# LONGITUDINAL IMPROVEMENT IN EPIDERMOLYSIS BULLOSA SIMPLEX PATIENTS WITH *DE NOVO KRT5* MUTATIONS

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**Keywords** Epidermolysis bullosa, epidermolysis bullosa simplex.

**Abbreviations** **EB** = epidermolysis bullosa; **EBS** = EB simplex.

**Materials and methods**. *Study design and population*. A retrospective chart review of patients followed at a interdisciplinary Epidermolysis Bullosa (EB) center was conducted. Patients were included if they had EB simplex (EBS) with genetically confirmed *denovo KRT5* mutations.

*Data collection*. Clinical records were reviewed from earliest available documentation through most recent follow-up. Extracted data included birth presentation, hospitalization metrics, cutaneous involvement, respiratory and infectious complications, electrolyte abnormalities, feeding interventions, vascular access, motor development, neurodevelopment and pain and pruritus.

*Definitions*. Early disease course was defined as the period from birth through 18 months of age to capture initial hospitalization and early post-discharge events. Longitudinal outcomes were evaluated across developmental stages, including infancy (0-1 year), early childhood (2-5 years), late childhood (6-9 years), and adolescence (10-12 years).

*Statistical analysis*. Analyses were descriptive using frequencies, ranges, and measures of central tendency.

**Case reports**. *Cohort Characteristics*. Four male patients with confirmed *de novo KRT5* mutations were identified. Two patients carried c.1429GA (p.E447K) mutations, one carried c.538G>C (p.A180P), and another carried c.526A>C (p.N176H). Follow-up began in infancy and extended to 17 months in one patient, 10 years in two patients, and 12 years in the remaining patient.

*Hospitalizations*. All patients required intensive care following birth for initial stabilization, with lengths of stay ranging from 30-90 days (mean 51). Three patients experienced additional hospitalizations (n=10) between 3-13 months of age. One had four admissions between 3-9 months of age for respiratory complications, including three brief admissions (3-5 days each) for respiratory infections and one prolonged admission (3 months) for acute respiratory distress syndrome (ARDS). Another patient had two admissions between 12-13 months of age for sepsis (11-14 days each). The third patient had three brief admissions between 6-7 months of age for respiratory infections (1-5 days each), and one 13-day admission for failure to thrive.

*EB involvement and wound care*. Generalized cutaneous involvement (Fig. 1) and localized absence of skin was present at birth across the cohort. Wound care consisted of petroleum-based emollients and non-adherent dressings, with dressing frequency decreasing from multiple times per day to once daily or every other day. One patient developed recurrent bleeding from aplasia cutis requiring escalation to medical and procedural management, including thrombin application, blood and platelet transfusions, intraoperative dressing changes with cautery support, and ultimately split-thickness skin grafting. Mucosal involvement occurred in 3 patients and contributed to feeding limitations. Nail dystrophy and palmoplantar keratoderma (PPK) emerged between 1-10 months of age and were managed with topical urea cream in two cases.

*Nutritional and gastrointestinal course*. Feeding impairment was universal. Oral intake was attempted in each case but remained minimal due to mucosal involvement, odynophagia, and/or aspi-

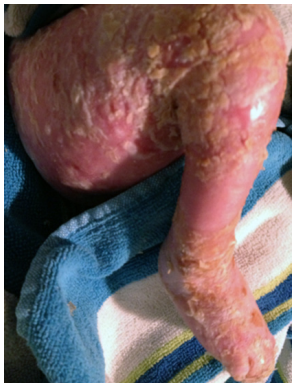
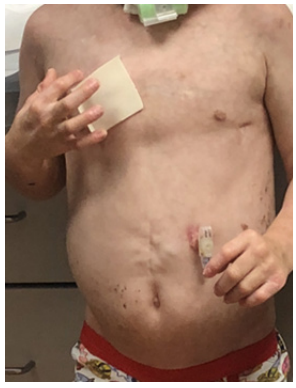


Fig. 1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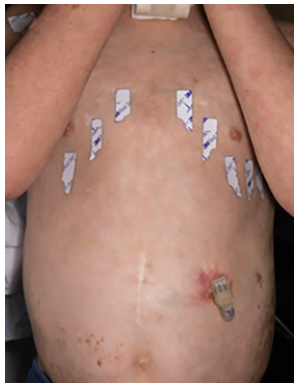
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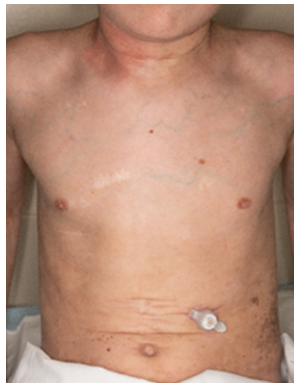
Fig. 1

Fig. 1, 2, 3, 4: Appearance of bullous skin lesions in a patient with a *de novo KRT5* mutation at 23 months (Fig. 1), 3 years (Fig. 2), 6 (Fig. 3), and 12 (Fig. 4) years.

ration risk. Nutritional support escalated in a stepwise manner, incorporating oral feeding strategies (including specialized bottles), parenteral nutrition, and nasogastric feeding. Establishing and maintaining nasogastric access was challenging due to skin and airway fragility, and 3 patients ultimately underwent gastrostomy tube placement between 3-6 weeks of age.

