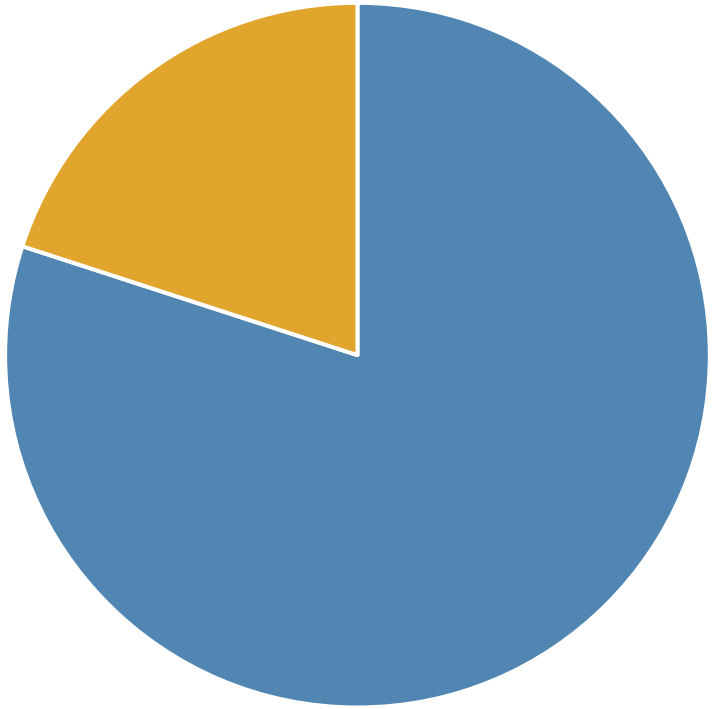
Difficult to Discern

Prevalence of Idiopathic Anaphylaxis

- How far did the researchers go to find a cause?
- What was the definition used?
- ED cohort or out patient allergy clinic?
- Oral challenge performed?
- Peds vs Adults

Prevalence

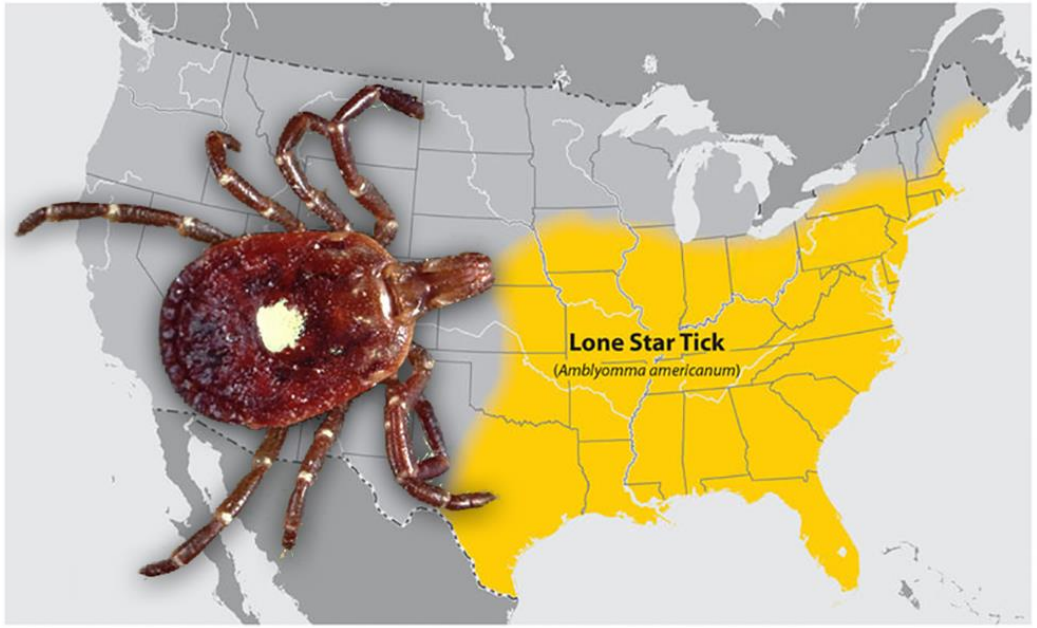
- In general, ranges from 4% to 60% depending on these factors
- Most widely quoted, however is ~20%, and appears more common in the adult population



Work up

- History – careful, detailed
  - Timing critical – nighttime
- Directed skin prick tests and/or in vitro specific IgE
  - NOT Panels!
  - May need fresh food for prick/prick testing
- Serum Tryptase
- ± cKIT mutation
- Oral challenge where appropriate

Most Important Differential Diagnoses



- Alpha-Gal Allergy
- Mammalian non-primate red meat
- Onset delayed – 3 to 8 h after ingestion
- Common in areas where Lone Star Tick is endemic

