

Supplementary Online Content

Fernández Faith E, Shah S, Witman PM, et al. Association between treatments and time to heal ulceration in patients with infantile hemangioma. *JAMA Dermatol*. Published online March 31, 2021. doi:10.1001/jamadermatol.2021.0469

eMethods. Statistical Analysis Plan

eTable. Classification System for Ulceration in Infantile Hemangiomas

eFigure. Distribution of Age at Ulceration

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Statistical Analysis Plan

Goals: Determine efficacy of different treatment interventions in the healing of ulcerated infantile hemangiomas (IH). Identify clinical characteristics as prognostic indicators in the healing of ulcerated IH. Compare clinical and prognostic characteristics by treatment group. Describe complications and resource utilization among ulcerated IH. Evaluate factors associated with secondary outcomes: ulceration while on active therapy, ulceration recurrence, and aggressive (relentless) ulceration. Among patients who received propranolol, determine efficacy of propranolol dose (defined in two ways: (1) ≤ 1 mg/kg/day vs. 1 to <2 mg/kg/day vs. ≥ 2 mg/kg/day and (2) ≤ 1 mg/kg/day vs >1 mg/kg/day) and compare clinical and prognostic indicators by dose.

Analysis: Data will be summarized using frequencies with percentages and medians with interquartile range (IQR). Group comparisons will be evaluated using chi-square or Fisher's exact tests for categorical variables and Wilcoxon rank sum or Kruskal-Wallis tests for continuous variables, with Benjamini-Hochberg corrections for multiple comparisons. Univariate and multivariable proportional hazards regression will be used to assess factors associated with shorter heal times, and multivariable logistic regression will be used to evaluate factors associated with odds of complications, ulceration under active treatment, ulcer recurrence, and aggressive ulcers. Variables will be considered for multivariable assessment if their univariate p-value was <0.2 , and variables will be retained in the model if their adjusted p-value was <0.1 or if their inclusion had a substantial impact on model goodness of fit (based on AIC). Treatment group will be retained in all models regardless of statistical significance since it is the primary independent variable of interest. All analyses will be conducted using R for Statistical Computing.

eTable. Classification system for ulceration in infantile hemangiomas

	Category	Definition
Ulceration type	Single	single site of ulceration within the infantile hemangioma
	Multifocal	2 or more sites of ulceration separated by non-ulcerated infantile hemangioma tissue
	Cribriform	Multiple small non-contiguous ulcerations within a single infantile hemangioma
Ulceration depth	Erosion / shallow ulceration	Any of the following criteria: <ul style="list-style-type: none"> • Loss of the epidermis only • Ulceration that is less than 2 mm below the surface of the infantile hemangioma
	Deeper	Any of the following criteria: <ul style="list-style-type: none"> • Depth of ulceration is more than 2 mm below the surface of the IH • Depth of ulcer to deep dermis or subcutis • Elevated borders or crateriform appearance
	Uncertain	Unable to determine based on available clinical photograph
Distinct ulceration	Aggressive ulceration	2 out of 3 criteria: <ul style="list-style-type: none"> • Significant soft tissue destruction • Worsening of ulceration despite multimodal therapy • Unusually prolonged healing time (more than 12 weeks)

eFigure. Distribution of age at ulceration

