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# Key features of skin eruptions in acute hemorrhagic edema of young children: systematic review of the literature

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**Abstract:** Acute hemorrhagic edema is a skin limited small-vessel leukocytoclastic vasculitis, which affects infants 4 weeks to 2 years of age and remits within 3 weeks. The diagnosis is made clinically in not-ill appearing children with acute onset of raised annular or nummular eruptions and edema. In this vasculitis, type, distribution and evolution of the rash have never been systemically investigated. To address this issue, we employed the data contained in the Acute Hemorrhagic Edema Bibliographic Database, which incorporates all reports on acute hemorrhagic edema. Key features of rash were documented in 383 children. Annular eruptions in strict sense, usually targetoid, were reported in 375 (98%) cases (many children also presented polycyclic or arciform eruptions). Nummular eruptions were also very common (N=358; 93%). Purpuric eruptions and ecchymoses were reported in the vast majority of cases. Macules and wheals were described in a minority of cases. Edema, detected in all cases, was mostly painful, indurated and non-pitting. Following regions were affected, in decreasing order, by annular or nummular eruptions: legs, feet, face, arms, ears, trunk, and genitals. With the exception of feet, which were very often affected, the same distribution was reported for edema. The initial eruption was often a wheal or a macule that evolved into a nummular or an annular eruption. Nummular eruptions successively evolved into annular ones. In conclusion, this study carefully characterizes type, distribution and evolution of skin eruption in acute hemorrhagic edema. The data help clinicians to rapidly and noninvasively make the clinical diagnosis of this vasculitis.

**Keywords:** acute hemorrhagic edema; cockade purpura with edema; Finkelstein-Seidlmayer disease; targetoid; skin eruption; systematic review

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## 1. Introduction

Acute hemorrhagic edema of young children, also termed cockade purpura with edema or Finkelstein-Seidlmayer disease, is a skin-limited small-vessel leukocytoclastic vasculitis, which characteristically occurs after a simple, mostly viral, febrile illness [1-4]. It affects infants 4 weeks to 2 years of age and spontaneously remits within 3 weeks with little propensity toward relapses [2-5].

Although vascular immunoglobulin A deposits are not detected in the overwhelming majority of cases [6], acute hemorrhagic edema is often deemed to be the infantile variant of immunoglobulin A vasculitis [1-5]. The latter condition presents with a palpable rash mainly affecting the lower extremities and the buttocks [3, 4]. Available narrative reviews on acute hemorrhagic edema state that affected children develop over 48 hours or less extensive and symmetrically distributed annular or nummular eruptions (Figure 1) and edema [2-4].

**Figure 1.** Nummular and annular skin eruptions in three boys affected by acute hemorrhagic oedema of young children.



However, type, distribution and evolution of the rash over the disease course have never been systematically investigated. To address this issue, we employed the data contained in the Acute Hemorrhagic Edema Bibliographic Database AHEBID.

## 2. Materials and Methods

AHEBID [5, 6] includes all original articles on acute hemorrhagic edema published after the initial communication by Irving Snow in 1913 [7]. As of December 31, 2020, the database incorporated 301 original reports (letters, case reports or full-length articles) published since 1970, which addressed 488 individually documented cases. In all cases, the diagnosis of acute hemorrhagic edema made in the original reports was reviewed

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using three classic predefined criteria: raised annular or nummular eruptions and skin edema in a not-ill appearing child [2-4]. The clinical diagnosis of acute hemorrhagic edema was supported by a biopsy disclosing a non-granulomatous neutrophil infiltration into small-vessel walls with karyorrhexis in 241 cases.

For the present analysis, we included exclusively cases with documented type, distribution or evolution of skin eruptions. Since numerous and sometimes confusing descriptive terms are used to denote skin eruptions, we developed the glossary reported in table 1 [8] to define annular or nummular eruptions, edema, petechiae, purpuric eruptions, ecchymoses, macules, simple or papular wheals, and scratch marks.

**Table 1.** Acute hemorrhagic edema of young children. Glossary of skin eruptions utilized for the present analysis of the literature.