Poor weight gain and increased metabolic demand were observed across the cohort, with one case of hypoalbuminemia. Nutritional optimization strategies included high-protein, high-calorie fortification, micronutrient supplementation, albumin supplementation, and multidisciplinary support with speech and occupational therapy. Gastrointestinal complications occurred in one patient and included diarrhea, reflux, and ileus, which were managed with antidiarrheal agents, acid suppression, and bowel rest, respectively.

*Respiratory course*. Three patients developed respiratory complications during initial hospitalization. One patient had mild respiratory symptoms related to laryngomalacia, requiring transient supplemental oxygen. Another, with opioid-induced respiratory suppression, required noninvasive ventilation and was discharged on supplemental oxygen. The remaining patient developed respiratory failure associated with epiglottic and pulmonary edema, requiring endotracheal intubation and mechanical ventilation, and later underwent tracheostomy placement during a subsequent hospitalization in the setting of ARDS and chronic lung disease.

*Infectious complications*. Each patient underwent evaluation for suspected infection during initial hospitalization; however, confirmed infection was identified in only one case. This patient developed methicillin-sensitive *Staphylococcus aureus* (*S. aureus*) (MSSA) central-line associated bloodstream infection complicated by endocarditis, as well as cellulitis and polymicrobial wound infections involving *Haemophilus parainfluenzae*, *S. aureus*, *Candida*, and *Pseudomonas*. Management required prolonged targeted intravenous antimicrobial therapy and central line removal for source control.

During subsequent hospitalizations, one patient developed MSSA sepsis followed by group A streptococcus septic shock, while two patients experienced recurrent respiratory infections, including viral upper respiratory infections, bronchiolitis and pneumonia.

*Electrolyte abnormalities*. Electrolyte abnormalities were observed in three patients during initial hospitalization, including hyponatremia, hypokalemia, hypocalcemia and hypophosphatemia, which were managed with targeted supplementation and serial laboratory monitoring.

*Pain and pruritus*. All patients experienced substantial pain related to extensive skin involvement and dressing changes. Management included multimodal analgesia with acetaminophen and opioids in all cases, with escalation to ketamine or benzodiazepines for dressing changes and severe pain. One

Fig. 5

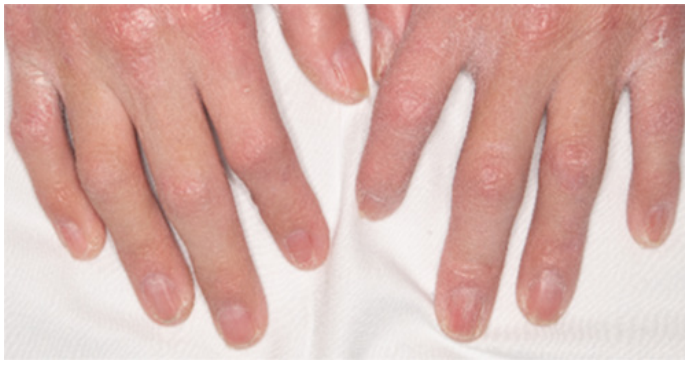

Fig. 6

Fig. 5, 6: Onychodystrophy in a patient with EBS caused by a *de novo KRT5* mutation at 23 months (Fig. 5) and 12 years (Fig. 6).

patient developed opioid dependence requiring methadone tapering. Pruritus was suspected in one patient and managed with antihistamines.

*Vascular access*. Central vascular access was utilized in all patients during initial hospitalization for delivery of nutrition, fluids, medications, transfusions, and laboratory monitoring. One patient required multiple line placements due to complications including dislodgement and infection, whereas the others were managed with a single umbilical venous catheter.

*Childhood and adolescent follow-up*. Longitudinal functional and symptom severity across domains were documented, with detailed domain-specific features and interventions provided in all patients.

*Feeding*. During infancy, three patients remained dependent on enteral support, while one maintained oral intake with ongoing nutritional supplementation. In early childhood, feeding challenges persisted and included oral aversion, limited dietary variety, gagging, and continued reliance on supplemental or enteral nutrition despite ongoing occupational and speech therapy. By late childhood, trajectories diverged. Two patients progressed to regular diets by ages 7-8, whereas one remained dependent on enteral feeding with minimal advancement in oral intake into adolescence.

