

Laryngoscopy diagnosis of inducible laryngeal obstruction during supervised challenge for suspected anaphylaxis

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1 | INTRODUCTION

Inducible Laryngeal Obstruction (ILO), also known as Vocal cord dysfunction (VCD) — episodic, paradoxical glottic closure during respiration — can mimic or even co-exist with asthma.^{1–3} Common triggers include inhaled irritants, odours and exercise.⁴ Proposed mechanisms include sensory neural dysfunction resulting in accentuation of the glottic closure reflex, which may be both irritant and stress mediated.⁵

It is less widely known that VCD also presents to allergists, mimicking anaphylaxis in response to allergen exposure via inhalation, ingestion or injection, and posing a diagnostic dilemma. Definitive diagnosis requires laryngoscopy confirmation of paradoxical vocal fold movement and exclusion of laryngeal angioedema, but this is rarely available during an acute episode.

2 | DIFFERENTIATING ILO FROM ANAPHYLAXIS

We describe four patients with ILO presenting to our allergy service with latex, food or drug-induced “anaphylaxis” (Table 1). In each case, we established the diagnosis on flexible laryngoscopy after deliberately provoking an event by supervised challenge to the relevant “allergen.” As reported previously,^{1,2} confirmation of ILO either at baseline or following provocation was achieved by laryngoscopic visualization of paradoxical vocal fold motion, defined by either (i) any vocal cord adduction during inspiration or (ii) >50% reduction in the area of the rima glottidis; laryngeal inlet airspace between the edges of true vocal cords or angle at the anterior commissure from

the position of the vocal processes during expiration. Provocation was performed using standardized graded or direct allergen challenge protocols. Speech pathology intervention sessions included behavioural breathing exercises focussing on maladaptive laryngeal postures and breathing patterns and educational counselling. Informed patient consent was obtained for inclusion in this series.

2.1 | Case 1: “Latex anaphylaxis” to glove challenge

A 37-year-old female schoolteacher attended the Emergency Department four times for breathlessness, throat tightness, tongue swelling, facial flushing and itch, but with normal arterial oxygen saturation, blood pressure, lung auscultation and skin examination. Each time, she received multiple doses of intramuscular adrenaline. Acute serum tryptase was 3.5 mcg/L (baseline 4.2 mcg/L).

Latex anaphylaxis was initially suspected, as she reported contact with latex balloons or gloves immediately before each episode while at school. However, latex serum specific IgE and skin prick were negative (<0.01 kU/L and 0 mm respectively).

We performed a blinded glove challenge (latex and non-latex in random order), with facilities both to treat anaphylaxis and perform flexible laryngoscopy. Non-latex glove exposure triggered her typical symptoms, but observations including peak expiratory flow (baseline 350 L/min, post challenge 340 L/min) and physical examination remained normal. Laryngoscopy showed inspiratory and expiratory vocal cord adduction with no laryngeal angioedema. Symptoms remitted to rescue breathing exercises. The patient underwent laryngeal retraining, and returned to work with no further episodes.

2.2 | Case 2: "Wheat anaphylaxis" to oral food challenge

A 31-year-old female had 14 episodes of upper chest and throat tightness, cough and dysphonia, occasionally with abdominal cramping. Observations and physical examination were normal, but each time, she received multiple doses of intramuscular or intravenous adrenaline. On some occasions, symptoms recurred at 48 h.

Wheat anaphylaxis was considered, but not confirmed. Wheat ingestion without exercise preceded some, but not all, events. The patient intermittently consumed wheat without issue. Serum specific IgE was positive to wheat (0.66 kU/L, with total IgE of 16 kU/L), but negative to Omega-5-gliadin (<0.10 kU/L). Wheat skin prick was negative (0 mm). Acute serum tryptase was 3.2 mcg/L (baseline 3.8 mcg/L).

A graded oral challenge to wheat provoked her laryngeal symptoms, plus abdominal cramping and non-specific chest erythema. Observations and examinations were normal with preserved peak expiratory flow (baseline 310 L/min, post-challenge 350 L/min). Laryngoscopy showed no laryngeal oedema but revealed >50% expiratory vocal cord adduction, which resolved completely with rescue breathing exercises.