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### **Annular eruption**

Annular eruption in strict sense: raised, ring-shaped (circular or ovoid) eruption with well-defined borders,  $\geq 10$  mm in maximal diameter that lasts  $\geq 24$  hours

- targetoid annular eruption: with three zones of color

- non-targetoid annular eruption: with only two zones of color (often referred to as atypical targets)

Polycyclic eruption: raised coalescing annular (or arciform) eruption\*

Arciform eruptions: raised arc-shaped eruptions (considered incompletely formed annular eruption)\*

### **Nummular eruption**

Raised coin-shaped eruption with well-defined borders,  $\geq 10$  mm in maximal diameter that lasts  $\geq 24$  hours

### **Edema**

Swelling produced by expansion of the skin fluid volume

### **Further eruptions**

Petechia: non-blanching spots eruption  $\leq 3$  mm in diameter

Purpuric eruption: non-blanching, typically raised eruption, 4-10 mm in diameter

Ecchymosis: non-blanching, typically raised eruption,  $> 10$  mm in diameter (with a non-round shape)

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Macule: blanching flat area of discoloration, usually  $\leq 10$  mm in diameter

Simple wheal: elevated eruption, usually ovoid or circular and  $\geq 10$  mm in diameter lasting  $< 24$  hours (usually pruritic)

Papular wheal: elevated eruption  $\leq 10$  mm in diameter resembling an insect bite (but without a central "focus")

Scratch mark: narrow elongate loss of skin (= excoriation)

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\* either targetoid or non-targetoid.

The distinctive signs of inflammatory skin edema, including tenderness (or pain), induration and absent indentation after pressure were specifically addressed.

A predesigned form was employed to record information about demographics of cases, and type, distribution or evolution of eruptions. Two authors independently extracted the data in a nonblinded fashion. Uncertainties were resolved through team discussions and consensus.

Categorical variables are presented as frequency, continuous variables as median and interquartile range. For statistics, the two-tailed  $\chi^2$ -test (with the post-hoc Bonferroni adjustment) and the two-tailed Mann-Whitney-Wilcoxon test were used [9]. P-values  $< 0.05$  were considered significant.

### 3. Results

#### 3.1. Type and regional distribution of rash

The skin eruptions were poorly documented in 105 (22%) cases, 74 boys and 31 girls, 12 [9-20] months of age. The key features of the rash were accurately documented in the remaining 383 (78%) cases (261 boys and 122 girls, 11 [8-18] months of age), mostly (N=321) with the support of photographs. Patients without and with accurately documented skin eruptions did not significantly differ with respect to sex and age.

The skin rash was bilateral and symmetrically distributed in 380 and unilateral in the remaining three (0.8%) cases. The skin eruptions reported in the 383 cases appear in table 2.

**Table 2:** Skin eruptions reported in 383 patients (261 males and 122 female) affected by acute hemorrhagic edema of young children.

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	<b>N (%)</b>
<b>Annular eruptions</b>	
Annular in strict sense	
Targetoid	314 (82)
Targetoid and non-targetoid	56 (15)
Non-targetoid	5 (1.3)
Polycyclic	
Targetoid	165 (43)
Targetoid and non-targetoid	5 (1.3)
Non-targetoid	4 (1.0)
Arciform	
Targetoid	91 (24)
Targetoid and non-targetoid	8 (2.1)
Non-targetoid	6 (1.6)
Total	375 (98)
<b>Nummular eruptions</b>	358 (93)
<b>Edema*</b>	383 (100)
<b>Further eruptions</b>	
Purpuric eruptions	374 (98)
Ecchymoses	241 (63)
Macules	50 (13)
Simple wheals	33 (8.6)
Petechiae	30 (7.8)
Papular wheals	16 (4.2)
Scratch marks	12 (3.1)

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\* tenderness or pain, N=103; induration, N=22; absent indentation after pressure, N=32; indentation after pressure, N=5.

Annular or nummular eruptions and edema, two inclusion criteria, were reported in all cases. Annular eruptions in strict sense, usually targetoid, were reported in 98% of cases and were very often associated with polycyclic (slightly less than every second case) or arciform (approximately every fourth case) eruptions. Nummular eruptions were also reported in more than 90% of cases. Purpuric eruptions and ecchymoses (and, occasionally, also petechiae) were reported in the vast majority of cases. Macules and simple or papular wheals were described in a minority of cases. Scratch marks were rarely observed.

