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Anaphylaxis knowledge gaps and future research priorities: a consensus report

Timothy E. Dribin, MD[1], **David Schnadower, MD, MPH**[1], **Julie Wang, MD**[2], **Carlos A. Camargo Jr, MD, DrPH**[3], **Kenneth A. Michelson, MD, MPH**[4], **Marcus Shaker, MD, MSc**[5], **Susan A. Rudders, MD, MS**[6], **David Vyles, DO, MS**[7], **David B.K. Golden, MD**[8], **Jonathan M. Spergel, MD, PhD**[9], **Ronna L. Campbell, MD, PhD**[10], **Mark I. Neuman, MD, MPH**[4], **Peter S. Capucilli, MD**[11], **Michael Pistiner, MD, MMSc**[12], **Mariana Castells, MD, PhD**[13], **Juhee Lee, MD**[9], **David C. Brousseau, MD, MS**[7], **Lynda C. Schneider, MD**[6], **Amal H. Assa'ad, MD**[14], **Kimberly A. Risma, MD, PhD**[14], **Rakesh D. Mistry, MD, MS**[15], **Dianne E. Campbell, FRACP, PhD**[16,17], **Margitta Worm, MD**[18], **Paul J. Turner, FRCPCH, PhD**[19], **John K. Witry, MS**[20], **Yin Zhang, MS**[21], **Brad Sobolewski, MD, MEd**[1], **Hugh A. Sampson, MD**[2]

[1]Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, and the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH

[2]Division of Allergy and Immunology, Icahn School of Medicine at Mount Sinai, New York, NY

[3]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

[4]Division of Emergency Medicine, Boston Children's Hospital, and the Department of Pediatrics, Harvard Medical School, Boston, MA

[5]Dartmouth Geisel School of Medicine, and Dartmouth-Hitchcock Medical Center, Hanover and Lebanon, NH

[6]Division of Immunology, Boston Children's Hospital, and the Department of Pediatrics, Harvard Medical School, Boston, MA

[7]Section of Pediatric Emergency Medicine, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI

[8]Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD

[9]Division of Allergy and Immunology, Children's Hospital of Philadelphia, Perelman School of Medicine at University of Pennsylvania, Philadelphia, PA

[10]Department of Emergency Medicine, Mayo Clinic, Rochester, MN

[11]Rochester Regional Health, Rochester, NY

Corresponding author: Timothy E. Dribin, MD. Cincinnati Children's Hospital, 3244 Burnet Ave, Cincinnati, OH 45229. Timothy.Dribin@cchmc.org; phone: 513-636-7966; fax: 513-636-2988.

[12]Department of Pediatrics, Massachusetts General Hospital *for* Children, Harvard Medical School, Boston, MA

[13]Division of Allergy and Clinical Immunology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[14]Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, and the Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH

[15]Section of Emergency Medicine, Department of Pediatrics, Children's Hospital Colorado, Aurora, CO

[16]Sydney Medical School, University of Sydney, Sydney, Australia

[17]Department of Allergy and Immunology, Children's Hospital at Westmead, Sydney, Australia

[18]Division of Allergy and Immunology, Department of Dermatology and Allergology, Charite-Universitätsmedizin Berlin, Germany

[19]National Heart & Lung Institute, Imperial College London, London, United Kingdom

[20]Division of Emergency Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[21]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Abstract

Background: Despite a better understanding of the epidemiology, pathogenesis, and management of patients with anaphylaxis, there remain knowledge gaps. Enumerating and prioritizing these gaps would allow limited scientific resources to be directed more effectively.

Objective: To systematically describe and appraise anaphylaxis knowledge gaps and future research priorities based on their potential impact and feasibility.

Methods: We convened a 25-member multidisciplinary panel of anaphylaxis experts. Panelists formulated knowledge gaps/research priority statements in an anonymous electronic survey. Four anaphylaxis themed writing groups were formed to refine statements: 1) Population Science, 2) Basic & Translational Sciences, 3) Emergency Department Care/Acute Management, and 4) Long-Term Management Strategies & Prevention. Revised statements were incorporated into an anonymous electronic survey and panelists were asked to rate the impact and feasibility of addressing statements on a continuous 0-100 scale.

Results: The panel generated 98 statements across the four anaphylaxis themes: Population Science (29), Basic & Translational Sciences (27), Emergency Department Care/Acute Management (24), and Long-Term Management Strategies & Prevention (18). Median scores for impact and feasibility ranged from 50.0-95.0 and from 40.0-90.0. Key statements based on median rating for impact/feasibility included the need to refine anaphylaxis diagnostic criteria, identify reliable diagnostic, predictive, and prognostic anaphylaxis bioassays, develop clinical prediction models to standardize post-anaphylaxis observation periods and hospitalization criteria, and determine immunotherapy best practices.

Conclusions: We identified and systematically appraised anaphylaxis knowledge gaps and future research priorities. This study reinforces the need to harmonize scientific pursuits to optimize the outcomes of patients with and at risk of anaphylaxis.

Capsule Summary

We established and appraised anaphylaxis knowledge gaps and future research priorities; multinational, multidisciplinary collaborations are needed to resolve these gaps with the ultimate goal of optimizing patient outcomes and lessening the societal burden of anaphylaxis.

Keywords

Allergy; anaphylaxis; basic science; emergency department; feasibility; impact; population science; research; translational science

Introduction

Anaphylaxis is an acute, potentially life-threatening systemic allergic reaction.[1] The most common triggers of anaphylaxis include foods, medications, insect stings, as well as allergen immunotherapy.[2] Although a precise estimate of global burdens are unknown, the incidence of anaphylaxis is increasing in the US and abroad.[3–6] Rising case counts are attributed to medications such as chemotherapy, monoclonal antibodies, and non-steroidal anti-inflammatory drugs as well as rising rates of food induced anaphylaxis in children and adolescents.[4–8] During the past decade, ED visits for anaphylaxis in the US doubled among all patients and tripled among children.[9] The estimated lifetime individual risk of anaphylaxis is between 1% and 3%, and although rare, fatal anaphylaxis is a pressing and pervasive concern for at-risk patients and their families.[10–12]

In 2006, the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN) developed a (now) widely accepted definition of anaphylaxis and established clinical diagnostic criteria.[1] These guidelines helped standardize anaphylaxis diagnosis and management.[2] However, anaphylaxis management frequently relies on a one-size-fits all approach, despite evidence that anaphylaxis is a heterogeneous condition with differences in clinical presentation, host susceptibility and mechanistic responses that necessitate personalized short and long-term management strategies to optimize clinical care and patient outcomes.[13–16] These gaps led to a proposed refinement of the NIAID/FAAN criteria by the World Allergy Organization (WAO) in 2020,[17,18] yet it is unclear whether global consensus will be achieved for the recommended changes.

