



## Perspective

# PRO: Peripheral intravenous access should always be secured before initiating food protein-induced enterocolitis syndrome oral food challenge



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Oral food challenge (OFC) is a major diagnostic tool for food protein-induced enterocolitis syndrome (FPIES) as biomarkers are currently lacking. Although this test is often used, the protocol is not standardized and there are considerable differences even among centers in the same country.<sup>1</sup> The use of systemic intravenous access in patients with FPIES undergoing OFC has been a subject of particular debate in recent years. In this review, we will highlight the advantages of always securing a peripheral intravenous access before initiating FPIES OFC.

Profuse vomiting is the hallmark of acute FPIES reactions, but the severity of FPIES reactions can vary greatly, ranging from mild isolated vomiting to more severe symptoms indicative of poor perfusion such as loss of consciousness, clamminess, hypotonia, and cyanosis.<sup>1</sup> The proportion of severe acute FPIES reactions varies considerably among cohorts of patients, ranging from 5% to 24% of cases.<sup>2</sup> The proportion of patients in whom hypotension has been reported varies even more widely, from 5% to 77% of cases.<sup>2</sup> Fluid repletion is the first line of management for hypotension. FPIES OFC reactions treated with intravenous fluids, steroids, or both are reported at rates from 7.7% to 95%.<sup>1,3</sup> In contrast, Katz et al<sup>4</sup> reported that oral rehydration and observation were sufficient treatment for 24 patients and questioned the need for an intravenous access. Nonetheless, this study suffered from selection bias, in that patients with more severe FPIES were not challenged.<sup>3</sup> Overall, despite the

wide variation in the proportion of patients requiring intravenous fluids, the fact that a minimum of 1 in 20 patients need intravenous access during FPIES OFC justifies establishing an intravenous access in all patients with FPIES undergoing OFC.

Clinical predictors of severe reaction during OFC would be of great benefit in identifying patients at risk, who consequently need intravenous access, but none have been firmly established. Recently, in a review of 169 FPIES OFCs, Wang et al<sup>5</sup> reported that a history of moderate to severe reaction requiring intravenous treatment does not consistently predict severe reactions at future OFC. They found considerable overlap of clinical features between those who required intravenous fluids and those who were orally rehydrated, except that the former were older. In contrast, in another study that focused on the need for an intravenous access during FPIES OFC, only 3 of 39 patients required intravenous fluids, 2 of whom had a history of severe reactions.<sup>3</sup> This study concludes that patients more likely to need intravenous access are younger and have a history of more severe reactions.<sup>3</sup> Most of the time, clinical history suggestive of FPIES negates the need for diagnostic OFC. Therefore, data from diagnostic OFC are biased toward those with a history of lower severity reactions, especially in infancy.<sup>3</sup> Intravenous access in infants with cow's milk FPIES challenged before 12 months of age may be particularly recommended, as it has been found that the shorter the time since the initial reaction, the more likely a moderate to severe reaction on OFC.<sup>3</sup> Similarly, owing to the potential risk of co-allergy, an intravenous access should be considered to introduce soy milk as an alternative in infants with severe cow's milk FPIES. On balance, the data suggest a need for early administration of intravenous fluids in at least a

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subgroup of patients, particularly those with a history of severe reactions.

Ondansetron hydrochloride is increasingly used to treat acute FPIES reactions during OFC as an adjunct to fluid resuscitation. The risk of cardiac arrhythmia is low and the drug can be considered safe. However, only a few studies have confirmed its efficacy. In a case series of 5 patients who develop systemic symptoms such as pallor, confusion, and lethargy after profuse vomiting during an OFC, ondansetron was found to be an effective antiemetic treatment. All patients had complete symptom resolution within 10 to 15 minutes. One patient who initially received oral ondansetron was only partially controlled. In another patient, symptoms relapsed an hour after improving but successfully responded to a second dose.<sup>6</sup> The time ( $t_{\max}$ ) to reach maximum concentration ( $C_{\max}$ ) ranges from 1 to 2.1 hours after oral administration of ondansetron and from 7 to 20 minutes after intravenous infusion. Compared with intravenous ondansetron, orally administered ondansetron has approximately 60% bioavailability. Intramuscular ondansetron is rapidly absorbed within 10 minutes, and  $C_{\max}$  was found to be only 39% compared with intravenous administration. Children and adults exhibit similar pharmacokinetics.<sup>7</sup> Thus, intravenous ondansetron is preferable to oral ondansetron owing to its more rapid onset of action. This is an additional reason to have an intravenous access readily available before OFC.

During FPIES food challenge, we place our patients at risk of entirely foreseeable symptoms and their associated morbidity. By securing a reliable intravenous access before commencement of OFC, in a nonemergency setting, we ensure that our patients are as safe and ready as possible to promptly receive the support they require. Dehydration is a known risk factor for difficult peripheral venous access, meaning that multiple attempts are more likely to be required in patients reacting at the time. Not only does the need for multiple attempts delay administration of treatment, but it increases the risk of complications such as infection and infiltration, increases cost owing to staff time and equipment, and increases anxiety and pain for the patient, potentially leading to increased anticipatory distress during subsequent encounters.

Nonetheless, planned intravenous insertion allows clinicians to harness known factors associated with success, such as patient cooperation (assisted by calm explanation to a well-feeling child and use of topical analgesia such as lidocaine and prilocaine cream) and enhancing visibility and palpability of veins, for example by warming the limb.<sup>8</sup>

In conclusion, any OFC for either diagnosing FPIES or assessing tolerance should be considered a high-risk procedure, as no factors predicting reaction severity have been clearly identified. In addition, to diminish both stress and failure to achieve a venous access in an emergency situation, peripheral venous catheter placement before OFC should be considered particularly in infants. Currently, on the basis of the 2017 International Consensus on FPIES, “it is advisable to have intravenous hydration readily available,” and this choice is left to physician discretion.<sup>1</sup> Further studies are urgently required to identify the risk factors for severe reaction during OFC.

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