The regional distribution of annular or nummular eruptions, edema and macules appears in table 3.

**Table 3.** Regional distribution of annular or nummular eruptions, edema and macules in 383 patients affected by acute hemorrhagic edema of young children.

	Annular Eruptions				Nummular Eruptions	Edema	Macules
	Total	Annula Strict Sense	Polycyclic	Arciform			
Face, N (%)	278 (73)	275 (72)	71 (19)	34 (8.8)	247 (64)	193 (50)	34 (8.9)
Ears, N (%)	89 (23)	87 (23)	5 (1.3)	4 (0.1)	56 (16)	117 (31)	24 (6.3)
Arms, N (%)	278 (73)	275 (72)	61 (16)	35 (9.1)	221 (58)	184 (48)	27 (7.0)
Hands, N (%)	219 (57)	219 (57)	31 (8.1)	9 (2.7)	170 (44)	234 (61)	23 (6.0)
Trunk, N (%)	58 (15)	58 (15)	17 (4.4)	11 (2.9)	48 (13)	31 (8.1)	13 (3.4)
Genitals, N (%)	8 (2.1)	8 (2.1)	1 (2.6)	0	4 (1.0)	30* (7.8)	2 (0.5)
Legs, N (%)	340 (89)	338 (88)	109 (28)	61 (16)	293 (77)	266 (69)	33 (8.6)
Feet, N (%)	257 (67)	255 (66)	34 (8.8)	12 (3.1)	212 (55)	282 (74)	29 (7.6)

The relative distribution of annular and nummular eruptions was very similar. Following body regions were affected, in decreasing order of frequency, by the two mentioned eruptions: legs, feet, face, arms, ears, trunk, and genitals. With the exception of feet, which were affected in about three quarter of cases, the same distribution was reported for edema. The mentioned tendency was found to be statistically significant, as shown in table 4.

**Table 4.** Acute hemorrhagic edema of young children. Distribution of annular or nummular eruptions, oedema and macules: statistical analysis.

**All annular eruptions**

	Face	Ears	Arms	Hands	Trunk	Genitals	Legs
<b>Face</b>							
<b>Ears</b>	P<0.001						
<b>Arms</b>	NS	P<0.001					
<b>Hands</b>	P<0.001	P<0.001	P<0.001				
<b>Trunk</b>	P<0.001	NS	P<0.001	P<0.001			
<b>Genitals</b>	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001		
<b>Legs</b>	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	
<b>Feet</b>	NS	P<0.001	NS	P<0.01	P<0.001	P<0.001	P<0.001

**Nummular eruptions**

	Face	Ears	Arms	Hands	Trunk	Genitals	Legs
<b>Face</b>							
<b>Ears</b>	P<0.001						
<b>Arms</b>	NS	P<0.001					
<b>Hands</b>	P<0.001	P<0.001	P<0.001				
<b>Trunk</b>	P<0.001	NS	P<0.001	P<0.001			
<b>Genitals</b>	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001		
<b>Legs</b>	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	
<b>Feet</b>	NS	P<0.001	NS	P<0.005	P<0.001	P<0.001	P<0.001

**Edema**

	Face	Ears	Arms	Hands	Trunk	Genitals	Legs
<b>Face</b>							

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<b>Ears</b>	P<0.001							
<b>Arms</b>	NS	P<0.001						
<b>Hands</b>	P<0.005	P<0.001	P<0.001					
<b>Trunk</b>	P<0.001	P<0.001	P<0.001	P<0.001				
<b>Genitals</b>	P<0.001	P<0.001	P<0.001	P<0.001	NS			
<b>Legs</b>	P<0.001	P<0.001	P<0.001	NS	P<0.001	P<0.001		
<b>Feet</b>	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	NS	

