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A Hub-and-Spoke Network Organizational Model in Liguria (Italy) for managing anaphylaxis in pediatric age: a retrospective analysis

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Abstract

Background: Anaphylaxis represents one of the most severe and potentially life-threatening emergencies in children. However, significant gaps persist in real-world recognition, management, and long-term follow-up of affected patients despite established diagnostic criteria and treatment guidelines. This study provides a comprehensive overview of the epidemiology, pathogenesis, and management of pediatric anaphylaxis, contextualized by a multicenter, retrospective observational study conducted within the "Gaslini Diffuso" Hub-and-Spoke Allergology Network in the Liguria region of Italy.

Methods The study cohort included children aged 0 to 16 years who met the 2006 NIAID/FAAN diagnostic criteria for anaphylaxis. Data were retrospectively collected from the Hub center, IRCCS G. Gaslini in Genoa, covering the period from 2013 to 2023, and from five satellite spoke centers, covering the period from 2022 to 2023. The primary objective was to evaluate and compare diagnostic and therapeutic management practices across these Hospital Pediatric Units.

Results The results demonstrate critical disparities in clinical practice across the network, specifically regarding the frequency of epinephrine administration, the utilization of tryptase measurement, the duration of clinical observation, and the rates of epinephrine autoinjector prescription upon discharge. These variations highlight significant differences in adherence to standardized protocols between the Hub center and the Spoke centers.

Conclusions: These findings underscore the urgent need to implement unified, standardized clinical protocols across a regional network. The study emphasizes that structured clinical education and improved resource allocation are essential to ensure consistent, high-quality care for pediatric patients experiencing anaphylactic episodes across both Hub and Spoke clinical settings.

Introduction

Anaphylaxis represents a severe, systemic hypersensitivity reaction characterized by rapid onset and potentially fatal outcomes [1]. Typically manifesting within minutes of exposure to a triggering agent, the condition involves multiple organ systems simultaneously, with clinical presentations spanning cutaneous, respiratory, cardiovascular, gastrointestinal, and neurological domains. Because delays in medical intervention, particularly in administering intramuscular epinephrine, are directly associated with increased morbidity and mortality, early recognition and prompt treatment remain the primary clinical imperatives [1-3].

The foundational diagnostic standard for this condition was established by the 2006 NIAID/FAAN symposium, which introduced a three-criterion framework for clinicians to identify anaphylaxis. Under this paradigm, the diagnosis is considered highly likely if a patient meets one of three scenarios: acute onset with cutaneous or mucosal involvement accompanied by respiratory or cardiovascular compromise; exposure to a probable allergen resulting in involvement of two or more organ systems; or, in the context of exposure to a known allergen, isolated arterial hypotension [2]. These criteria have been

widely adopted and were confirmed by subsequent practice parameters in 2023 [3]. Namely, the diagnostic definition has continued to evolve to address challenges in identifying atypical presentations, which are particularly common in infants and toddlers who may be unable to articulate subjective symptoms such as throat tightness or pruritus. Recent advancements, formalized in the 2023 Practice Parameters, have expanded the diagnostic scope to include a fourth criterion involving isolated, sudden respiratory compromise following known allergen exposure, even in the absence of cutaneous symptoms [3]. This conceptual shift reflects a growing professional recognition that rigid adherence to classical clinical presentations often leads to the underdiagnosis of anaphylaxis. Addressing these diagnostic gaps is essential to ensure that clinicians do not miss critical treatment windows, thereby preventing the potentially catastrophic consequences associated with unrecognized or inadequately managed anaphylactic episodes.

Pathogenetic Mechanisms

The pathogenesis of anaphylaxis is defined by a complex interplay of immunological and non-immunological pathways that culminate in systemic mast cell and basophil degranulation. The most prevalent mechanism is IgE-mediated, in which specific allergen binding to IgE antibodies bound to the surface of effector cells triggers the rapid release of potent vasoactive mediators, including histamine, tryptase, leukotrienes, and platelet-activating factor [4]. This pathway accounts for the majority of severe reactions to food allergens, b-lactam antibiotics, and *Hymenoptera* venom.

Beyond IgE-dependent activation, anaphylaxis may also be precipitated by immunological mechanisms that bypass the IgE pathway, such as those involving immune complex formation and subsequent complement activation [5]. These mechanisms are characteristically associated with reactions to blood products and various biological agents. In contrast, direct non-immunological pathways facilitate mast cell degranulation independent of antibody binding. Agents such as non-steroidal anti-inflammatory drugs (NSAIDs), radiocontrast media, and opioids are known to engage these pathways, leading to the clinical syndrome through mechanisms distinct from traditional sensitization [6]. Finally, exercise-induced anaphylaxis constitutes a clinically distinct and frequently underrecognized entity [7]. Rather than functioning via a single pathway, this form of anaphylaxis involves multiple interacting mechanisms, often manifesting in the presence of specific cofactors such as food intake or NSAID use [8]. The heterogeneity of these pathogenetic processes underscores the necessity for a nuanced understanding of the diverse triggers and mechanisms that can initiate an anaphylactic episode.

