

Using a Multiple-Case Study Design to Explore the Experiences of Caregivers of Children with Rare Disease: Lessons Learned from a Study in Leukocyte Adhesion Deficiency, Type I (LAD-I)



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Background and Objectives

- Although rare diseases affect approximately 400 million people globally¹, the small populations within each disease require researchers to use innovative methods to generate evidence
- Leukocyte adhesion deficiency, type I (LAD-I) is a rare, inborn error of immunity that affects approximately 1 in 1 million children globally** and presents during infancy.^{2,3} Children with LAD-I experience recurrent, often severe bacterial and/or fungal infections affecting the skin, mouth, respiratory tract, and other organs, as well as hyperinflammation.^{3,4}
 - More than half of children with LAD-I have a severe form of the condition. Among those, only 31-39% will survive past age 2 without allogeneic hematopoietic stem cell transplantation (allo-HSCT).⁵⁻⁸
- Given the rarity of severe LAD-I, recruiting a large sample for research was not feasible; however, case studies are an effective way to use a small sample to explore a phenomenon in depth.**⁹
 - A multiple-case study design enhances this approach by providing an opportunity to compare and contrast cases to identify themes that are both cross-cutting and unique.⁹
- This study highlights the use of a multiple-case study design to capture the experiences of caregivers of children with severe LAD-I.

Methods

- Using purposive sampling**, the study team leveraged the study sponsor's existing network of LAD-I families and clinicians.
 - Parents from 6 families in North America, Europe, and Asia with 1 or more child with severe LAD-I were identified and invited to participate in the study.
- Each participant completed at least 1 **one-on-one, semi-structured interview** conducted by a trained qualitative researcher who followed a study-specific interview guide.
- Open-ended questions were designed to elicit descriptions of life caring for a child with severe LAD-I, including impacts on the caregiver's life, observed symptoms and impacts on the child's life, and experiences with treatment(s).**
- A set of **20 stock photo image cards was also used to facilitate discussion through a photo elicitation exercise** (Figure 1).
 - Participants selected 3-4 images they felt aligned with or represented the strengths or challenges they faced as someone caring for a child with severe LAD-I and then described why they selected each image, further delving into their experiences with this rare condition.