2.3 | Case 3: "Anaphylaxis" to multiple monoclonal antibody therapies.

A 41-year-old female reported throat tightness with dysphagia on two occasions 9 years apart, both following injection of the anti-TNF monoclonal antibody Infliximab for treatment of her inflammatory bowel disease. An injection of the anti-IL-12/23 monoclonal antibody Ustekinumab also induced dyspnoea, throat tightness, cough, and non-specific chest erythema within 45 min. Blood pressure, oxygen saturation and chest auscultation were normal. Symptoms slowly responded to one dose of intravenous adrenaline, and symptom recurrence four hours later remitted spontaneously. Acute serum tryptase was 1.2 mcg/L.

Under our supervision, a therapeutic dose of subcutaneous Ustekinumab induced her previous symptoms. Observations and peak expiratory flow remained stable (baseline 400 L/min, post-challenge 380 L/min). Laryngoscopy confirmed inspiratory vocal cord adduction and excluded laryngeal oedema. Rescue breathing techniques effectively reversed both symptoms and laryngoscopic findings. Following laryngeal retraining, the patient tolerated subsequent doses of Ustekinumab.

2.4 | Case 4: "Multi-drug anaphylaxis."

A 53-year-old female had multiple reactions to numerous unrelated oral and injected medications. Her symptoms were throat and upper chest tightness, stridor, dysphonia, generalized itch without urticaria, flushing of the face and upper chest, and tingling of the lips

Key Messages

- Inducible Laryngeal Obstruction may mimic anaphylaxis in response to 'allergen' exposure via inhalation, ingestion, or injection
- Laryngoscopy acutely or following supervised 'allergen' challenge is useful to confirm ILO and exclude laryngeal oedema
- Diagnosis requires systematic evaluation by physicians experienced in both allergy and ILO

and peripheries. She received intramuscular adrenaline on multiple occasions.

Evaluation for IgE-mediated allergy to various suspect agents revealed negative skin tests to a corticosteroid and general anaesthetic panel, and negative serum specific IgE to latex (0.00 kU/L) and chlorhexidine (0.02 kU/L). Baseline tryptase was 3.7–4.4 mcg/L. A graded oral challenge to prednisolone triggered her usual symptoms, but with normal observations and skin examination, and remitted without adrenaline.

We supervised an intramuscular injection of influenza vaccine, which induced her usual symptoms and signs at 45 min. Observations and examinations were normal with preserved peak expiratory flow (baseline 500 L/min, post-challenge 480 L/min). Laryngoscopy confirmed almost complete adduction of the vocal cords throughout respiration, but no laryngeal angioedema. All symptoms responded rapidly to rescue breathing techniques. Nevertheless, the patient remained convinced of multiple drug allergies.

3 | ROLE OF LARYNGOSCOPY FOR DISTINGUISHING ILO FROM ANAPHYLAXIS

ILO and anaphylaxis have overlapping symptomatology. In the first instance, acute episodes should usually be treated as life-threatening anaphylaxis. However, ILO should be suspected when laryngeal symptoms predominate without objective cardio-respiratory compromise or true urticaria and angio-oedema. Symptoms refractory to high doses of adrenaline or which resolve without specific treatment may also prompt consideration of ILO.

As illustrated in our patient cases, clinical diagnosis is challenging. Non-laryngeal symptoms were often present; facial flushing or chest erythema, abdominal cramping, reported tongue swelling (difficult to confirm or refute), and lip tingling (hyperventilation vs. early angio-oedema). In isolation, a lack of acute tryptase elevation was insufficient to exclude anaphylaxis. Laryngoscopy was not available during Emergency Department presentations.

Laryngoscopy performed acutely or following supervised "allergen" challenge is an important tool for definitively confirming ILO and excluding laryngeal oedema.