Epidemiology

The epidemiological landscape of anaphylaxis remains characterized by substantial heterogeneity, primarily stemming from the historical absence of a universally accepted diagnostic definition and variability in international coding systems, such as ICD-9 versus ICD-10 [9]. A 2023 systematic review and meta-analysis of 46 articles estimated a global incidence of approximately 46 cases per 100,000 persons per year, with an alarming annual increase of 7.4% [10]. Pediatric populations exhibit particularly wide-ranging incidence rates, as evidenced by a 2019 systematic review by Wang et al., which included

59 PRISMA-selected studies and documented rates ranging from 1 to 761 cases per 100,000 children annually [11]. In Europe, individuals under the age of 18 account for over 25% of all anaphylaxis cases, with the peak incidence consistently recorded in the 0–4 year age group [12]. Conversely, the highest case-fatality rates are observed in adolescents and young adults, an observation often linked to behavioral risk factors, suboptimal adherence to prescribed emergency medications, and delayed access to clinical care [13].

Therefore, these epidemiological data underscore a critical public health challenge. The steady global increase in anaphylaxis incidence necessitates the implementation of coordinated, structured prevention strategies, including enhanced educational programs tailored for healthcare professionals, patients, and their families to mitigate the rising clinical and societal burden of this systemic condition.

Risk Factors and Triggers in Pediatric Anaphylaxis

The etiology of pediatric anaphylaxis is characterized by a distinct profile of triggers, with food allergens remaining the predominant cause in children, in marked contrast to adult populations, where drug-induced reactions and *Hymenoptera* venom are more frequently implicated [14-16]. The allergen sensitization profile exhibits a significant age-dependent progression: in the first 24 months of life, cow's milk proteins and hen's egg are the primary causative agents. As patients transition into school age, this landscape shifts, with tree nuts, peanuts, and fish emerging as the leading triggers after age 6 [17,18]. Such developmental changes in sensitization patterns are critical for clinical practice, as they dictate the focus of longitudinal dietary management counseling and inform the strategic planning of allergen-specific immunotherapy.

The identification of high-risk profiles for severe or fatal anaphylaxis is paramount in pediatric care [19]. Among the most critical comorbidities is uncontrolled bronchial asthma, which dramatically amplifies the risk of lethal bronchospasm during a systemic allergic event [20]. Clinical outcomes are also heavily influenced by the timeliness of intervention; even a delay of a few minutes in administering epinephrine significantly may increase the risk of biphasic reactions and mortality [21]. The adolescent age group is particularly vulnerable, often due to complex psychosocial factors, including risk-taking behaviors, suboptimal compliance with prescribed epinephrine autoinjectors, and a reluctance to seek medical care promptly [22]. As a result, a comprehensive risk assessment must therefore account for the convergence of clinical and patient-level factors. Beyond adolescent age and uncontrolled asthma, additional markers of heightened severity include a history of prior severe reactions, concomitant use of beta-blockers or ACE inhibitors [23]. Furthermore, systemic mastocytosis and elevated baseline tryptase levels are established biomarkers of increased reaction severity [24]. Mitigating these risks requires a robust clinical strategy centered on early, decisive epinephrine administration, the consistent availability of emergency autoinjectors, and personalized educational programs designed to address the unique challenges of pediatric and adolescent patients [25].

Diagnostic Criteria and Clinical Recognition

The diagnostic framework for anaphylaxis has evolved significantly to better capture its diverse clinical manifestations. Historically, the 2006 NIAID/FAAN criteria established a foundational three-scenario model based on acute onset, multisystem involvement, and exposure to known or likely allergens [2]. Building on this, the World Allergy Organization (WAO) 2020 criteria adopted a more clinically operational approach, emphasizing acute onset and systemic involvement while introducing a five-grade severity classification system; this model notably highlighted the need to identify anaphylaxis even in the absence of cutaneous symptoms [27]. Subsequently, the 2021 EAACI guidelines refined these structures by distinguishing between "confirmed" and "suspected" anaphylaxis, formalizing the role of cofactors such as exercise, NSAIDs, and alcohol in lowering the threshold for systemic reactions, and integrating serum tryptase measurement into the diagnostic workup [1]. These guidelines reinforce the critical clinical observation that cutaneous symptoms may be absent in up to 10–20% of severe anaphylactic cases.

Clinical recognition of anaphylaxis in pediatric patients presents distinct challenges due to developmental limitations and atypical physiological responses. Infants and toddlers are often unable to verbalize subjective distress, such as throat tightness or dizziness [25]. Early symptoms frequently manifest nonspecifically, with clinicians misattributing irritability, inconsolable crying, or reflux-like symptoms to non-allergic etiologies. Furthermore, bradycardia may paradoxically replace the expected tachycardia during infant shock states, complicating hemodynamic assessment [28]. The distribution of symptoms by system highlights the need for a high index of clinical suspicion, as summarized in Table 1.

Management of anaphylaxis must also account for biphasic reactions, defined as the recurrence of symptoms without new allergen exposure [29]. Published incidence rates for biphasic anaphylaxis range from 0.4% to 20%, with a 2025 Canadian study reporting an incidence of 15.94% and a mean onset time of 19 hours following the initial event [30]. Given that second episodes are often milder but carry the potential for morbidity, current clinical practice dictates structured observation periods. Patients presenting with high-risk features, such as initial hypotension, hypoxia, delayed epinephrine administration, or those requiring multiple doses, warrant prolonged observation ranging from at least 12 to 24 hours.