Figure 2. Data Analysis Methods

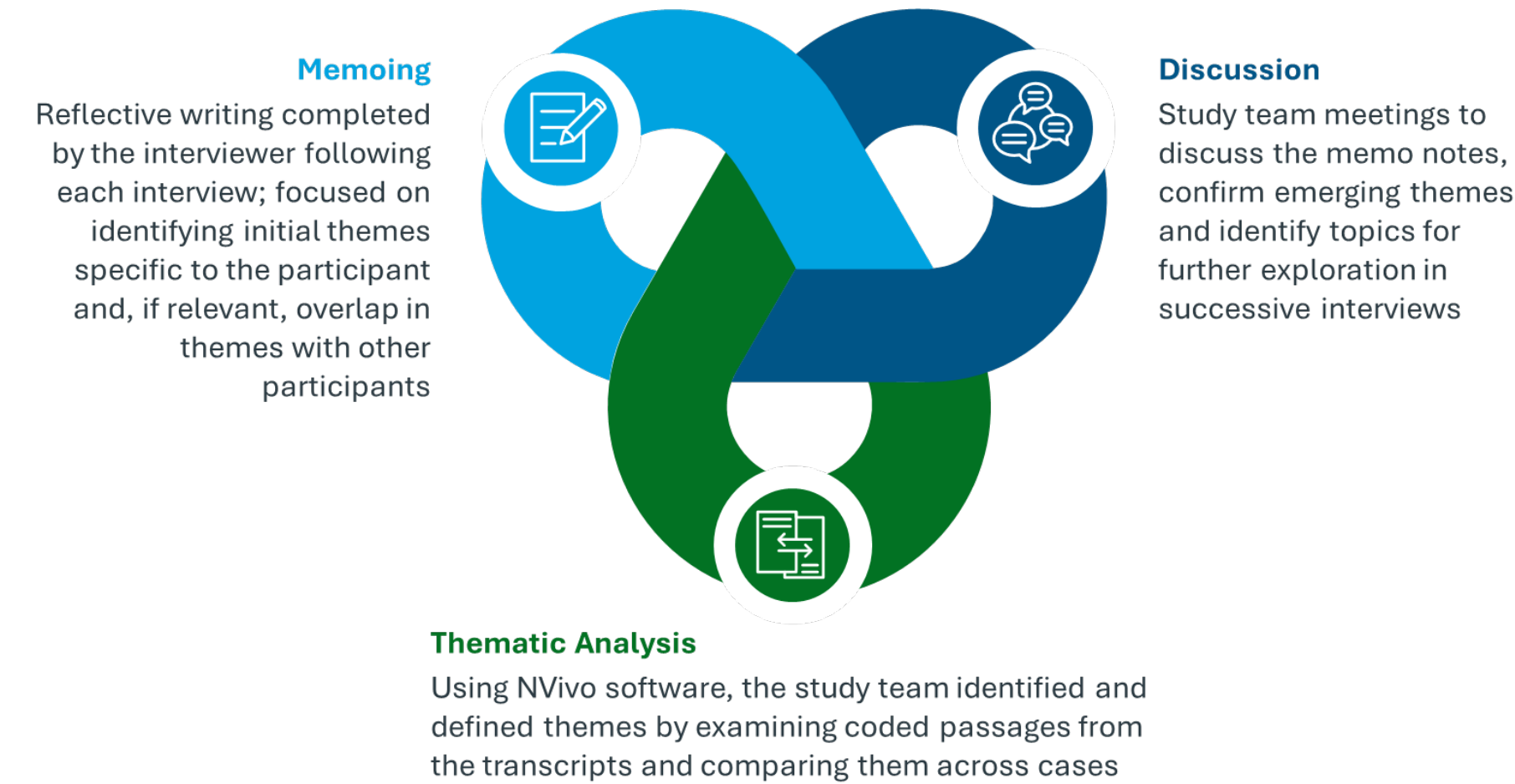


Figure 1. Selection of Image Cards Used for Photo Elicitation

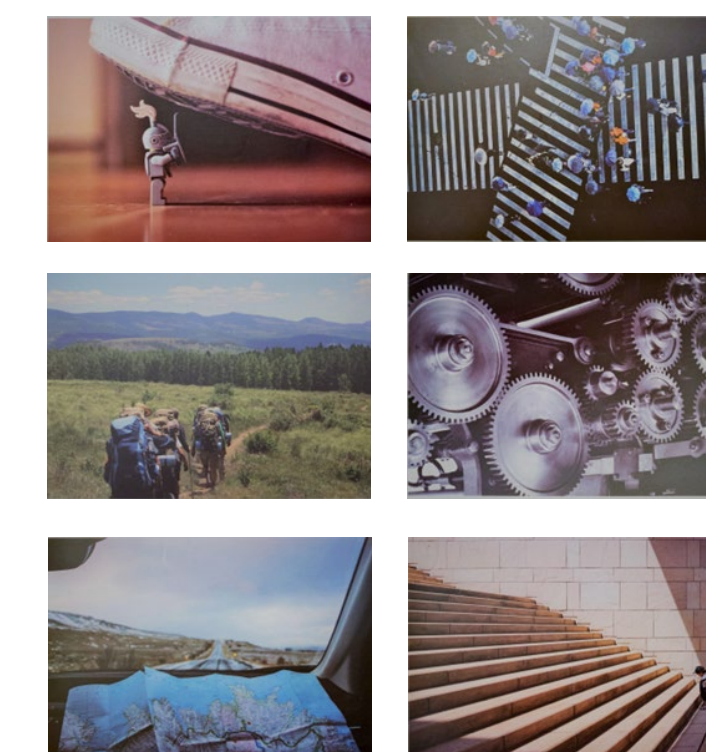


Image Source: metaFox Coaching Tools. Germany. "Growing Together" image cards. Card names were assigned by the study team for reference only.