Although there have been promising advances to reduce the risk of anaphylaxis among high-risk patients (e.g. through allergen immunotherapy),[19–21] acute anaphylaxis management has not changed significantly since the advent of epinephrine auto-injectors in the 1980s.[22] Additionally, we lack a clear understanding of the global epidemiology of anaphylaxis, including factors associated with increased disease incidence across broad populations and geographies.[3,23] Knowledge gaps also exist regarding anaphylaxis pathogenesis including genetic risk factors and humoral and cellular responses, which is particularly evident with respect to human IgE-independent disease pathways.[16,24–27] Furthermore, in clinical care

there are no validated clinical or biomarker-based models which reliably predict disease courses or outcomes. Such tools could be used by providers to inform decisions about acute clinical management and the potential benefits of long-term risk-reduction strategies, including immunotherapy.[13]

To optimize clinical care and patient outcomes, it is paramount that we elucidate and devise strategies to collectively address these as well as other anaphylaxis knowledge gaps. In pursuit of these goals, the objective of this study was to systematically establish and appraise anaphylaxis knowledge gaps and future research priorities based on their perceived potential impact and feasibility. Dissemination and assimilation of these findings by clinicians, researchers, patients/families, policymakers, and funders alike will support a comprehensive, deliberative approach to conduct practice-changing research to optimize patient outcomes and diminish the societal burden of anaphylaxis.

Methods

From September 2020 through May 2021, we convened a 25-member panel of experts in the field of anaphylaxis, including allergists/immunologists and general and pediatric emergency medicine specialists from the United States (22), Australia (1), Germany (1), and the United Kingdom (1).[28,29] Panelists were selected based on their clinical expertise, prior published research, expert recommendations, and membership in research networks and anaphylaxis interest groups.[28,29] Panelists were asked to submit anaphylaxis knowledge gaps, research strategies, and future research priority statements (hereafter referred to as statements) via an anonymous electronic survey to ensure all panel members felt comfortable contributing ideas no matter their seniority or prior contributions to the field.[30] The primary investigator (TD) combined survey responses, removed duplicate statements, and organized statements into the following four predetermined themes: 1) Population Science, 2) Basic & Translational Sciences, 3) Emergency Department (ED) Care/Acute Management, and 4) Long-Term Management Strategies & Prevention.

Conference call

A conference call was conducted to ensure panel members agreed with the four proposed themes and whether there was need to reclassify statements under different themes or propose additional statements that were omitted from the initial survey. An audio recording of the call was made available to panel members who could not join the live call.

Writing groups

Following the conference call, the primary investigator solicited volunteers to serve on one of four writing groups: Population Science (JW, CC, KM, PC), Basic & Translational Sciences (JS, HS), ED /Acute Management (DV, DG, RC, MN, MP), and Long-Term Management Strategies & Prevention (MS, SR). Writing groups reviewed theme-specific statements for content, clarity, and to provide background/contextual information and were encouraged to generate additional statements if potentially important topics were omitted from the initial survey. After the draft statements were finalized, the complete list of statements was distributed to panel members for feedback and revisions to ensure statements

were written clearly and to elicit additional statements. Writing groups revised the updated statements which were incorporated in the survey as described below.[30] Following data analysis, writing groups reviewed theme-specific results and summarized key topics.

Survey

Statements finalized by writing groups were incorporated into an anonymous electronic REDCap survey.[30] Panel members were asked to answer two questions specific to each statement: 1) the *Impact* (e.g. how important would it be to answer this question to advance knowledge, drive the field, and/or improve patient outcomes directly or indirectly) of addressing the statement on a continuous 0-100 scale (0 = no impact to 100 = highest impact), and 2) the *Feasibility* (e.g. accounting for logistics, infrastructure, sample size, cost, and/or ethical considerations) of addressing the statement on a continuous 0-100 scale (0 = not feasible to 100 = highest feasibility). Panel members were encouraged to provide free text comments for statements and could choose “not applicable” if they did not have the experience or knowledge about a particular statement. Survey results for impact and feasibility were presented as median with corresponding interquartile ranges (IQRs).

The institutional review board at Cincinnati Children’s Hospital Medical Center approved this study.

Results

Panelists generated 98 statements across the four anaphylaxis themes: Population Science (29), Basic & Translational Sciences (27), Emergency Department Care/Acute Management (24), and Long-Term Management Strategies & Prevention (18). Survey results – including the number of responses for each statement, median scores for impact and feasibility with associated IQRs, as well as free text comments – are presented in Table E1 in the online repository. Median scores for impact and feasibility across the four themes ranged from 50.0-95.0 and from 40.0-90.0, respectively. Figures 1–4 depict the top 10 statements for summed median impact and feasibility scores for each anaphylaxis theme: Population Science (Figure 1), Basic & Translational Sciences (Figure 2), Emergency Department Care/Acute Management (Figure 3), and Long-Term Management Strategies & Prevention (Figure 4). A graphical representation of statements accounting for impact and feasibility scores is presented in Figure 5 (an online interactive version of the figure is available at http://dribin.pemcincinnati.com/).

Population Science

Current state—The incidence of anaphylaxis hospitalizations is increasing globally, especially for medication and food-induced anaphylaxis; but there is little data to indicate a parallel increase in anaphylaxis deaths.[3] It is challenging to determine a precise estimate of disease burden globally (or to evaluate potential causes of increased disease incidence) because current estimates are often based on ED or hospital registries, which are susceptible to diagnosis code biases and do not account for patients who do not receive in-hospital care.[3,12] This makes it difficult to establish accurate trends in anaphylaxis cases and outcomes[28] across demographic groups and regions. In addition, variations in

diagnostic criteria, miscoding and the lack of detail about specific triggers further confounds epidemiological analyses.[3] Without accurate data, it is difficult to prioritize and maximize the impact of anaphylaxis investigations.