Alpha-Gal

- galactose-alpha-1,3-galactose
- found in all mammals except apes, humans, and Old World monkeys
- Transmitted by European castor bean tick and *Ioxides australiensis* elsewhere in the world

Most Important Differential Diagnoses

- Mast Cell Disorders
  - Systemic Mastocytosis
  - Monocolonal Mast Cell Activation Syndrom (MMAS)
  - Mast Cell Activation Syndrome

Systemic Mastocytosis

- myeloproliferative neoplasm characterized by infiltration of clonally derived mast cells in different tissues, including bone marrow, skin, gastrointestinal tract, liver, and spleen
- Diagnosis requires serum tryptase and bone marrow biopsy

Diagnostic Criteria:

- Need 1 Major and 1 Minor, or at least 3 minor
- Major
  - Multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)
- Minor
  - >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs
  - KIT point mutation at codon 816 in the BM or another extracutaneous organ
  - MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25
  - Baseline serum tryptase level >20 ng/mL (in case of an unrelated myeloid neoplasm, item d is not valid as an SM criterion)

Monoclonal Mast Cell Activation Syndrome (MMAS)

- MMAS is a term coined to designate patients who present with symptoms of mast cell activation (often diagnosed as idiopathic anaphylaxis) and lack cutaneous findings and have either:
  - the cKIT D816V mutation
  - or CD25+ mast cells in their bone marrow
- These patients have tryptase levels of less than 20 ng/mL
- Have a normal to low burden of mast cells and therefore do not satisfy the full criteria for the diagnosis of systemic mastocytosis
- Diagnosis of MMAS requires a high degree of clinical suspicion and confirmation via bone marrow biopsy
- Diagnosis should be particularly be considered in patients presenting with symptoms of hypotensive anaphylaxis.

Idiopathic Mast Cell Activation Syndrome

- Recurrent episodes of anaphylaxis
- Normal baseline serum tryptase
- Negative c-KIT mutation
- Tryptase level during acute episodes rises by the following factor:
  - Increase of >20% + 2ng/mL within 4 hr of a reaction

Other Diagnoses to consider

- **Acute respiratory decompensation**
  - severe asthma
  - foreign body aspiration
  - pulmonary embolism

- **Loss of consciousness**
  - vasovagal reaction (lack of pruritus, urticaria)
  - seizure disorder
  - myocardial infarction and/or arrhythmias

- **Other disorders resembling anaphylaxis**
  - systemic mastocytosis
  - hereditary angioedema
  - scombroid poisoning (histamine fish poisoning)
  - carcinoid syndrome

Management

Moving Forward

First Line Treatment

- **Epinephrine**
  - 0.3 to 0.5 cc of 1:1000 aq solution (1 mg/mL)
  - given IM
  - administer in lateral thigh (Guidelines)
  - repeat PRN q5 - 15min until effect or AE’s

Why Epinephrine?

Stimulates all adrenergic receptors:

- **α1** – **vasoconstriction** and relaxation of GI tract

- **β1** – **inotropic and chronotropic cardiac effects** and relaxation of GI tract

- **β2** – **bronchodilation**, ↑ noradrenaline release from nerve terminals, ↑ **intracellular cyclic adenosine monophosphate (cAMP)** in mast cells and basophils→ ***reduction in release of cellular mediators***

First Line Treatment

- Recumbent position, elevate legs if possible
  - DO NOT SIT UP
- Oxygen
- IV Fluids
  - Normal Saline or Ringer's Lactate for volume expansion
  - 1 - 4 L often required

Second Line Therapy

- Antihistamines:
  - diphenhydramine 50mg IV or cetirizine 20mg PO
  - H2 blockers – currently ranitidine not readily availablbe
  - combined H1/H2 antagonism better than H1 blockade alone for control of skin manifestations
- Corticosteroids:
  - methylprednisolone 125mg IV, or prednisone 50mg PO
- $Beta_2$-agonist:
  - salbutamol 5.0 mg via nebulizer q15min PRN
- Vasopressors

Long Term Management

- Daily use of 2nd generation, non-sedating antihistamines (cetirizine, fexofenadine, loratadine, desloratadine)
- Start with licensed doses and increase to 4 fold up dosing
- Montelukast, ketotifen, H2 receptor antagonists, cromolyn other add on options for refractory cases
- Omalizumab

Conclusion

- Idiopathic anaphylaxis can occur in up to 20% of cases
- Work up includes careful history, directed allergy testing, serum tryptase
- Occasionally cKIT mutation and bone marrow biopsy may be warranted
- Acute management of IA identical to anaphylaxis of known cause

Questions?

- Please write your question into the ”Question” box on your webinar control panel
- We’ll get to as many questions as we can!