Treatment of Anaphylaxis: Epinephrine as First-Line Therapy

Intramuscular (IM) epinephrine, administered into the anterolateral aspect of the thigh (vastus lateralis), remains the unconditional, evidence-based first-line treatment for anaphylaxis [1]. According to the 2023 Practice Parameters, there are no age, weight, or comorbidities that contraindicate the use of epinephrine in this clinical setting [3]. The primary cause of preventable anaphylaxis fatalities is the delayed or absent administration of epinephrine; consequently, early intervention, ideally within 5–10 minutes of the onset of systemic symptoms, is the most critical determinant of clinical outcome [31,32].

The established management sequence endorsed by clinical guidelines is to recognize, treat, and observe. Treatment should prioritize immediate epinephrine injection before addressing other

pharmacological interventions. All other agents, including antihistamines, corticosteroids, bronchodilators, and intravenous fluids, must be considered strictly adjunctive and should never replace or delay epinephrine administration[1,23,24]. Antihistamines, while useful for managing cutaneous symptoms, lack efficacy in treating cardiovascular or respiratory compromise[1,25]. Similarly, corticosteroids have a delayed onset of action and are ineffective in preventing the immediate progression of systemic anaphylaxis[1,26,27]. The reliance on these adjunctive therapies as primary or sole treatments in emergency settings constitutes a dangerous misconception that necessitates ongoing clinical education. Epinephrine dosing is based on a standard concentration of 1:1000 (1 mg/mL). The recommended dose for IM administration is 0.01 mg/kg, up to a maximum single dose of 0.5 mg as summarized in Table 2 [33]. For clinical convenience and rapid deployment, autoinjector dosing is guided by weight ranges [34]. Patients weighing 7.5–15 kg should receive 0.15 mg, while those weighing 15–25 kg are typically administered 0.15–0.3 mg. For patients weighing 25-30 kg, a 0.3 mg dose is appropriate; adolescents or patients weighing 30 kg or more should receive 0.3–0.5 mg. If there is no clinical response after 5–10 minutes, a second dose is indicated, underscoring the need for clinicians always to prescribe two autoinjectors to patients at risk.

Materials and Methods

This multicenter, retrospective observational study was conducted across five pediatric centers within the Ligurian regional health network. The research was centered at the IRCCS Istituto Giannina Gaslini in Genoa, which functioned as the Hub Center, integrating services from both the Allergy Center and the Pediatric Emergency Department. Data collection at this primary site spanned a decade, from January 1, 2013, to December 31, 2023, yielding a longitudinal cohort of 168 patients who accessed to the emerging rooms. To expand the scope of the investigation, the study incorporated five Spoke Centers operating under the "Gaslini Diffuso" organizational framework, an initiative launched on July 1, 2022, to extend specialized pediatric services throughout the Liguria region. These centers included the Pediatric and Neonatology Units of Lavagna (GE) (n=13), Savona–Pietra Ligure (n=19), La Spezia (n=15), and Imperia (n=2), with data collection covering the active project period from January 1, 2022, to December 31, 2023.

The study population comprised pediatric patients aged 0 to 16 years who fulfilled the clinical diagnostic criteria for anaphylaxis as defined by Sampson et al. [35]. Cases were excluded from the analysis if a comprehensive retrospective review of medical records failed to confirm adherence to these diagnostic requirements. Clinical and demographic information for all eligible subjects was systematically recorded in a structured database. It was a retrospective study, and the cases were drawn from a database in which the patients' names were anonymized. Evaluated variables included patient age, sex, and the causal allergen class. Furthermore, the dataset captured detailed information regarding the clinical presentation, specifically the involvement of mucocutaneous, respiratory, gastrointestinal, or cardiovascular systems, and the documentation of biphasic anaphylaxis. Comprehensive data on treatment modalities were also compiled, including intramuscular epinephrine, antihistamines,

corticosteroids, nebulized epinephrine, salbutamol, oxygen therapy, and intravenous fluids, along with both acute and baseline serum tryptase measurements.

The statistical analysis was descriptive, considering the nature of this report.

Results

Figures 1,2, and 3 summarize the main findings obtained in this cases' collection. The Hub Center cohort comprised 168 patients, with a male predominance (114; 67.9%) compared with 54 females (32.1%). The mean age at the time of the acute anaphylactic episode was 7.1 years (SD 4.9). In 75% of these cases, the event represented the patient's primary anaphylactic reaction. Regarding the mode of arrival at the Emergency Department, 57.8% of patients were transported by private vehicle, while 42.2% utilized emergency medical services.