- Interviews were audio recorded and then transcribed verbatim; each transcript was also reviewed for accuracy.
- Interviews were analyzed using a combination of memoing and thematic analysis supplemented by regular discussion among the study team members (Figure 2).
- Themes were organized under burdens of illness, treatment, and caregiving.
 - Each burden was defined in advance based on the literature.

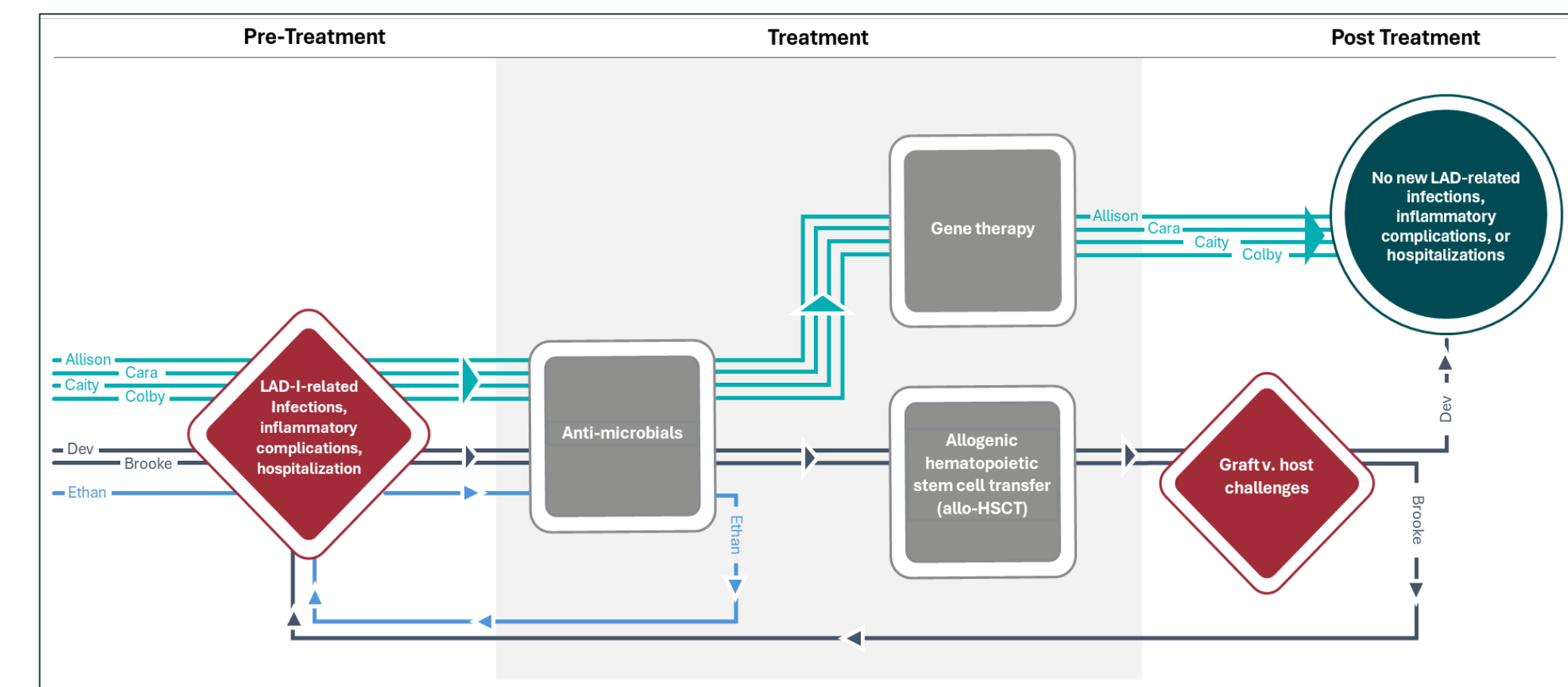
Results

- Of the 6 families invited, 5 – represented by 9 parents – participated in this study;** to protect participants' anonymity, all names were replaced with pseudonyms. Each family represents one case.
 - Four of the families included both parents, each of whom participated in one interview; 1 family included one parent, who participated in 2 interviews.
 - The families were based in North America and Europe and included 7 children with severe LAD-I who ranged in age from 3 to 18 years at the time of the interviews.
 - The parents reported on their experiences with at least 1 of 3 treatment approaches: investigational gene therapy, allo-HSCT, and/or anti-microbials.
- Each of the children experienced recurrent health issues and multiple hospitalizations.**
 - Multiple children experienced omphalitis shortly after birth, ear infections (and burst eardrums), rashes, slow-healing wounds, gingivitis, and lung infections.
- The parents' experiences with their child's journey to a diagnosis varied, but all needed to rearrange their lives to reduce risk of infection (Table 1).**
 - Despite a similar set of signs and symptoms among their children, the families had varying experiences of the journey to diagnosis and treatment. Although 3 children were diagnosed in infancy, the other 4 experienced signs and symptoms of severe LAD-I from 1 to 8 years before receiving a correct diagnosis.
 - The families experienced communication challenges with healthcare providers (HCPs) who were undereducated about the signs, symptoms, and risks of severe LAD-I; they wished for more up-to-date and patient-friendly information about the condition.
 - The mothers stopped working full-time and/or outside of the home to focus on caring for their children; fathers maintained full-time work but stressed the importance of having a job with flexibility and sufficient medical insurance coverage.
 - All families implemented physical and social restrictions to reduce the risk of exposure to potentially life-threatening infections for their child(ren) with severe LAD-I.