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**Macules**

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	<b>Face</b>	<b>Ears</b>	<b>Arms</b>	<b>Hands</b>	<b>Trunk</b>	<b>Genitals</b>	<b>Legs</b>
<b>Face</b>							
<b>Ears</b>	NS						
<b>Arms</b>	NS	NS					
<b>Hands</b>	NS	NS	NS				
<b>Trunk</b>	P<0.05	NS	NS	NS			
<b>Genitals</b>	P<0.01	P<0.01	P<0.01	P<0.01	P<0.05		
<b>Legs</b>	NS	NS	NS	NS	P<0.05	P<0.01	
<b>Feet</b>	NS	NS	NS	NS	NS	P<0.01	NS

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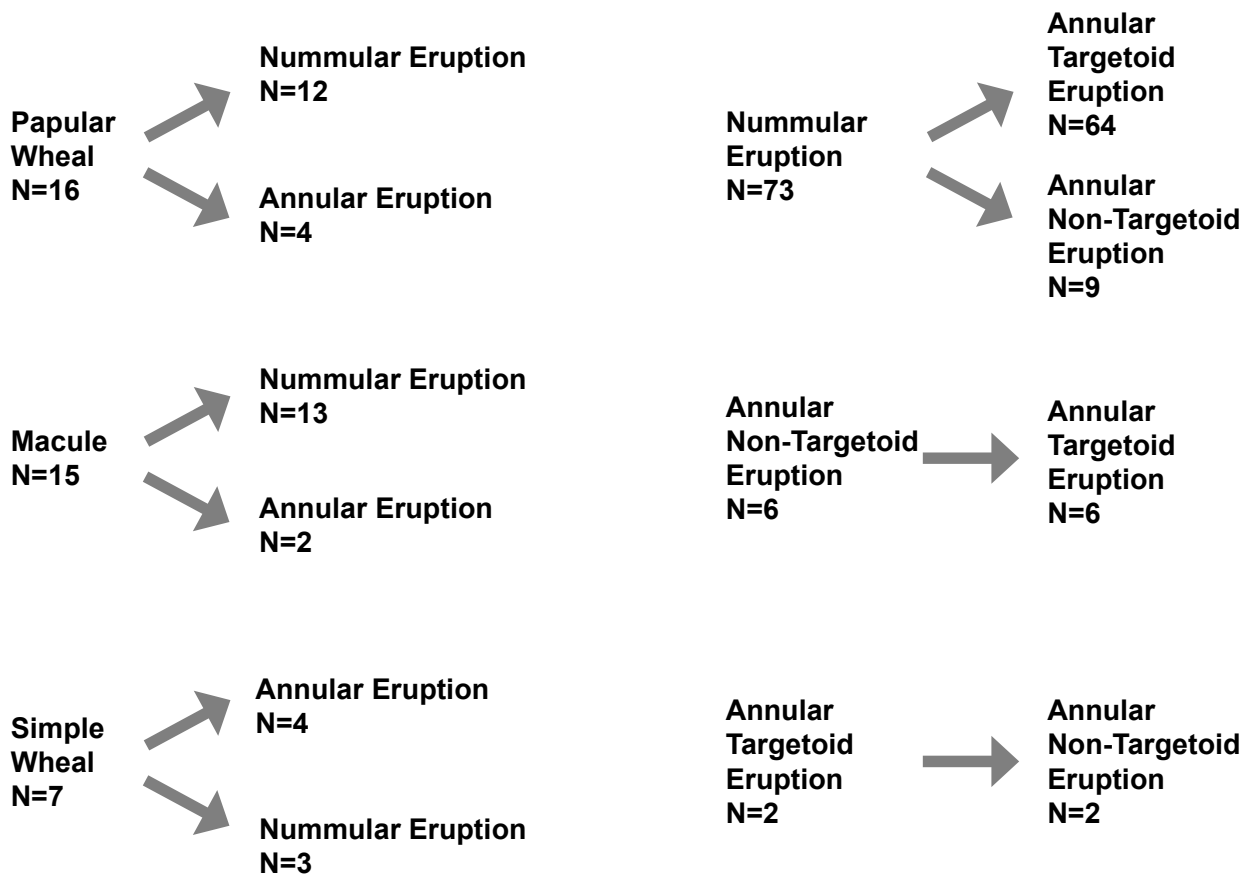
**3.2. Evolution of eruptions over the disease course**

No detailed information about the evolution of round skin eruptions was provided for 407 cases: 280 boys and 127 girls 11 [9-17] months of age. These data were extracted for the remaining 81 cases: 55 boys and 26 girls 11 [9-17] months of age. Patients without and with documented evolution of eruptions did not significantly differ with respect to sex and age.