Food allergens were identified as the primary trigger in 82.7% of cases, followed by medications (8.3%), hymenoptera venom (3.0%), and cases in which no causal allergen was identified (6.0%). Among the implicated food allergens, cow's milk accounted for 30.9% of cases, followed by egg (11.5%), tree nuts (7.9%), crustaceans (6.5%), and kiwi (5.8%). An age-stratified analysis revealed a clear developmental shift in trigger etiology. In children aged 0–6 years, food allergens were responsible for 95.7% of reactions, with medications and unknown triggers accounting for 2.9% and 1.4%, respectively. In the 6–12-year age group, food allergens remained the leading cause (75.7%), followed by medications (8.6%), hymenoptera venom (5.7%), and unknown causes (10.0%). Among patients older than 12 years, food allergens accounted for 67.9% of cases, while medication-related cases increased to 21.4%, with hymenoptera venom and unknown causes accounting for 3.6% and 7.1%, respectively.

The clinical presentation was characterized primarily by cutaneous involvement (95.8%), followed by respiratory compromise (65.1%), gastrointestinal symptoms (56.6%), and cardiovascular involvement (24.7%). Severity of the reactions, assessed according to the Dribin et al. grading system, showed that 23.5% of cases were Grade 2, 18.7% Grade 3, 52.4% Grade 4, and 5.4% Grade 5. The high proportion of Grade 4 reactions highlights the clinical severity of the presentations managed at the Hub Center.

Treatment, Tryptase, and Discharge Management

Therapeutic management patterns at the Hub Center indicated significant deviations from evidence-based anaphylaxis guidelines, characterized by a marked over-reliance on adjuvant therapies. Antihistamines were administered in 89.2% of cases and corticosteroids in 87.3%, whereas intramuscular epinephrine—the universally recommended first-line treatment—was utilized in only 34.9% of patients. Adjunctive interventions included salbutamol aerosol therapy in 28.3% of cases, intravenous fluid administration in 24.1%, nebulized epinephrine in 12.7%, and oxygen therapy in 2.4%.

Biochemical assessment via serum tryptase measurement was performed with variable frequency. Acute tryptase, assayed within two hours of symptom onset, was obtained in 43.4% of cases, while

baseline tryptase, measured at least 24 hours after resolution, was documented in only 21.1%. A total of 20 patients (12%) underwent both measurements; in these cases, the 2010 Working Conference equation (acute tryptase > baseline tryptase × 1.2 + 2 ng/mL) was satisfied in 95%. Although acute tryptase levels were significantly higher in patients experiencing hypotension compared to normotensive counterparts (Mann-Whitney U test, $p = 0.017$), no statistical correlation was observed between acute tryptase levels and the overall severity grade of the anaphylactic reaction.

Regarding post-acute management and secondary prevention, the majority of patients (79.5%) were observed for 12 hours or longer, a practice reflecting a conservative approach to the potential risk of biphasic anaphylaxis, which occurred in 5.4% of the cohort. The prescription of an epinephrine autoinjector at discharge was documented in 26.5% of newly eligible patients. In 21.1% of patients, an autoinjector was already in possession, while in 1.2% of cases, the prescription was omitted due to inadequate body weight. These findings highlight a persistent gap between current clinical guidelines and real-world discharge practices.

Hub vs. Spoke Comparative Analysis

A comparative analysis of the Gaslini Diffuso network from 2022 to 2023 evaluated 83 patients across five centers, including 36 at the Hub (Gaslini Genoa), 19 at Savona–Pietra Ligure, 15 at La Spezia, 13 at Lavagna, and 2 at Imperia, the latter of which provided limited data beyond allergen classification. Analysis of management practices revealed significant variation in the administration of intramuscular epinephrine, which remained the most critical deviation from evidence-based protocols. While 52.8% of patients at the Hub received intramuscular epinephrine, utilization rates were markedly lower at the spoke centers: 21.1% in Savona–Pietra Ligure, 15.4% in Lavagna, and 6.7% in La Spezia, resulting in an overall cohort administration rate of 31.3%. In contrast, adjuvant treatments were applied consistently across all institutions, with antihistamines (86.7%) and corticosteroids (81.9%) representing the most frequently administered interventions, followed by nebulized epinephrine (19.2%), intravenous saline (18.1%), nebulized salbutamol (7.2%), and oxygen therapy (4.8%).

Observation durations of 12 hours or longer also exhibited substantial inter-institutional variability, occurring in 83.3% of Hub cases and 76.9% of Lavagna cases, compared to significantly lower rates of 31.6% at Savona–Pietra Ligure and 33.3% at La Spezia. Furthermore, discharge practices regarding the provision of epinephrine autoinjectors varied: prescriptions were documented for 27.8% of patients at the Hub, 15.4% at Lavagna, 13.3% at La Spezia, and 5.3% at Savona–Pietra Ligure.

Biochemical diagnostic practices, specifically the measurement of serum tryptase, demonstrated profound disparities reflecting differences in point-of-care laboratory infrastructure. At the Hub, acute and baseline tryptase levels were obtained in 69.4% and 30.6% of cases, respectively, and all 9 dual-measured cases satisfied the Working Conference equation. At Lavagna, acute tryptase was measured in 61.5% of patients and baseline in 15.4%, with full equation compliance observed in the 2 dual-measured cases. In La Spezia, both metrics were obtained in 13.3% of cases with 50% equation compliance, while tryptase measurement remained entirely unavailable at the Savona–Pietra Ligure

center. These results collectively highlight deep-seated differences in the availability of diagnostic tools and adherence to standardized management protocols across the regional healthcare network.