Key statements summary—The top 10 statements for summed median impact and feasibility scores for *Population Science* are shown in Figure 1. The panel affirmed that understanding the causes and effects of anaphylaxis is dependent on a scientifically based, consensus definition of anaphylaxis, and approaches to recording and measuring it using population-based datasets and biomarkers. Developing such a definition is predicated on a clearer understanding of disease pathogenesis and epidemiology. The lack of consensus for a singular anaphylaxis definition (as well as variation in interpreting that definition) limits severity assessment/assignment and strategies to mitigate severe anaphylaxis outcomes.[17,18] Addressing these issues will help elucidate disease and outcomes risk factors, and to determine the causes and impact of prevention, diagnostic, and treatment approaches. In particular, even with an incomplete understanding of anaphylaxis biology, clinical trials of different treatment strategies are warranted.

Next steps—A multispecialty group with broad international input and representation across key global organizations should refine anaphylaxis diagnostic criteria.[1,17,18] Consideration should also be given to how such a definition relates to severity assessment,[29,31,32] and how both anaphylaxis diagnostic criteria and severity assignment should incorporate recent evidence of disease pathogenesis and phenotypes.[33,34] Additionally, the global epidemiology of anaphylaxis should be evaluated. Improved diagnostic code systems are needed to describe and detail reactions (including specific triggers) and to reflect our current understanding of allergic reaction severity and phenotypes. This would facilitate advanced disease surveillance and help evaluate barriers to improving outcomes. An improved understanding of population-based anaphylaxis trends (as well as trends in predisposing allergic conditions) will help researchers elucidate the complex, dynamic, and interdependent contributors of increased disease incidence. Studies evaluating public health measures and treatment approaches (including clinical trials) should be designed and undertaken. These advances will have the positive impact of informing not only novel public health paradigms but potentially agricultural, food production, and environmental policies to mitigate the societal burden of anaphylaxis.

Basic & Translational Sciences

Current state—There have been promising advances in our understanding of anaphylaxis pathogenesis over the past decade,[35] including identifying and understanding the role of anaphylaxis mediators in disease severity.[15,16] This includes characterizing genetic risk factors for food allergies[27] and the role of the microbiome in allergic diseases including how the intestinal microbiome may be protective against food allergies and thus potentially against anaphylaxis.[36,37] For example, a newly described genetic trait due to the duplication of alpha tryptase genes at the TPSAB1 gene locus on chromosome 16 and present in 4-6 % of the world's population is the only known genetic risk factor for anaphylaxis.[38,39] Still, we lack a clear understanding of conditions that increase the risk for anaphylaxis such as clonal and non-clonal mast cell activation disorders.[40]

Despite promising murine-based discoveries elucidating the complex pathogenesis of anaphylaxis (e.g. IgE dependent and independent pathways),[24,25] it is difficult to extrapolate these findings to humans.[41] Investigations in human subjects are challenging due to ethical concerns and the heterogonous nature of human anaphylaxis. This is further confounded by the fact that a key effector cell – mast cells – do not circulate in the blood and we currently lack simple, reliable, and minimally invasive techniques to obtain mast cells.[42]

Key statements summary—The top 10 statements for summed median impact and feasibility scores for *Basic & Translational Sciences* are shown in Figure 2. Despite recent advances, there is a need for further research before these and other discoveries can be integrated into routine clinical care. This includes evaluating the role of current biomarkers (histamine, tryptase, leukotrienes) and diagnostic modalities (e.g. basophil activation test) in improving anaphylaxis diagnosis (particularly where there is diagnostic ambiguity such as in fatal anaphylaxis), informing management, and in predicting clinical courses and future risk. There is also a need to identify other anaphylaxis mediators, which may serve as more reliable diagnostic, predictive and prognostic biomarkers. Complementary to this is the need to understand compensatory mechanisms responsible for anaphylaxis recovery,[43,44] how these mechanisms relate to the risk of severe reactions, and how therapies (epinephrine, intravenous fluids, oxygen) – including their timing – impact outcomes. Such research is challenging given ethical constraints, and the need for large, prospective cohorts to obtain the requisite clinical and biological data from patients with severe, life-threatening reactions. There is also a need to develop novel preventive treatments including targeted therapies to block IgE and the release of anaphylaxis mediators from effector cells. Likewise, there is opportunity to improve strategies (e.g. therapies, early food exposures) to prevent the development of food allergies in infancy, which is the most common cause of anaphylaxis in children.[2]

Next steps—There is need for ongoing collaboration among basic scientists and clinical/translational researchers to develop, adapt, and integrate mechanistic animal-based research strategies and techniques to study human anaphylaxis. Given the difficulties of human studies, there is a need to prospectively enroll patients at risk of anaphylaxis to facilitate longitudinal clinical and biological data acquisition and the creation of robust biological repositories. This approach will support investigations to elucidate the pathogenesis of anaphylaxis and to translate these findings to bedside care in order to improve short and long-term management strategies and patient outcomes.

Emergency Department Care/Acute Management

Current state—Although the 2006 NIAID/FAAN anaphylaxis diagnostic criteria helped standardize anaphylaxis recognition and management[1], they do not capture all anaphylaxis phenotypes and there is variation in definition interpretation (for example, how “persistent symptoms” is defined by clinicians in the context of an acute reaction). The WAO recently proposed refinements to the NIAID/FAAN criteria, yet the impact of these recommendations on acute management is uncertain.[17,18] There is also variation in the use of intramuscular epinephrine to treat anaphylaxis, with significant underuse to treat anaphylaxis and overuse to treat non-anaphylaxis (such as isolated angioedema). Furthermore, there are no validated

decision aids to determine which persistent and/or biphasic symptoms[28] warrant treatment with epinephrine versus those that do not. There are also no prospectively derived and validated prediction models to inform the duration of ED observation periods or hospitalization criteria, nor have there been definitive randomized controlled trials (RCTs) to standardize the use of adjunctive anaphylaxis therapies.[2,45] These knowledge gaps may contribute to underuse of epinephrine and overuse of ineffective medications as well as prolonged ED lengths of stay, unnecessary hospitalizations, and undue healthcare costs.[2,45–48]