- Although all children started out experiencing recurring infections and hyperinflammation, their journeys diverged depending on treatment type (Figure 3).**
 - All 4 children who had gene therapy experienced fewer or no infections and thus were able to attend school outside the home, socialize, and play without worries.
 - The 2 children who had allo-HSCT had mixed results depending on the effectiveness of the transplant; both experienced a reduced risk of infection and were able to attend school, but one required a second transplant and was experiencing waning effectiveness by the time of the interview.
 - One child who only received anti-microbials remained in a loop of infection and treatment.

Table 1. Parents' Experience of Coping with Severe LAD-I Prior to Potentially Definitive Treatment

	Case Family				
	A	B	C	D	E
Long, complex journey to diagnosis	●		●		●
Desire for more disease-specific information	●	●	●	●	●
Desire for network of LAD-I families	●		●	●	●
Challenges with uninformed HCPs	●		●		●
Social isolation	●	●	●	●	●
Constant worry	●	●	●	●	●
Rearranging life around severe LAD-I	●	●	●	●	●
Financial challenges	●		●		●

Figure 3. Severe LAD-I Symptom Journeys Based on Treatment Type



Lessons Learned and Conclusions

- In a rare disease like LAD-I, the small patient population limits participant recruitment for studies; thus, creativity was needed in designing this study to overcome this limitation. **The multiple-case study design, in which a small sample is intentional, allowed the study team to delve deeply into the specific experiences of each case family.**
- Purposive sampling leveraged the study sponsor's existing network of families with severe LAD-I, facilitating recruitment.**
- Using photo elicitation in addition to verbal probing gave participants an alternative way to think about and describe their experiences, as they connected to the feelings and ideas the images raised for them.**
- The use of multiple analysis methods and regular analytic discussions helped the team to identify and explore shared and unique experiences among the cases.**
 - As a result, it was possible to create visuals like Figure 3 that demonstrate the experiences that are common across patients with severe LAD-I and how those may shift depending on treatment type.**
- To our knowledge, this is the first time a multiple-case study has been used to study the experience of caregivers of children with severe LAD-I; the results shed light on this rare condition and demonstrate the utility of the multiple-case study approach in rare disease.

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