Discussion

The data from the Hub Center provide a comprehensive, decade-long portrait of the diagnostic and therapeutic management of pediatric anaphylaxis in a tertiary referral setting. The observed demographic profile, characterized by a male predominance (67.9%) and a mean age of 7.1 years at the time of the first episode, is consistent with European registry data and reflects the established epidemiology of food-driven sensitization in pediatric populations [17]. Notably, 75% of these cases represented the patient's first anaphylactic event, a finding with significant clinical implications. It underscores the lack of prior exposure to emergency protocols among families and highlights the critical need for structured education at the time of initial diagnosis and discharge.

The age-stratified distribution of allergens aligns precisely with literature from the European EAACI Pediatric Registry, with food allergens predominating across all age groups before yielding to medications and hymenoptera venom in adolescents [17]. Within the food category, cow's milk proteins emerged as the primary trigger (30.9%), a result of particular relevance to the Italian clinical context, given the high prevalence of cow's milk allergy in infancy and the associated management challenges. Furthermore, the high proportion of patients classified as Grade 4—exceeding 50% of the cohort—confirms the Hub Center's role as a tertiary reference point for the most complex and severe cases within the regional network.

The clinical management of these patients, however, revealed significant discrepancies between established guidelines and real-world practice in Liguria [1–3]. Most alarmingly, the underuse of intramuscular epinephrine remains the most clinically urgent finding. Although the administration rate at the Hub Center (34.9%) surpassed the EAACI Registry baseline of 12%—and its subsequent 25% post-activation rate—it remains markedly suboptimal given that the majority of patients presented with Grade 4 severity. The situation is more critical at spoke centers, with La Spezia reporting administration rates as low as 6.7%. The persistent over-reliance on antihistamines and corticosteroids as primary or sole therapeutic measures indicates a pervasive educational gap at all levels of care. These medications lack proven efficacy in preventing the progression of anaphylaxis or reducing mortality, and their administration must never delay or replace the use of epinephrine.

Diagnostic practices regarding serum tryptase measurement also highlight profound disparities that reflect underlying constraints in laboratory infrastructure. The validation of the Working Conference equation in 95% of dual-measured cases at the Hub confirms the biomarker's clinical utility in a pediatric setting and its reliability in distinguishing anaphylaxis from other acute allergic syndromes [36]. Moreover, the significant association observed between acute tryptase elevation and hypotension ($p = 0.017$) supports its incorporation into standardized acute diagnostic protocols. The systemic failure to measure tryptase, particularly at the Savona–Pietra Ligure center, where it was entirely unavailable,

represents a missed diagnostic opportunity that necessitates urgent correction through the provision of appropriate equipment and the implementation of mandatory protocols.

Finally, substantial inter-institutional variability was observed in post-acute care and secondary prevention. While 83.3% of Hub patients were observed for 12 hours or longer, this rate fell to 31.6% at Savona–Pietra Ligure and 33.3% at La Spezia, durations that are dangerously insufficient for high-risk patients with potential for biphasic reactions. Similarly, the discharge prescription of epinephrine autoinjectors—ranging from 27.8% at the Hub to a mere 5.3% at Savona–Pietra Ligure—represents a critical failure in secondary prevention, leaving a majority of eligible patients vulnerable to future reactions. Collectively, these findings illustrate a persistent gap between international guidelines and regional clinical practice, emphasizing the need for standardized management frameworks across the entire healthcare network.

This study represents the first systematic analysis of pediatric anaphylaxis management across a structured hub-and-spoke network in Italy, revealing clinically significant disparities in recognition and therapeutic management between the specialized tertiary referral center and peripheral pediatric emergency units. The findings demonstrate a deficit in adherence to international guidelines: anaphylaxis remains an underrecognized clinical entity, intramuscular epinephrine is underutilized in favor of antihistamines and corticosteroids, serum tryptase measurement is inconsistently applied, post-reaction observation protocols lack standardization, and the provision of epinephrine autoinjectors at discharge remains inadequate across all levels of care, even if an allergological evaluation is regularly planned and performed within ten days after Emercency Department discharge.

These disparities represent more than statistical variance; they must be resolved to prevent morbidity and the risk of more severe reactions in the future. Each delay in epinephrine administration, each missed diagnostic assessment of tryptase, and each instance of patient discharge without an autoinjector constitute avoidable risks to pediatric safety. Consequently, the implementation of standardized, network-wide clinical protocols is an immediate imperative. We propose five core recommendations to address these gaps: the implementation of network-wide, epinephrine-first acute treatment protocols; the standardization of acute and baseline serum tryptase measurement workflows across all spoke centers; the enforcement of a minimum 12-hour observation period for all patients presenting with Grade 3–5 anaphylaxis; the mandatory prescription of epinephrine autoinjectors at discharge for all eligible patients; and the development of structured educational programs targeting emergency physicians, nursing staff, and families across the Gaslini Diffuso network.

The Gaslini Diffuso framework offers a unique organizational opportunity to drive quality improvement in pediatric allergy across the Liguria region. By leveraging the Hub-and-Spoke model through shared protocols, targeted training, and systematic audits of clinical performance indicators, the network can harmonize care standards and eliminate the dangerous clinical disparities observed in this analysis. Furthermore, future prospective data collection within the network should serve not only as a tool for epidemiological surveillance but as a continuous feedback mechanism to measure the longitudinal

impact of these educational and organizational interventions. In addition, this organizational model is also well-suited for the development of telemedicine within the context of hospital-primary care integration, as demonstrated by a previous study conducted on a large sample of families with children who have celiac disease [37].