Key statements summary—The top 10 statements for summed median impact and feasibility scores for *Emergency Department Care/Acute Management* are shown in Figure 3. The panel recognized the need to develop improved diagnostic and management strategies for infants and young children presenting to the ED with anaphylaxis, as signs and symptoms within this age group are often difficult to discern, and may overlap with normal behavior.[49,50] The assignment of reaction severity and its utility in guiding acute treatment and/or need for in-hospital observation needs to be determined and validated.[28,29,31,32] The panel identified the need to explore the mechanism of action, pharmacokinetics/pharmacodynamics, and clinical outcomes of epinephrine given by different routes/devices, including non-injectable delivery systems. This includes evaluating what constitutes delayed epinephrine administration and the degree to which this increases the risk for adverse outcomes (including refractory and/or biphasic reactions).[28] There is also a need to clarify and disseminate data about shelf-life and temperature requirements of epinephrine. RCTs are needed to evaluate the efficacy of adjunctive anaphylaxis therapies including systemic steroids and H_1 and H_2 antagonists.[2,51] Such studies will be resource intensive, as they require large patient enrollments and because of perceived lack of equipoise given the routine use of these medications in current practice.[2] Lastly, the panel identified the need to evaluate how to best implement and standardize anaphylaxis action plans and epinephrine auto-injector (EAI) prescription programs.

Next steps—The panel emphasized the need for high-quality multisite prospective observational and interventional studies to improve patient outcomes. This line of research is less feasible owing to the challenge of timely ED based enrollment, randomization, and collecting accurate longitudinal data to power predictive models. Despite existing obstacles, developing and refining novel enrollment, data collection, and follow-up procedures will help the ED become not only a clinical laboratory to optimize management strategies but also a biological laboratory to support innovative translational research through refined biospecimen collection processes.

Long-Term Management Strategies & Prevention

Current state—As outlined in international anaphylaxis guidelines (including from the American College of Allergy, Asthma, and Immunology/American Academy of Allergy, Asthma & Immunology, the European Academy of Allergy and Clinical Immunology, and the WAO), existing strategies to prevent anaphylaxis are predicated on allergen avoidance, allergen immunotherapy, drug desensitization protocols, and precautionary observation for high risk medications and procedures.[18–20,52,53] Although food allergen immunotherapy

shows promise in reducing the risk of anaphylaxis from accidental ingestion, the evidence clearly indicates an increased risk of anaphylaxis during treatment.[54] However, anaphylaxis in the context of a treatment dose given in a controlled setting (where there is anticipation of a reaction) may be distinct from anaphylaxis secondary to unintended allergen exposure in the community. Choosing preventative therapies requires patient-centered discussions regarding potential risks and benefits. The benefits of any allergen immunotherapy (which may include improved quality of life in addition to a reduced risk of anaphylaxis) must be weighed against potential risks, including treatment-related anaphylaxis.[54–56] While current practice often requires universal in-clinic observation for patients to receive certain therapies (e.g. allergen immunotherapy), the health and economic impacts of such practices are not equally distributed across the population.[57–59]

Key statements summary—The top 10 statements for summed median impact and feasibility scores for *Long-Term Management Strategies and Prevention* are shown in Figure 4. The panel identified the need to improve our understanding of immunotherapy best practices, including the effectiveness of allergen immunotherapy (AIT) at more prolonged dosing intervals and the ideal duration of AIT in high-risk patients. Other priorities include determining best practices for AIT and identifying and addressing barriers to implementing research evaluating earlier allergen introduction as a food allergy prevention strategy. There is a need to explore the degree to which immunotherapy protocols could be adapted in specific patient-preference sensitive contexts – for example performing AIT maintenance dosing in the non-medically observed setting for eligible patients. Regarding the management of drug allergy, there is a need to understand how variations in practice contribute to a failure to de-label those with an incorrect diagnosis and under-utilization of drug desensitization. Knowledge gaps also exist related to patient/family perspectives about longer-term anaphylaxis management, specifically the need to determine how patient risk perceptions may drive clinically meaningful outcomes and the need to address barriers to EAI use (including cost). Finally, understanding the impact of the determinants of health literacy would promote the development of improved shared decision-making models and patient decision aids.

Next steps—Addressing these gaps requires a concerted and sustained effort (as well as the resources) to design and execute transformative studies. Clarifying patient-centered approaches to long-term anaphylaxis management requires multimodal and potentially multidisciplinary research approaches. Research programs should seek to incorporate mixed-methods study designs to ensure study outcomes and interventions are truly patient-centric and result in optimal, equitable health outcomes for all patients.[60] Mixed-methods study designs (combining quantitative and qualitative research components) are ideal because they strengthen the conclusions, impact, and validity of research findings.[61] Additionally, since anaphylaxis impacts a wide range of patients, clinicians, and community members, diverse stakeholder representation should be included when designing and conducting studies.

Discussion

We convened a multidisciplinary group of anaphylaxis experts to establish anaphylaxis knowledge gaps and future research priorities, appraise their potential impact and feasibility,

and propose strategies to address them. Dissemination and uptake of the knowledge gaps and research priorities outlined in this manuscript by clinicians, researchers, funders, and policymakers will help harmonize, accelerate and direct research efforts to improve the care and outcomes of patients with and at risk of anaphylaxis.

Our study methodology improves upon smaller studies leveraging expert opinion, because we convened a multispecialty, multi-national panel representing diverse clinical and scientific experience, and because we applied a rigorous consensus methodology. Consequently, study results are less likely to be constrained to a limited patient population, clinical setting, causative agent, research concentration or study design. Additionally, we included statements that did not directly reference *anaphylaxis* but instead were specific to advancing our understanding of the pathogenesis, management, and/or prevention of conditions that predispose patients to anaphylaxis (e.g. food, medication, venom allergies). This was intentional, given that scientific questions related to common predisposing conditions are connected with advancing anaphylaxis research, and only by addressing these complementary topics will we optimize short and long-term patient outcomes. By considering impact and feasibility and encouraging panelists to provide contextual details specific to study execution (e.g. study design and limitations, patient population, cost, and ethical considerations), we hope our findings will serve as an actionable framework and tool for researchers and funders to identify, prioritize and strategically address the most pressing scientific questions in the field of anaphylaxis.