*Motor development*. Motor impairment was evident in all patients beginning in infancy and was characterized by delayed or absent motor milestones, reduced strength, muscular atrophy, and contractures involving the hands and lower extremities, requiring initiation of physical and occupational therapy. Mobility remained limited into early childhood, largely due to pain, and patients adopted adaptive movement strategies such as crawling on fists or knee-walking. Ambulation began to emerge between ages 3-4, but was initially inconsistent and often required support or assistive devices. By late childhood, all patients achieved independent ambulation with progression to age-appropriate activities, including participation in sports and extracurricular activities. However, residual limitations persisted, including subtle gait abnormalities in one patient and intermittent wheelchair use for school or long distances in another.

*Neurodevelopment*. In infancy and early childhood, all patients exhibited neurodevelopmental differences, most commonly involving speech, language, or social domains. In early childhood, additional features emerged, including chorea and tics in one patient, and sensory sensitivities in another. By school age, hyperactivity and attentional difficulties became apparent and required school-based support, therapeutic intervention and/or pharmacologic treatment. In later childhood, anxiety was observed in two patients. These behavioral and emotional challenges persisted throughout late childhood and into adolescence, necessitating ongoing intervention at the end of follow-up.

*Pain and pruritus*. All patients experienced significant pain in infancy requiring multimodal analgesia with escalation for dressing changes and baths. By early childhood, pain decreased in both frequen-

cy and intensity and became mainly activity-related. Around age 4, patients transitioned to as-needed medication use, with pain remaining intermittent throughout late childhood and adolescence.

Pruritus was present in infancy but required escalation of care in early childhood at approximately 4 years of age, coinciding with the period of decreasing pain burden. Throughout late childhood and adolescence, pruritus demonstrated a variable course, with resolution in one patient, and persistent symptoms of varying severity in the others.

*Cutaneous involvement*. Blistering during infancy was generalized in all patients and required frequent dressing care. Between 2-4 years of age, blistering decreased in frequency and became localized to friction- and activity-dependent areas, particularly the feet, with a concurrent reduction in the need for routine dressings. By late childhood and adolescence, blistering was minimal or resolved (Figure 4), and dressing care was minimal or no longer required.

Palmoplantar keratoderma remained prominent during infancy and early childhood but gradually improved throughout late childhood and adolescence. Nail dystrophy persisted into late childhood in all patients, with subsequent improvement observed in two cases (Figs. 5, 6).

Reticulated pigmentation became apparent between 1-2 years of age, while EB nevi typically emerged between ages 2-4. Reticulated pigmentation began to fade in late childhood in two patients but persisted in the remaining patient, whereas EB nevi persisted or progressed throughout follow-up in all patients.

**Discussion**. This study demonstrates that severe early presentation in *de novo KRT5* epidermolysis bullosa simplex (EBS) does not predict long-term disease severity. Although patients may appear critically ill, they show substantial improvement across cutaneous, functional, and symptom-based domains, with normalization in some domains by adolescence. These observations indicate that initial severity should not be used to predict long-term prognosis and support the use of life-sustaining interventions during the early phase of disease, as patients may stabilize and achieve meaningful recovery over time.

Previous literature has emphasized severe presentation at birth, followed by impairments in feeding, motor development, and neurodevelopment, as well as the development of cutaneous features including palmoplantar keratoderma, nail dystrophy, and reticulated hyperpigmentation (6-8). Disease severity has also been reported to lessen over time, primarily through reductions in blister frequency and overall cutaneous involvement (6). This study expands upon these observations by demonstrating longitudinal improvement across feeding, motor function, and pain burden, while also highlighting the variable trajectories of pruritus and neurodevelopmental outcomes. Together, these findings suggest that the early disease course represents a phase of maximal disease burden, followed by an evolving clinical course generally characterized by improvement.

From a clinical perspective, management should follow a staged, multidisciplinary approach that aligns with the evolving disease trajectory. The early disease course is characterized by high disease burden that requires intensive management, including wound care, nutritional support, respiratory stabilization, infection surveillance, and electrolyte monitoring. As patients transition into infancy and early childhood, care priorities shift toward rehabilitation, including feeding advancement, pain control and motor development, often supported by speech, occupational, and physical therapy services. In later childhood, management focuses on optimizing functional participation, addressing persistent symptoms, and supporting neurodevelopment and psychosocial needs. Anticipatory guidance for patients and families should emphasize that disease burden and care needs evolve over time, with improvement in cutaneous involvement, pain, and functional capacity, and variable trajectories in pruritus and neurodevelopmental outcomes.

This study is limited by small sample size, retrospective design, and availability of long-term data for only three patients, which may limit generalizability. Additionally, functional outcomes were derived from clinical documentation rather than standardized assessments. Prospective studies with larger cohort sizes and standardized outcome measures are needed to further define the natural history of de novo *KRT5* EBS and optimize treatment strategies.

**Conclusion**. Patients with *de novo KRT5* EBS present with severe early disease but demonstrate meaningful improvement across cutaneous, functional, and symptom-based domains over time, with resolution of some features by adolescence. Management should include early life-sustaining care, followed by ongoing multidisciplinary support tailored to evolving clinical needs.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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