On the other hand, this study had some limitations, including its retrospective observational design, which relied on the accuracy and completeness of medical records and therefore introduced the possibility of missing, inconsistent, or non-standardized information across participating centers. Case identification based on ICD coding may also have led to underascertainment of anaphylaxis episodes, particularly if documentation was incomplete or coding practices differed between institutions. The absence of prospective, harmonized data collection further contributed to variability in documentation quality and in the availability of key clinical and laboratory variables. In particular, tryptase measurement was not available at Savona–Pietra Ligure, and substantial inter-institutional differences in laboratory infrastructure and clinical protocols may have affected the completeness and interpretation of diagnostic workup. Additional limitations relate to the distribution of the study population and the analytical approach. The hub center contributed data over a 10-year period (2013–2023), whereas the spoke centers were active only from July 2022 within the “Gaslini Diffuso” network and contributed data over a much shorter observation window (2022–2023), with markedly smaller sample sizes, including very limited data from Imperia. This imbalance reduces the robustness of comparisons across sites, and constrains the generalizability of findings from the spoke centers. Moreover, the analysis was descriptive only, without multivariable or inferential modeling, so potential confounding factors could not be formally assessed. Finally, the study was conducted in a single Italian region and included only patients who accessed emergency departments, thereby excluding cases managed in the community or milder reactions not requiring hospital evaluation. The lack of post-discharge follow-up also precluded assessment of long-term outcomes, recurrence rates, and adherence to allergy management plans, limiting insights into the broader prognostic and organizational impact of the hub-and-spoke model.

In conclusion, the clinical message derived from these data is unequivocal: for any child presenting with suspected anaphylaxis, the immediate intramuscular administration of epinephrine—rather than antihistamines or corticosteroids—is the first and only non-deferrable treatment. Every emergency department providing pediatric care must ensure that epinephrine is immediately accessible, that standardized dosing protocols are prominently displayed, and that a mandatory discharge checklist, incorporating autoinjector prescription and comprehensive family education, is strictly enforced.

Abbreviations

ACE = angiotensin converting enzyme

EAACI = European Academy of Allergy and Clinical Immunology

FAAN = Food Allergy & Anaphylaxis Network

ICD = International Classification of Diseases

NIAID = National Institute of Allergy and Infectious Diseases

NSAIDs = non-steroidal anti-inflammatory drugs

PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses

WAO = World Allergy Organization

Declarations

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Authors' contributions

MAT and VN conceptualized and designed the study. VN collected data from Gaslini Diffuso and wrote the initial draft. TB collected data from emergency department. RO revised data. IS analyzed the preliminary data and conducted the analyses. GC wrote the final version of the paper. MAT, VN, RS, and MA revised and edited the manuscript. All authors participated in the paper discussion, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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Human Ethics and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. As this was a retrospective observational study based on anonymized data routinely collected during standard clinical care in the Emergency Department, formal ethical committee approval and written informed parental consent were not required under applicable Italian regulations (Legislative Decree 196/2003 and GDPR Regulation EU 2016/679). The study was conducted with the approval of the Institutional Direction of IRCCS Istituto Giannina Gaslini. All patient data were fully anonymized prior to analysis, and no identifying information was retained in the study database.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 frequency of anaphylaxis symptoms

System	Main Symptoms	Frequency	Clinical Warning Sign
Cutaneous/Mucosal	Urticaria, angioedema, erythema, pruritus	80–90%	Absent in 10–20% of severe cases
Respiratory	Bronchospasm, stridor, dyspnea, hypoxia	40–70%	Leading cause of death
Cardiovascular	Hypotension, tachycardia, syncope, shock	30–35%	Worsens rapidly without epinephrine
Gastrointestinal	Vomiting, nausea, abdominal pain	30–45%	Often, the first symptom in children
Neurological	Altered consciousness, hypotonia, agitation	10–15%	Reflects severe hypoperfusion

Table 2 Posology of adrenaline, considering the administration route and body weight.

Weight/Age Range	Autoinjector Dose	IM Syringe Dose
7.5–15 kg (<3–4 yrs)	0.15 mg	0.01 mg/kg
15–25 kg (4–10 yrs)	0.15–0.3 mg	0.01 mg/kg
25–30 kg	0.3 mg	0.01 mg/kg
≥30 kg/adolescents	0.3–0.5 mg	0.3–0.5 mg