Towards a precision medicine model of anaphylaxis care

Clinical care and research is hampered by the lack of global, consensus anaphylaxis diagnostic criteria and the assignment of reaction severity and outcomes. There is a need to transform care away from the one-size-fits all care model to a precision medicine care model that accounts for host susceptibility (genetics, environmental exposures, comorbidities, socioeconomics), causative agents and host responses (phenotypes, endotypes) to inform targeted short and long-term management and therapeutic strategies and improved patient outcomes.[13,62] Central to this is a need to better describe the global epidemiology of anaphylaxis, which will help align investigations and systematically evaluate their longitudinal impact. The International Classification of Diseases-11 is also an important advancement to improve the codification of anaphylaxis and may provide more accurate global epidemiological data.[63] Although the 2006 NIAID/FAAN anaphylaxis diagnostic criteria are validated and widely used in clinical care and research,[1,64,65] there is inconsistent interpretation and application of the criteria in clinical care.[17,18,31] Specifically, there is a need to account for milder patient reported symptoms, symptoms specific to infants, the severity and duration of gastrointestinal symptoms (as well as the causative agent), the potential for patients to have delayed onset of symptoms after allergen exposure, and patients who develop acute, isolated respiratory compromise after known/likely allergen exposure.[17,18] These definitional limitations contribute to variation in determining which persistent and/or recurrent symptoms necessitate treatment with epinephrine.

To advance clinical care we must move beyond relying solely on patient and reaction characteristics (e.g. triggers, phenotypes) and response to therapies to inform clinical

decision making. Instead, there is need to understand the role of currently available but not widely used biomarkers and diagnostic modalities[13,16,26,66] as well as novel mediators, and whether and how these biomarkers can be translated into routine bedside care to optimize management strategies. We imagine that clinicians will one day be able to obtain point-of-care biomarkers to confirm the diagnosis of anaphylaxis when there is diagnostic uncertainty and to standardize management decisions including the need for prolonged observation periods/hospitalization to monitor for biphasic reactions. These advances may also promote the discovery of biochemical targets for drug development including efficacious abortive (in cases of refractory anaphylaxis), preventive (e.g. novel biologies, Bruton's tyrosine kinase inhibitors)[67], and curative therapies.

Finally, crucial to the delivery of precision medical care is the need to evaluate and account for the perspectives and preferences of patients and families from diverse racial/ethnic, cultural, religious, and socioeconomic backgrounds. This will ensure that evidence-based practice parameters and care pathways will be tailored to the needs of patients/families in the context of the communities in which they live, learn, and grow. Such an approach will ensure that management and treatment strategies result in optimal, equitable health outcomes for all patients.[68]

To improve patient outcomes and decrease the societal burden of anaphylaxis, we encourage the further development of innovative, collaborative research networks with experts in basic science, clinical, translational, population, health services, and public health research, pharmaceuticals, bioengineering, and healthcare policy. Only through strategic, integrated research networks will we be able to advance our understanding of the epidemiology and pathogenesis of anaphylaxis and translate these discoveries into novel and efficacious diagnostic, management, and therapeutic strategies.

Limitations

This study is subject to limitations, especially the potential that key statements/themes or research strategies (e.g. technologies such as e-health) were omitted.[69] To address this issue, we sought input from a large panel of researchers with broad expertise and encouraged panel members to suggest additional statements during all study phases to ensure important topics were not omitted. Our study is also limited by the absence of perspectives from patients, clinicians from other specialties, allied health providers, and community members. Because the preponderance of panelists were from the US (with no representatives from Asia, Africa, or Latin America), we recognize that the statements outlined in this study do not encompass all anaphylaxis knowledge gaps and research priorities in different cultural or social backgrounds – and encourage researchers globally to build upon our findings to pursue other relevant and innovative research questions.

Panel members may have rated the impact and/or feasibility of statements differently based on the potential to employ different study designs to address the same statement. For example, a retrospective or prospective study could be used to address the statement, "There is need to validate the severity grading system for acute allergic reactions."[29] Although a prospective study would be more impactful than a retrospective study, it would be less feasible. The panel intentionally did not limit statements to only "gold standard" study

designs given grant applications to conduct clinical practice changing research are often based on pilot data from lower impact/high feasibility studies. We attempted to account for potential differences in statement interpretation by including a large panel of experts (25), providing IQRs, and including free text comments. Additionally, some statements included specific study designs (e.g. an RCT to evaluate the efficacy of systemic steroids) if only one methodological approach could sufficiently address a research question, and thus results for these statements should be less subject to differences in interpretation.

Conclusions

We established and systematically appraised the potential impact and feasibility of addressing anaphylaxis knowledge gaps and future research priorities. Our intention is that this study will serve as a foundation and catalyst for purposeful, collaborative research to accelerate scientific discoveries and to translate these discoveries into novel management and therapeutic strategies to optimize patient care and clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AIT	allergen immunotherapy
EAIs	epinephrine auto-injectors
ED	emergency department
IQR	interquartile range
NIAID/FAAN	National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network
OIT	oral immunotherapy
RCT	randomized controlled trial
VIT	venom immunotherapy
WAO	World Allergy Organization

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Clinical Implication

The anaphylaxis knowledge gaps and research priorities outlined in this study provide a framework for clinicians and researchers to align and accelerate scientific discoveries to optimize patient outcomes.