In the mentioned 81 cases, a papular wheal, a macule or a simple wheal often preceded the classic nummular or annular eruption (Figure 2).

**Figure 2.** Evolution of round skin eruptions in 81 patients affected by acute hemorrhagic edema of young children.





A nummular eruption often evolved into an annular targetoid or, less frequently, into an annular non-targetoid eruption. Finally, both the evolution of an annular non-targetoid into an annular targetoid eruption and, less frequently, the opposite were also reported.

#### 4. Discussion

Acute hemorrhagic edema of young children is typically confined to the skin. Textbooks and reviews state that extensive edema and round (either nummular or annular) eruptions characterize this condition [1-4]. The results of this careful review point out that the rash of this vasculitis is more heterogeneous than so far believed and may be summarized and discussed as follows.

Tenderness (or pain), induration and absent indentation after pressure characterize skin edema in most children with acute hemorrhagic edema. In our experience, warmth is a further feature. Terms such as acute inflammatory skin edema or, more rarely, non-infectious pseudo-cellulitis have been used to denote this rare but peculiar form of skin edema [10].

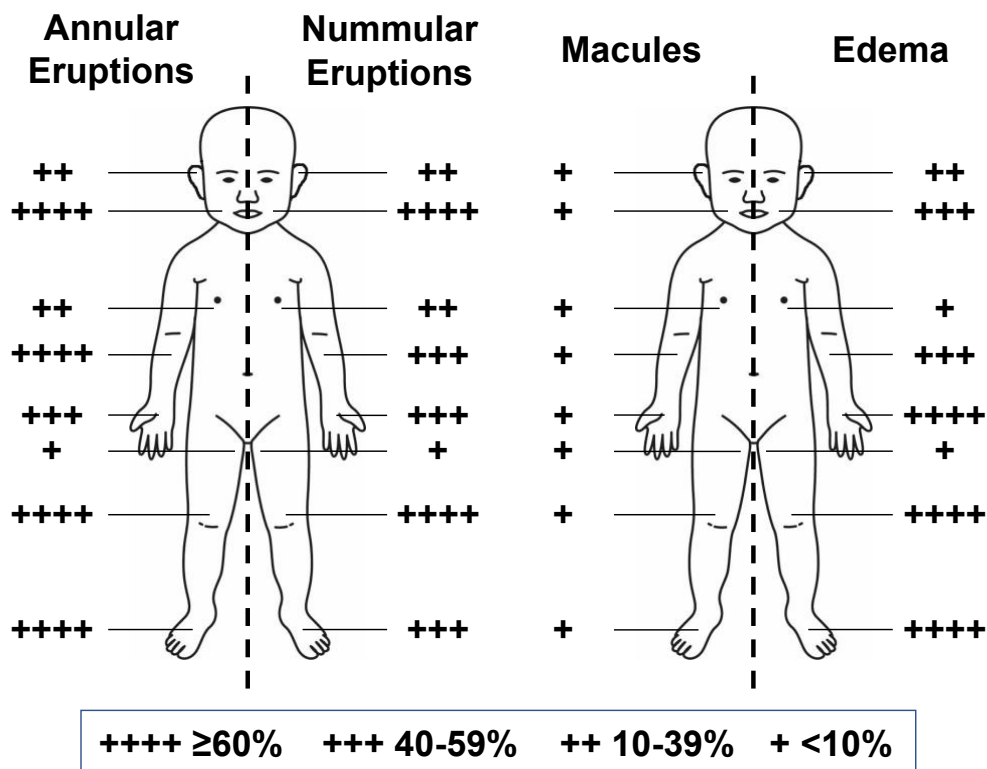
The vast majority of children present with both nummular and annular eruptions. In addition to annular eruptions in strict sense, many children present with polycyclic or arciform eruptions. On the other hand, annular eruptions in broad sense may be either

non-targetoid (i.e. with only two zones of color) or targetoid (i.e. with three zones of color).