Figures

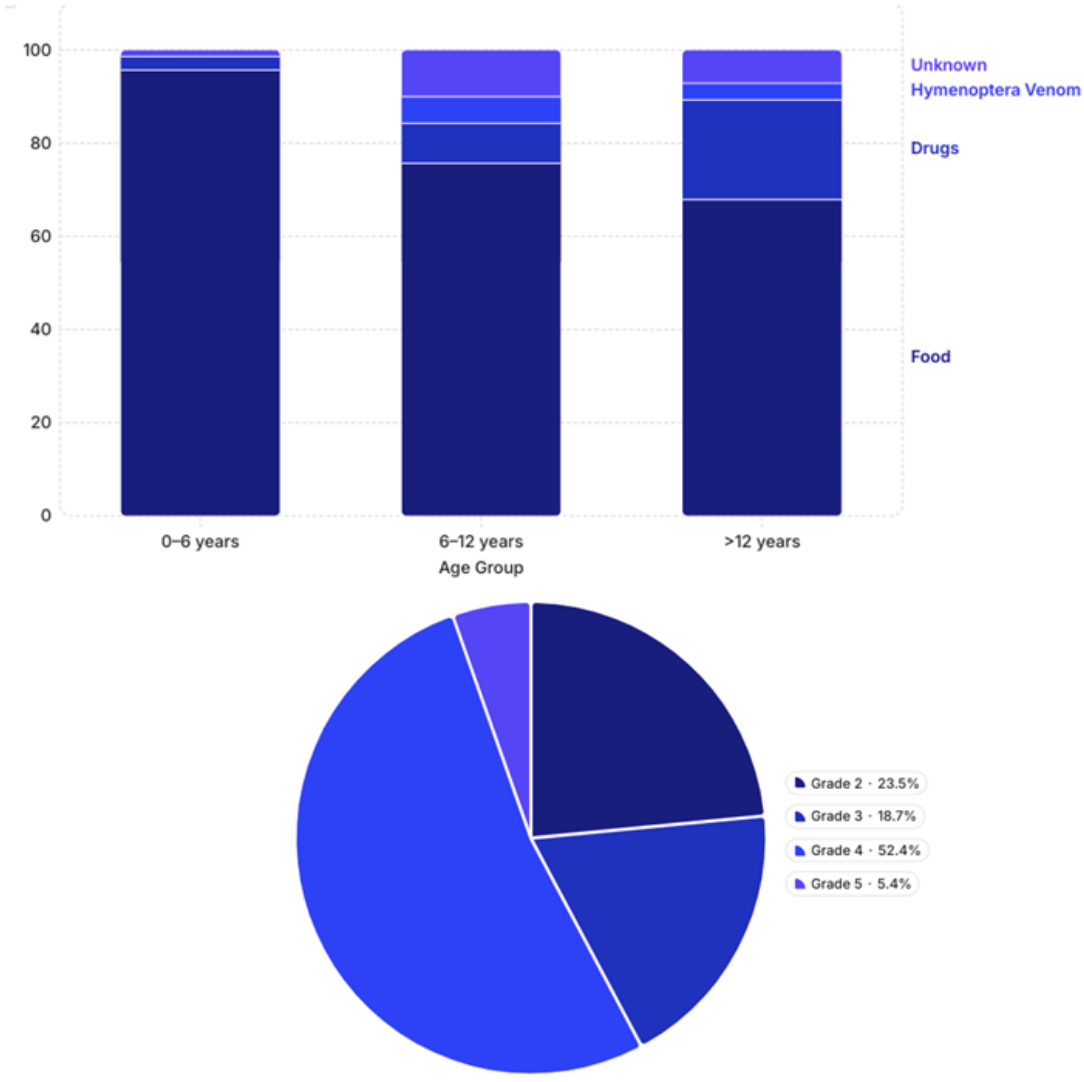


Figure 1

Age-stratified distribution of causal allergen classes and severity grading of anaphylactic reactions at the Hub Center (IRCCS G. Gaslini, Genoa) over the 2013–2023 period (n=168). Severity graded according to Dribin et al.