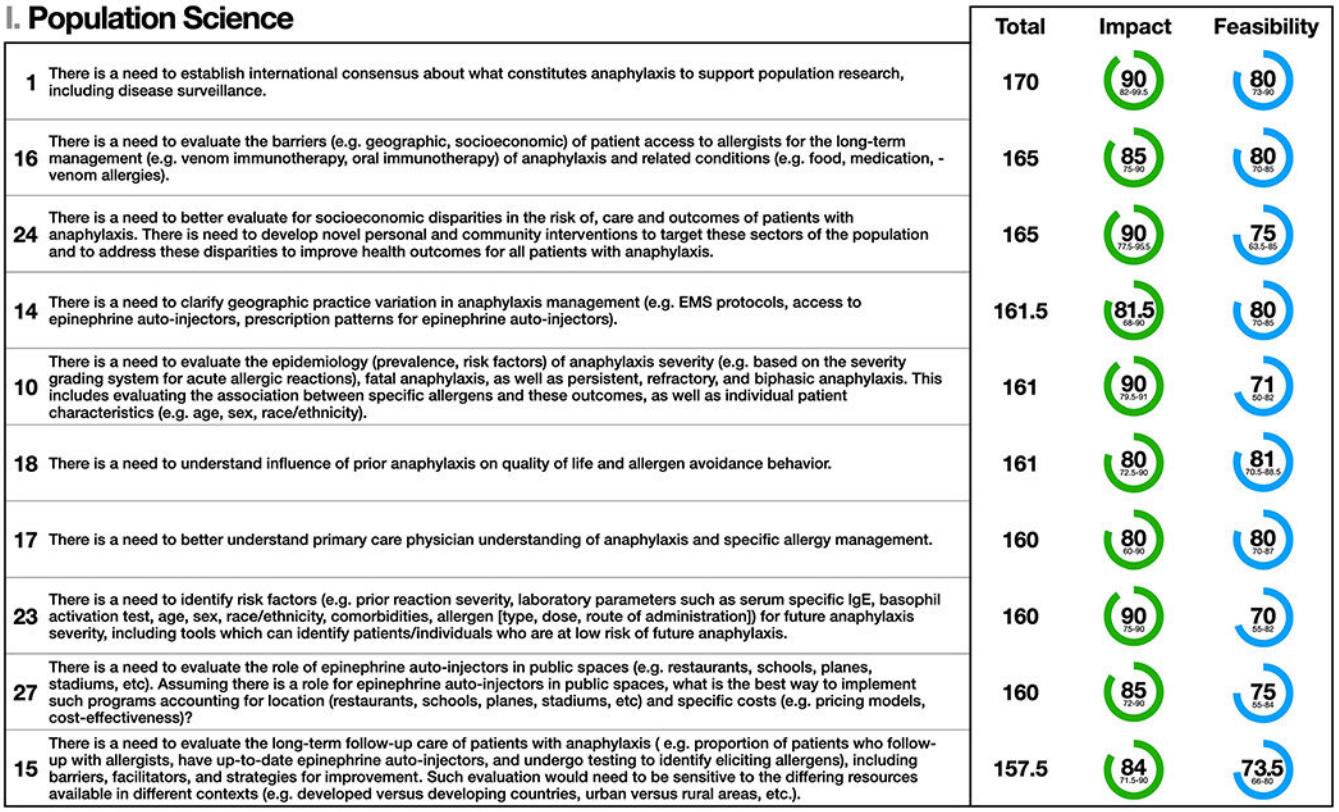

Figure 1.

Population Science: the top 10 statements for summed median and impact and feasibility scores (maximum possible score = 200). Statement numbers corresponding to statements in the Online Repository are displayed to the left of each statement. Interquartile ranges are presented below median scores for impact and feasibility. Statement text may be abridged for clarity; a complete list of statements with unabridged text as well free text comments are detailed in Table E1 in the Online Repository.

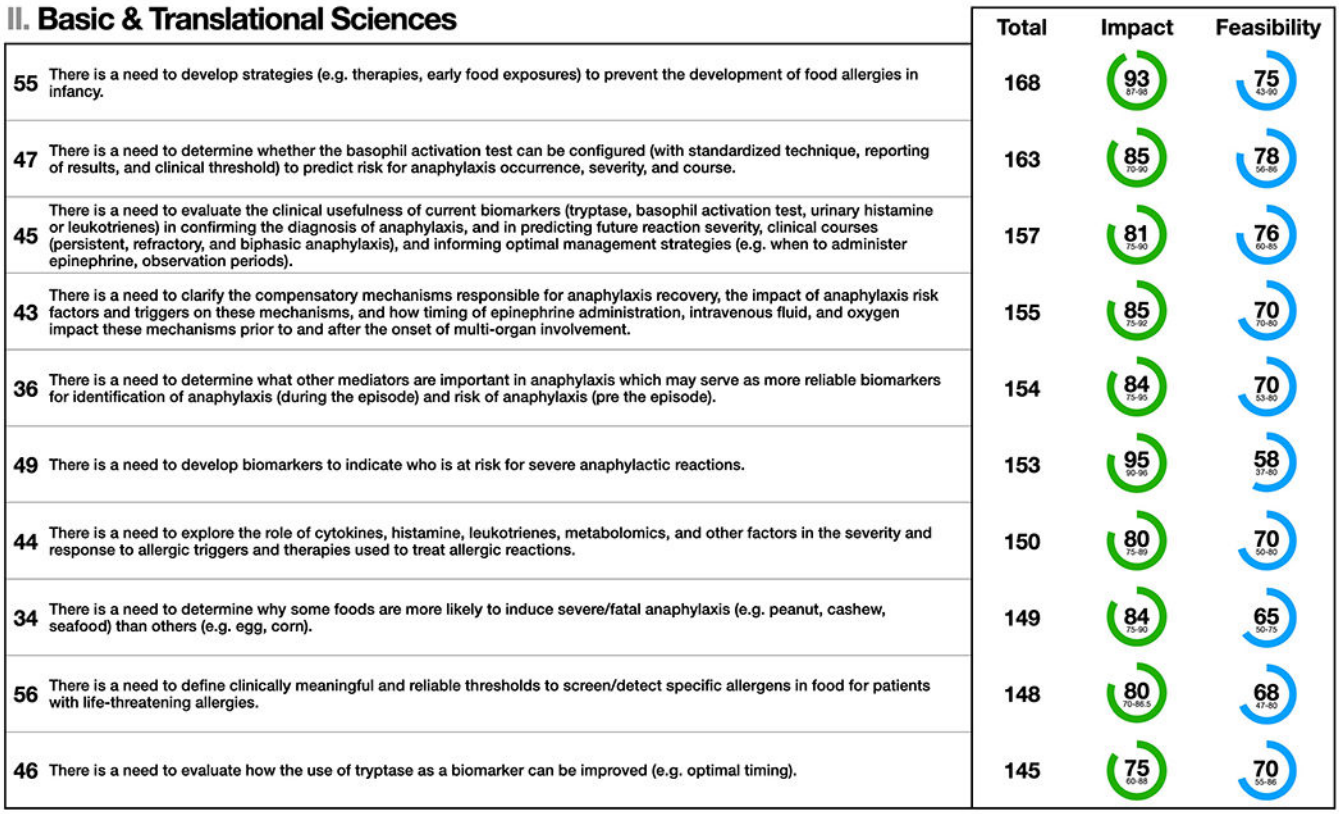

Figure 2.