TABLE 1 Four patients with ILO mimicking anaphylaxis

Clinical syndrome	Symptoms	Testing for IgE-mediated allergy	On challenge to suspected trigger:		
			Symptom replication	ILO on laryngoscopy	Response to rescue breathing
Latex allergy in a 37-year-old female	Laryngeal	Latex serum specific IgE < 0.01 kU/L	Yes	Yes	Yes
	-Dyspnoea, throat tightness	Latex skin prick test 0 mm			
	Non-laryngeal	Acute serum tryptase 3.5 mcg/L			
	-Tongue swelling, pruritus, facial flushing	Baseline serum tryptase 4.2 mcg/L			
Wheat allergy In a 31-year-old female	Laryngeal	Wheat serum specific IgE 0.66 kU/L	Yes	Yes	Yes
	-Cough, dysphonia, upper chest and throat tightness	Omega-5-gliadin serum specific IgE < 0.10 kU/L			
	Non-laryngeal	Wheat skin prick test 2 mm			
	-Abdominal cramping	Acute serum tryptase 3.2 mcg/L Baseline serum tryptase 3.8 mcg/L			
Monoclonal Ab Allergy (anti-TNF and anti-IL-13/23) in a 41-year- old female	Laryngeal	Acute serum tryptase 1.2 mcg/L	Yes	Yes	Yes
	-Cough, dyspnoea, throat tightness Non-laryngeal -Chest erythema	Baseline serum tryptase 1.1 mcg/L			
Multi-drug allergy in a 53-year-old female	Laryngeal	Skin prick tests to corticosteroid and general anaesthetic panels all negative (0 mm)	Yes	Yes	Yes
	-Dysphonia, stridor, throat and upper chest tightness	Latex serum specific IgE 0.00 kU/L			
	Non-laryngeal	Chlorhexidine serum specific IgE 0.02 kU/L			
	-Chest erythema, facial flushing, pruritis, tingling of lips and peripheries	Graded oral challenge to prednisolone negative Baseline serum tryptase 3.7–4.4 mcg/L			

Note: Specific IgE reference range 0–0.34 kU/L Serum tryptase reference range 0–11.4 mcg/L.

Abbreviations: Ab, antibody; IgE, immunoglobulin E; ILO, inducible laryngeal obstruction.

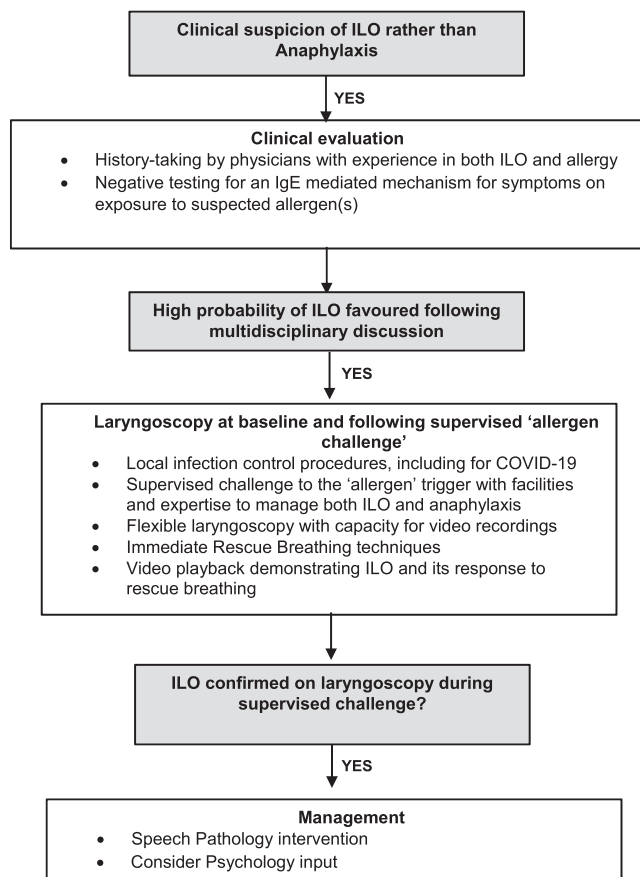


FIGURE 1 Suggested management pathway when ILO is suspected in patients presenting with “Anaphylaxis.” ILO, inducible laryngeal obstruction