Purpuric eruptions and ecchymoses are reported in the majority of cases (sometimes in association with petechiae). Macules and both simple and papular wheals may also occur. Scratch marks, specific signs associated with pruritus, are uncommon.

The mentioned skin eruptions and edema are distributed symmetrically, as illustrated in Figure 3.

**Figure 3.** Sketch depicting the distribution of annular or nummular eruptions, macules and edema in acute hemorrhagic edema of young children.



The initial eruption may be either a simple or papular wheal or a macule that evolves into a nummular or, less frequently, directly an annular eruption. Nummular eruptions successively evolve into annular ones. Finally, both the evolution of an annular non-targetoid into a classic annular targetoid eruption and, less frequently, the opposite may also occur.

Non-targetoid and especially targetoid annular eruptions are the classic hallmark of erythema multiforme [11, 12]. However, recent reports suggest that no more than one quarter of children with the mentioned skin eruption suffer from erythema multiforme [13, 14]. In this age group, acute ordinary or multiformis urticaria and acute hemorrhagic edema underlie, in the vast majority of cases, targetoid-like eruptions [13-15]. Since erythema multiforme is rare before the age of 4 years, acute hemorrhagic edema accounts for targetoid-like eruptions in many children 3 years or less of age. The rather unfortunate term "infantile erythema multiforme" has been sometimes utilized in the past to denote acute hemorrhagic edema of young children [14]. Syphilis and

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paintball injuries are further rare causes of targetoid or non-targetoid annular eruptions in childhood [13-15].

Dispute exists as to whether immunoglobulin A vasculitis and acute hemorrhagic edema of young children are different clinical features of the same disease or if, on the contrary, are separate diseases. Some believe that acute hemorrhagic edema is the infantile variant of immunoglobulin A vasculitis. This statement is sustained by a report documenting the concomitant appearance of acute hemorrhagic edema and immunoglobulin A vasculitis in first degree-relatives [16]. Cases also exist of children with findings overlapping between the two vasculitides [17]. On the other hand, there are sufficient data to consider acute hemorrhagic edema a distinct entity, including the failure to detect depositions of immunoglobulin A in most biopsy specimens and the skin-limited involvement. The present systematic analysis, which documents type and distribution of skin eruptions in acute hemorrhagic edema, further supports this assumption. A report recently released by some of us identified a truncating variant in the HCK gene in four subjects affected by acute hemorrhagic edema [18]. This gene is located on chromosome 20 and encodes for a protein-tyrosine kinase that is predominantly expressed in hemopoietic cells. Furthermore, aberrant activity of the HCK gene has been noted in inflammatory and cancer diseases. Further investigations are warranted to determine if and how the HCK gene is involved not only in acute hemorrhagic edema but also in immunoglobulin A vasculitis.

The most important limitation of the present analysis comes from the small number of published articles on children affected by acute hemorrhagic oedema, which were published over 50 years. A second limitation is that the analysis incorporated exclusively data from case reports. Finally, because the diagnosis of acute hemorrhagic edema is mostly made on clinical grounds, diagnostic accuracy depends on experience and skills of the examiner.

## 5. Conclusions

This is the first study which carefully characterizes type, distribution and evolution of skin eruption in acute hemorrhagic edema of young children. These data help clinicians to rapidly and noninvasively make the clinical diagnosis of this apparently alarming but very benign vasculitis.