Basic & Translational Sciences: the top 10 statements for summed median and impact and feasibility scores (maximum possible score = 200). Statement numbers corresponding to statements in the Online Repository are displayed to the left of each statement. Interquartile ranges are presented below median scores for impact and feasibility. Statement text may be abridged for clarity; a complete list of statements with unabridged text as well free text comments are detailed in Table E1 in the Online Repository.

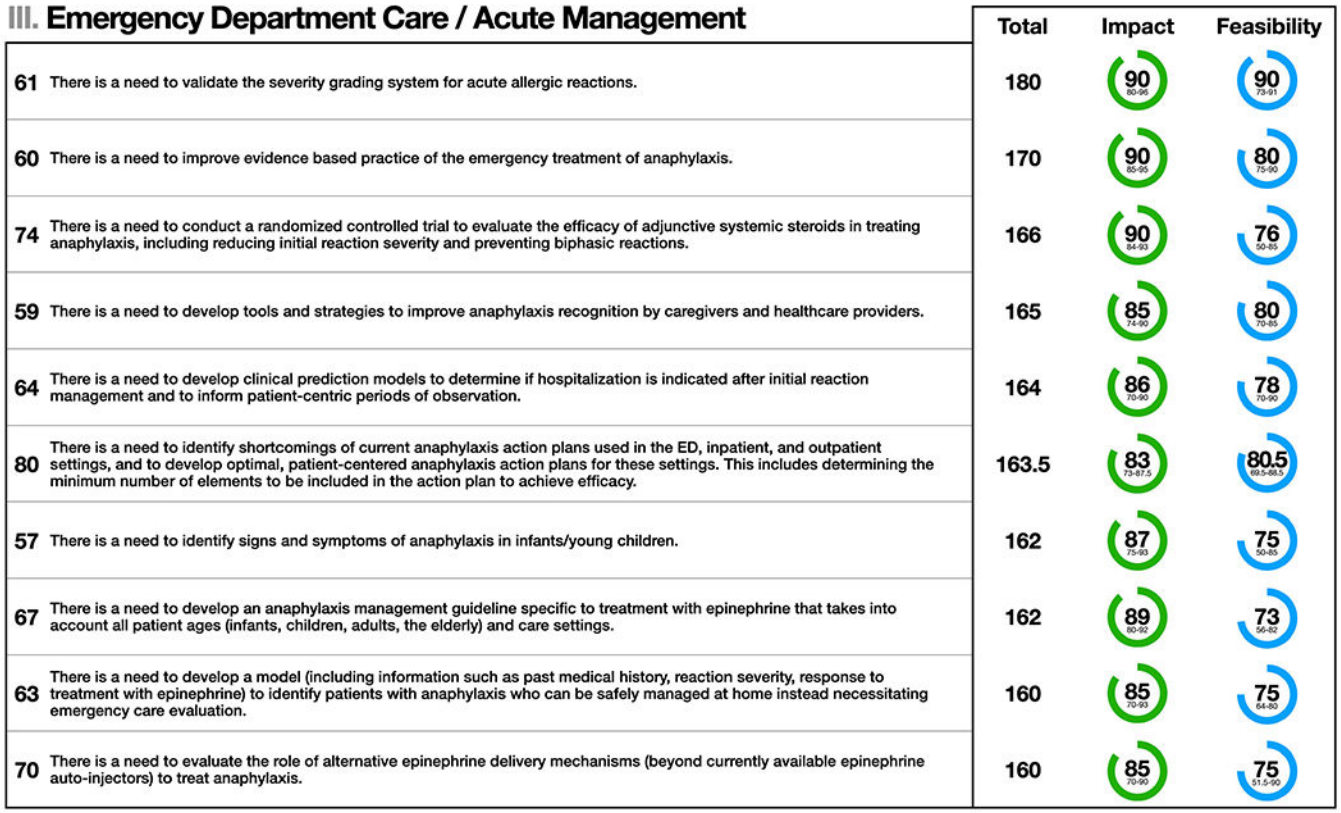

Figure 3.

Emergency Department Care/Acute Management: the top 10 statements for summed median and impact and feasibility scores (maximum possible score = 200). Statement numbers corresponding to statements in the Online Repository are displayed to the left of each statement. Interquartile ranges are presented below median scores for impact and feasibility. Statement text may be abridged for clarity; a complete list of statements with unabridged text as well free text comments are detailed in Table E1 in the Online Repository.

