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Symptom Association: An imperfect pairing

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One of the primary indications for pH/pH-impedance testing is to correlate symptoms with esophageal reflux events to prove or disprove that reflux events are causing symptoms. To try to determine the degree to which the reflux-symptom relationship is clinically significant, three different symptom indices have been proposed as a way to report the relationship: the symptom index (SI), the symptom sensitivity index (SSI) and the symptom association probability (SAP). In this issue of JPGN, Funderburk et al describe the rates of positivity for the three indices in preterm infants undergoing pH-MII testing for the evaluation of gastroesophageal reflux disease. There are two important conclusions to this research (1). First, there are significant difference in the rates of positivity between the three indices which highlights the dangers of relying solely on only one index in making significant management decision such anti-reflux surgery. Second, the study also highlights, what other studies have shown, that despite the frequent NICU consults, symptoms in infants rarely are attributable to gastroesophageal reflux disease. (2, 3)

While documentation of different symptom indices is an integral part to pH-MII and pH-metry testing, there is little to no evidence to show that there indices predict any meaningful clinical outcome. In the adult literature, while many studies document ranges of symptom index positivity, several studies have shown that symptom index positivity fail to predict clinical outcome including response to fundoplication or medications (4) (5). Similarly, in the pediatric literature, the symptoms indices have not been shown to predict fundoplication outcome or response of symptoms to medications (6). Therefore, while symptom associations may suggest a temporal relationship, proving causality is difficult and the current literature fails to support the use of symptom indices to prove causality when resolution of symptoms with medical or surgical therapies is used as the gold standard.

One of arguments for why the rates of index positivity are low or why they fail to predict outcomes is that the method for recording symptoms is flawed, particularly in infants and children who cannot verbalize symptoms or in patients whose symptoms only occur at night or are so frequent that the patient and/or parents cannot accurately record the symptoms; symptoms are often not reported or there is a lag between symptom occurrence and log recording so, without an objective symptom marker, the utility of symptom association is suspect. Studies have shown that, during pH-MII testing, up to 50% of symptoms are not

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recorded during the study (7-9). When symptom recording is inaccurate, symptom-reflux correlations become meaningless. Therefore, new methods for recording symptoms need to be developed to relieve the patient and their families from this responsibility. For example, intraesophageal pressure recording (to detect cough), acoustic recording (to detect cough and wheeze) and video recording (to detect arching, fussiness) have been proposed as alternative methods for recording symptoms to better correlate symptoms with reflux events(8-10). Clearly new tools are needed to improve the documentation of symptoms.

Another complication to using symptom indices is the time interval chosen by which reflux episodes are considered associated with reflux. The longer the time interval chosen, the higher the degree the symptom association (i.e. a symptom is more likely to occur by chance near a reflux episode of the window is longer). In the study by Funderburk et al, a five minute symptom association interval was chosen which is at the upper end of length of duration and even with this long window, their rate of positivity of the three indices was low. To address the ideal symptom window in children, Omari et al describe how varying the length of association changes the rate of symptom index positivity (11). For example, the 2 minute symptom window is appropriate, based on statistical analysis, for some symptoms but not all. Unfortunately, with this study, with the Funderburk et al study and with all other pediatric studies, the optimization of the symptom window is based on statistical definitions rather than therapeutic outcomes. Pediatric studies are needed in which a symptom index cut off is determined based on the response to therapy because ultimately that is what the clinician wants to know: what window or index cut off will predict if my patient's symptoms will go away after fundoplication or after medical therapy?

In summary, the Funderburk et al study highlights the discrepancies in index positivity depending on the index chosen and the lack of association between symptoms in infants regardless of the index chosen. This study brings into question the role of the most key components of a standard pH-MII report. Clearly, additional studies are needed to define the symptom indices cutoffs based on response to therapies and not just statistical association.

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