4 | PRACTICAL APPROACH TO LARYNGOSCOPY DURING SUPERVISED “ALLERGEN” CHALLENGE

Acknowledging the paucity of high-quality evidence addressing this clinical question, we describe a systematic diagnostic approach to patients with ILO mimicking anaphylaxis (Figure 1), and propose appropriately supervised “allergen” challenge as a valuable addition to the array of ILO provocation agents during functional laryngoscopy.⁶

Optimal diagnosis and management requires multidisciplinary expertise in *both* allergic disease and laryngeal dysfunction.^{1,2,7} Close liaison with Speech Pathology is critical.⁸ In our service, history-taking by physicians experienced in both allergy and ILO, supplemented by appropriate testing for IgE-mediated allergy, informed the decision to proceed to supervised “allergen” challenge.

While not reported in this series, we recommend baseline laryngoscopy prior to performed “allergen” challenge and have incorporated this into our standard protocol. For maximum safety and effectiveness, such challenges should be performed with expertise and facilities to diagnose and treat *both* (i) anaphylaxis; continuous pulse oximetry, peak expiratory flow and blood pressure monitoring, capabilities for intravenous access, emergency medications

including adrenaline, resuscitation personnel and equipment *and* (ii) ILO; flexible laryngoscopy with capacity for video recordings and immediate Rescue Breathing techniques. Our Allergy team has extensive expertise in functional laryngoscopy following irritant and odour provocation^{1,2,5}; units without such experience must liaise closely with Otolaryngology, as laryngoscopy performed acutely is essential to confirm ILO and exclude laryngeal oedema.

Universal infection prevention precautions including personal protective equipment (PPE) in line with local infection prevention control policies, including for COVID-19, and standardized room cleaning with standing time following each procedure is recommended.

Whenever possible, patients should be shown live or recorded video of the laryngeal diagnosis and its response to rescue breathing. For many, this therapeutic demonstration can be immensely reassuring and transform their disease understanding, although some remain unshaken in their belief of an allergic diagnosis. Most benefit from ongoing Speech Pathology intervention,⁸ and some require Psychology input for what we presume to be a powerful psychogenic trigger. Symptoms induced post “allergen” challenge without laryngoscopy evidence of ILO or objective signs of IgE-mediated allergy may be most appropriately termed a stress-related response.⁹

We acknowledge limitations associated with this case series. The ability to induce ILO during supervised “allergen” challenge requires further validation, and is made more challenging still by a paucity of knowledge surrounding the mechanism for ILO to both inhalant and non-inhalant triggers. Similarly, a lack of paradoxical vocal cord movements observed during laryngoscopy during “allergen” challenge does not exclude a diagnosis of ILO. This challenging, real life diagnostic problem faced by clinicians therefore requires further prospective evaluation.

To conclude, we describe a systematic diagnostic approach to patients with VCD mimicking anaphylaxis (Figure 1), and propose appropriately supervised “allergen” challenge as a valuable addition to the array of VCD provocation agents during functional laryngoscopy.

AUTHOR CONTRIBUTIONS

The study was conceived by SS and MH. Observational data were collected by SS, MH, AS and CZ. Data interpretation was performed by all authors. The first draft was written by SS and MH. All authors participated in review, editing and discussion.

CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work. Unrelated to this study, MH has received grants-in-aid, consulting and speaker fees from GlaxoSmithKline, AstraZeneca, Novartis, Teva and Sanofi, all paid to his institutional employer Alfred Health; CZ has received a grant and speaker fees from Seqirus, Stallergenes, Mylan and Novartis; and JL has received speaker fees from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca and Sanofi; no other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL

This research letter was exempt from ethics approval by our institutional assessment board, The Alfred Ethics Committee. Under Alfred Ethics Committee guidelines written consent from each patient is not mandatory unless the subject matter is particularly sensitive or it is considered likely that an individual could be identified. All patients provided individual verbal informed consent for utilization of deidentified information in this series.

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