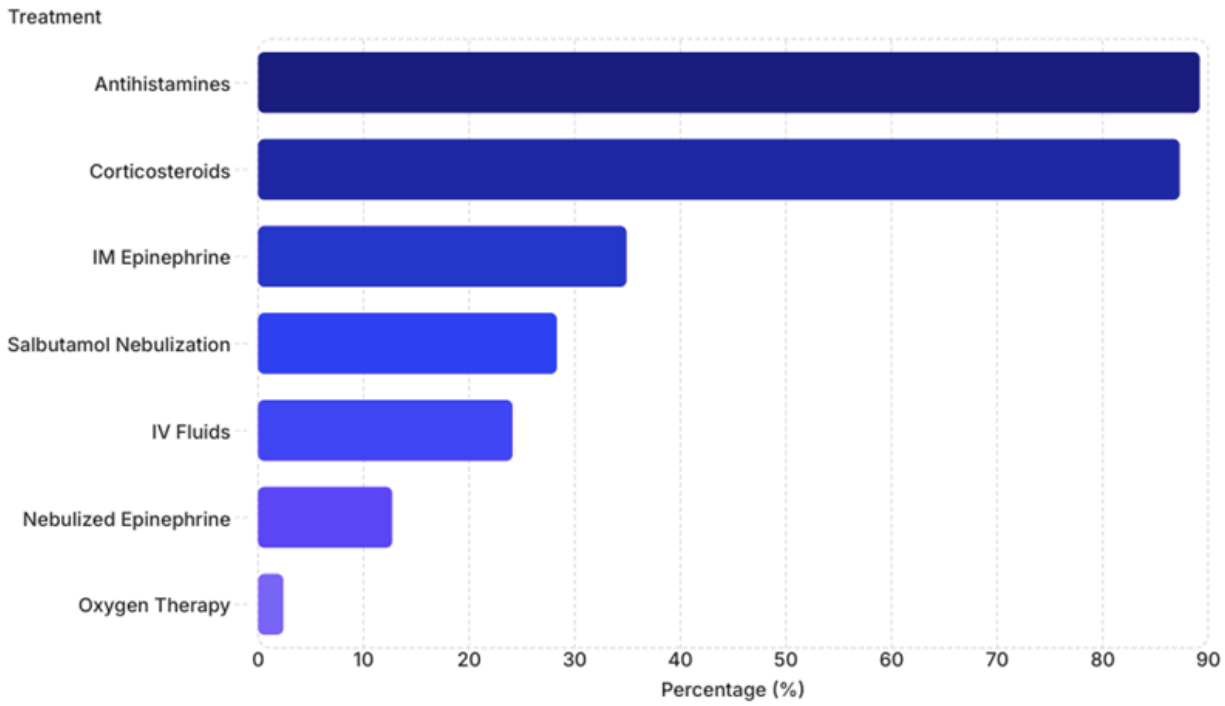


Fig 2

Figure 2

Distribution of pharmacological and supportive treatments administered during acute anaphylactic episodes at the Hub Center (IRCCS G. Gaslini, Genoa), 2013–2023 (n=168). IM = intramuscular; IV = intravenous. Note the marked underutilization of IM epinephrine relative to adjuvant therapies.

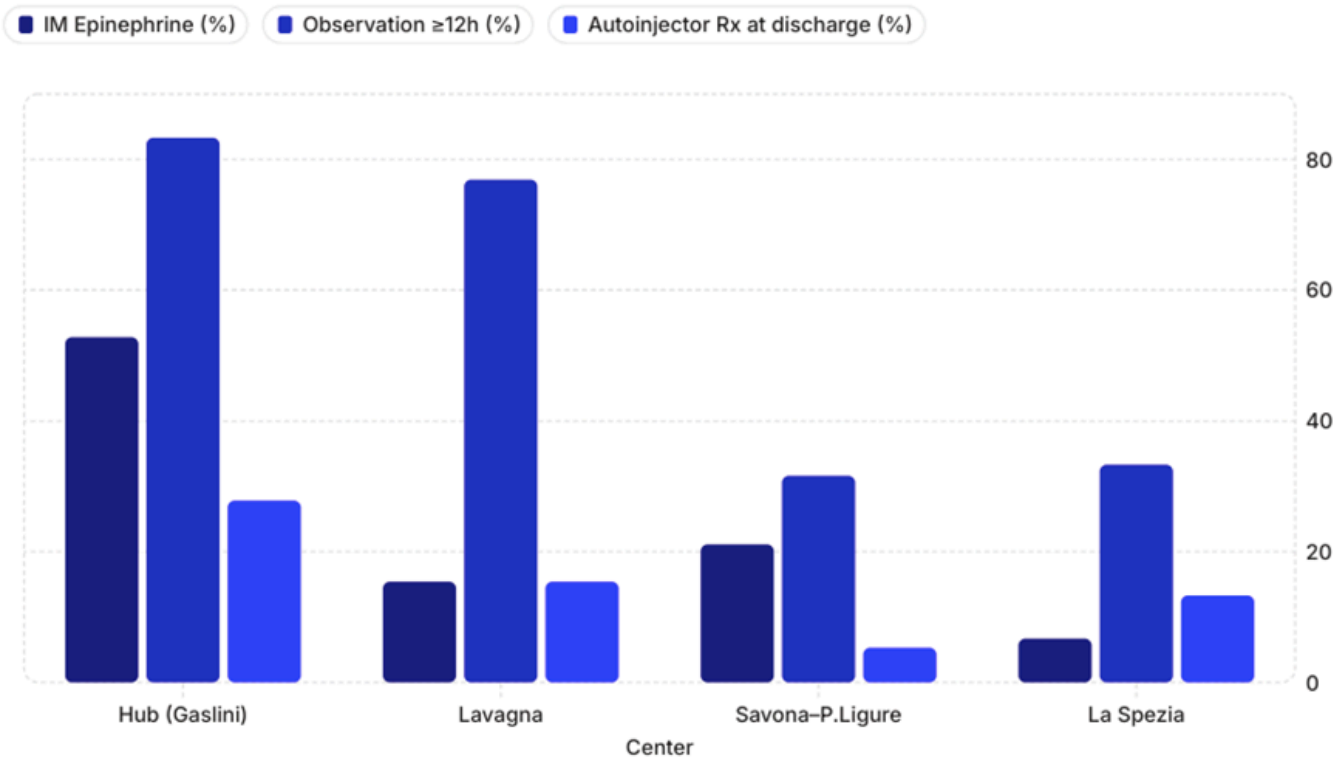


Fig 3

Figure 3

Comparison of three key anaphylaxis management indicators across the centers of the Gaslini Diffuso network during the 2022–2023 period (n=83). Rx = prescription. Data for Imperia (n=2) were insufficient for comparative analysis and are not shown.