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## References

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1. Smitt JH, Vermeer MH, Faber WR. Acute hemorrhagic edema of infancy (AHEI). *Clin Dermatol*. 2002;20(1):2-3. doi: 10.1016/s0738-081x(01)00232-2.
  2. Fiore E, Rizzi M, Ragazzi M, Vanoni F, Bernasconi M, Bianchetti MG, Simonetti GD. Acute hemorrhagic edema of young children (cockade purpura and edema): a case series and systematic review. *J Am Acad Dermatol*. 2008;59(4):684-695. doi: 10.1016/j.jaad.2008.06.005.
  3. Ting TV. Diagnosis and management of cutaneous vasculitis in children. *Pediatr Clin North Am*. 2014;61(2):321-346. doi: 10.1016/j.pcl.2013.11.007.
  4. Lava SAG, Milani GP, Fossali EF, Simonetti GD, Agostoni C, Bianchetti MG. Cutaneous manifestations of small-vessel leukocytoclastic vasculitides in childhood. *Clin Rev Allergy Immunol*. 2017;53(3):439-451. doi: 10.1007/s12016-017-8626-3.
  5. Rinoldi PO, Bronz G, Ferrarini A, Mangas C, Bianchetti MG, Chelleri C, Lava SAG, Milani GP. Acute hemorrhagic edema: uncommon features. *J Am Acad Dermatol*. 2020;S0190-9622(20)33224-2. doi: 10.1016/j.jaad.2020.12.033.
  6. Pellanda G, Lava SAG, Milani GP, Bianchetti MG, Ferrarini A, Vanoni F. Immune deposits in skin vessels of patients with acute hemorrhagic edema of young children: A systematic literature review. *Pediatr Dermatol*. 2020;37(1):120-123. doi: 10.1111/pde.14041.
  7. Snow IM. Purpura, urticaria and angioneurotic edema of the hands and feet in a nursing baby. *JAMA*. 1913;61(1):18-19. doi:10.1001/jama.1913.04350010020008.
  8. Nast A, Griffiths CE, Hay R, Sterry W, Bologna JL. The 2016 International League of Dermatological Societies' revised glossary for the description of cutaneous lesions. *Br J Dermatol*. 2016;174(6):1351-1358. doi: 10.1111/bjd.14419.
  9. Brown GW, Hayden GF. Nonparametric methods. Clinical applications. *Clin Pediatr (Phila)*. 1985;24(9):490-8. doi: 10.1177/000992288502400905.
  10. Marchionne EM, McCalmont TH, Pincus LB, LeBoit PE, Fox LP. Acute inflammatory edema: A mimicker of cellulitis in critically ill patients. *J Am Acad Dermatol*. 2019;81(4):931-936. doi: 10.1016/j.jaad.2019.05.083.
  11. Hughey LC. Approach to the hospitalized patient with targetoid lesions. *Dermatol Ther*. 2011;24(2):196-206. doi: 10.1111/j.1529-8019.2011.01395.x.
  12. Wolf R, Lipozencic J. Shape and configuration of skin lesions: targetoid lesions. *Clin Dermatol*. 2011;29(5):504-508. doi: 10.1016/j.clindermatol.2010.09.020.
  13. Siedner-Weintraub Y, Gross I, David A, Reif S, Molho-Pessach V. Paediatric Erythema Multiforme: Epidemiological, clinical and laboratory characteristics. *Acta Derm Venereol*. 2017;97(4):489-492. doi: 10.2340/00015555-2569.
  14. Milani GP, Lava SAG, Bianchetti MG. Differential diagnosis of erythema multiforme in childhood: A Comment to Siedner-Weintraub et al. *Acta Derm Venereol*. 2018;98(1):169. doi: 10.2340/00015555-2785.
  15. Mathur AN, Mathes EF. Urticaria mimickers in children. *Dermatol Ther*. 2013;26(6):467-475. doi: 10.1111/dth.12103. PMID: 24552410.
  16. Gattorno M, Picco P, Vignola S, Di Rocco M, Buoncompagni A. Brother and sister with different vasculitides. *Lancet*. 1999;353(9154):728. doi: 10.1016/s0140-6736(98)05109-5.
  17. Nussinovitch M, Prais D, Finkelstein Y, Varsano I. Cutaneous manifestations of Henoch-Schönlein purpura in young children. *Pediatr Dermatol*. 1998;15(6):426-428. doi: 10.1046/j.1525-1470.1998.
  18. Bronz G, Lava SAG, Ramelli GP, Luedeke M, Biskup S, Mainetti C, Ferrarini A. Whole exome sequencing revealed a candidate gene for Finkelstein-Seidlmayer disease. *Am J Pediatr*. 2019;5(4):196-199. doi: 10.11648/j.ajp.20190504.15.