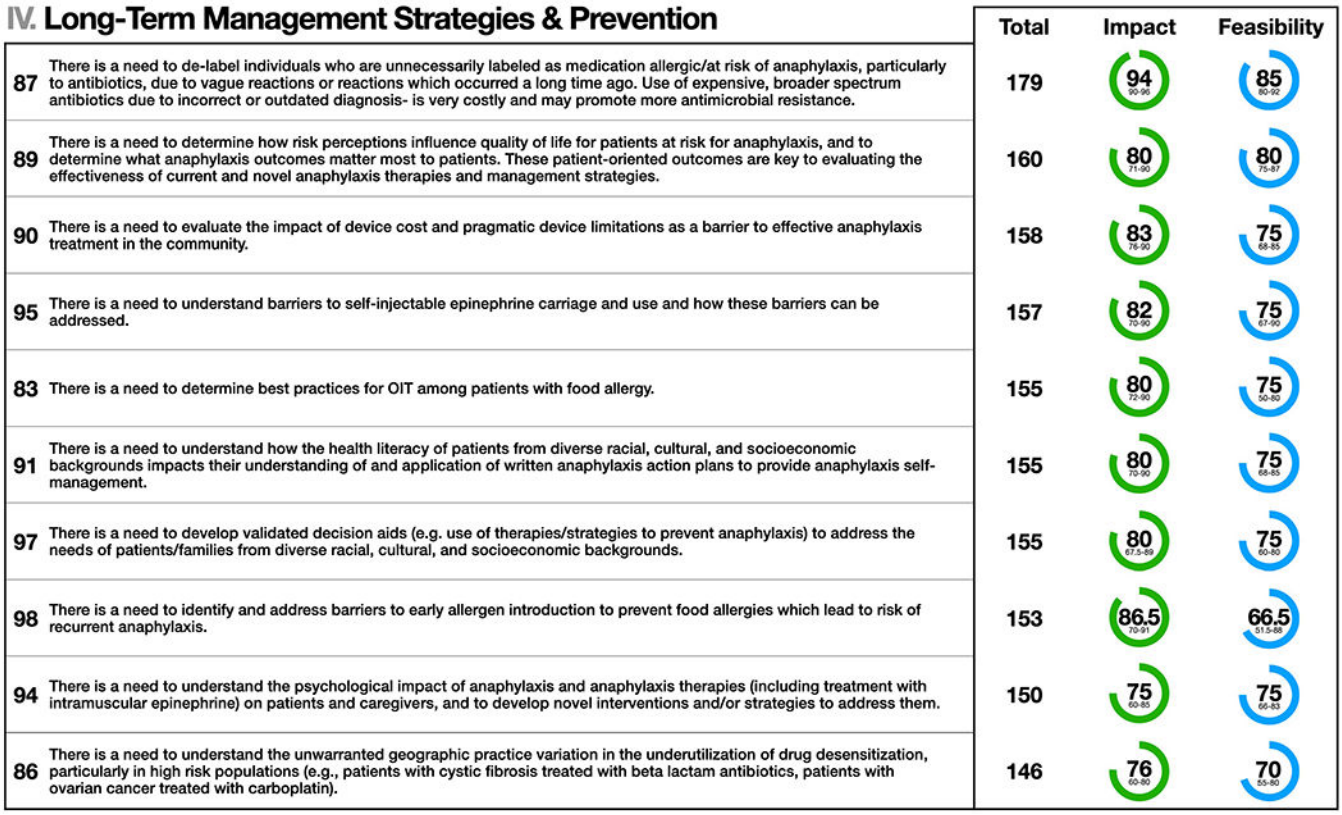

Figure 4.

Long-Term Management Strategies & Prevention: the top 10 statements for summed median and impact and feasibility scores (maximum possible score = 200). Statement numbers corresponding to statements in the Online Repository are displayed to the left of each statement. Interquartile ranges are presented below median scores for impact and feasibility. Statement text may be abridged for clarity; a complete list of statements with unabridged text as well free text comments are detailed in Table E1 in the Online Repository.

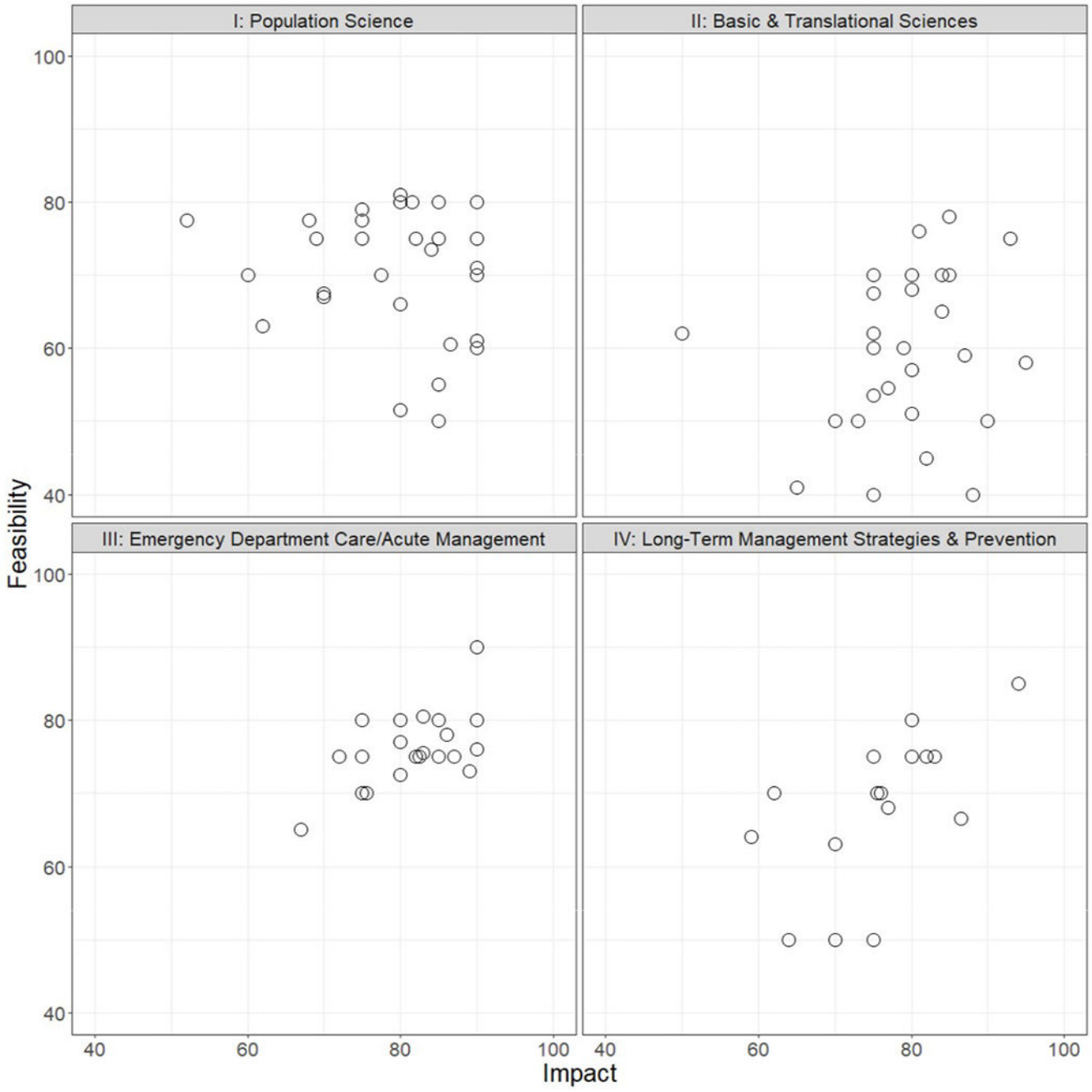

Figure 5.

Distribution of anaphylaxis knowledge gaps and future research priorities accounting for the potential impact and feasibility of addressing statements across the four anaphylaxis themes: I) Population Science, II) Basic & Translational Sciences, III) Emergency Department Care/ Acute Management, IV) Long-Term Management Strategies & Prevention.