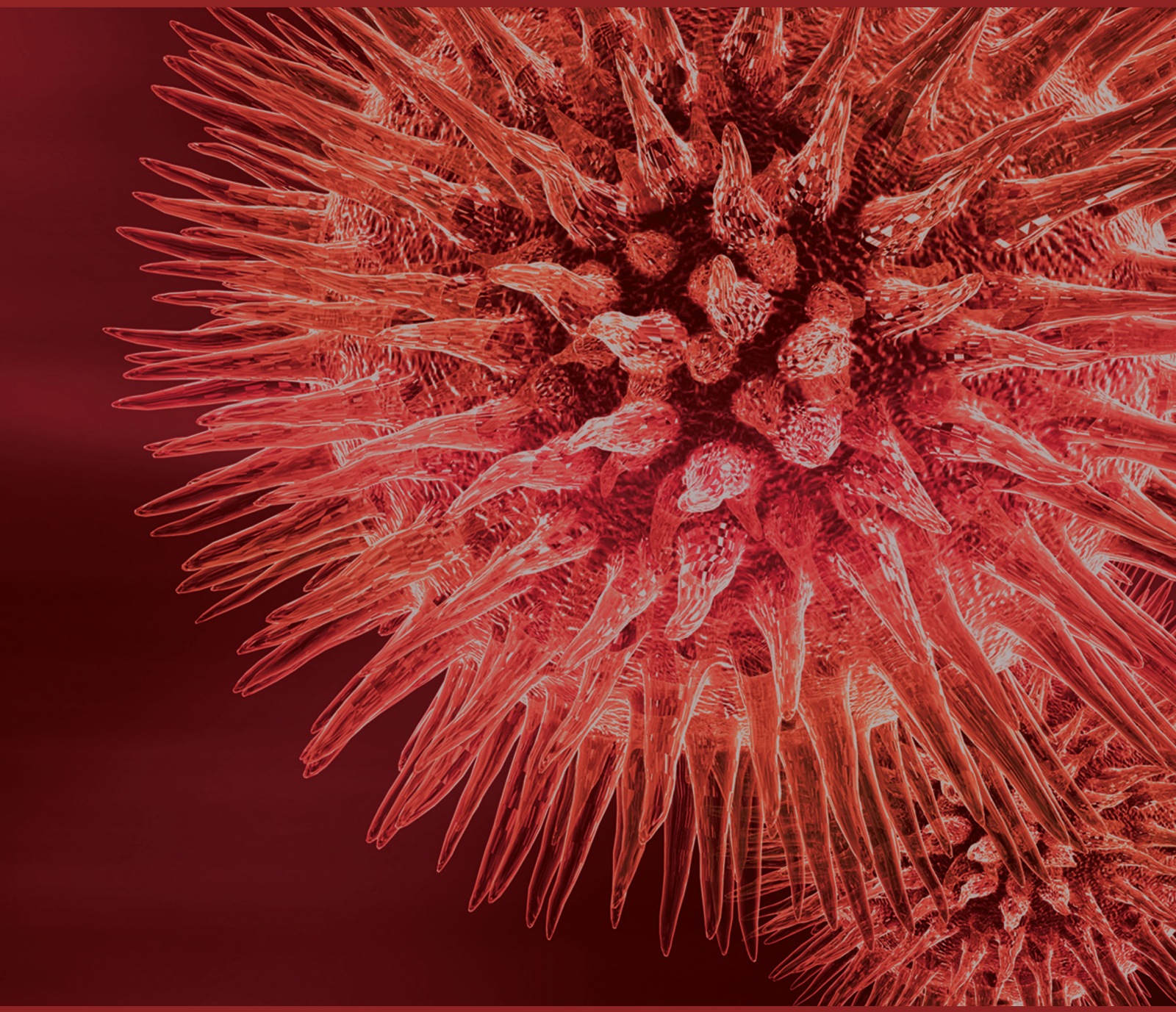
BioMed Research International

Protein Drugs Related to Allergic Reaction

Guest Editors: Ji-Fu Wei, Tian-Rui Xu, Ming-Can Yu, Xing-Ding Zhou, Zuo-Tao Zhao, and Yang Jin



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Editorial

Protein Drugs Related to Allergic Reaction

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Allergic reactions are sensitive to substances called allergens that come into contact with the skin, nose, eyes, respiratory tract, and gastrointestinal tract. Many allergic reactions are mild, while others can be severe and life threatening. Protein drugs related to allergic reaction include two categories. The first is protein drugs that are used to treat or prevent allergic reaction. Compared to other small molecule drugs, pharmaceutical peptides and proteins offer low toxicity and high specificity and demonstrate fewer toxicology issues. The second is protein drugs which are used to treat other disease and have the adverse effect causing serious allergic reaction. In this respect, this special issue will add a few new points in the picture of protein drugs related to allergic reaction.

C. Xu et al. in "Efficacy of Sublingual Immunotherapy with *Dermatophagoides farinae* Extract in Monosensitized and Polysensitized Patients with Allergic Rhinitis: Clinical Observation and Analysis" investigated differences in the efficacy of sublingual immunotherapy (SLIT) with *Dermatophagoides farinae* drops in monosensitized and polysensitized allergic rhinitis patients. They divided the patients into two groups: monosensitized group ($n = 20$) and a polysensitized group ($n = 30$). Total nasal symptom scores of patients before and after SLIT were analyzed to evaluate the curative effect. The phylogenetic tree of dust mite allergens as well as other allergens that were tested by skin prick was constructed to help the analysis. They concluded that there was no significant difference in the efficacy of SLIT between dust mite monosensitized and polysensitized patients. Both dust mite monosensitized and polysensitized patients could be cured by SLIT using *Dermatophagoides farinae* drops. This study provides a reference for the selection of allergens to use in immunotherapy for polysensitized AR patients.

In 1997, the first monoclonal antibody (MoAb), the chimeric anti -CD20 molecule rituximab, was approved by the US Food and Drug Administration for use in cancer patients. Since then, the panel of MoAbs that are approved by international regulatory agencies for the treatment of hematopoietic and solid malignancies has continued to expand, currently encompassing a stunning amount of 20 distinct molecules for 11 targets. M. Guan et al. in "Adverse Events of Monoclonal Antibodies Used for Cancer Therapy" provided a brief scientific background on the use of MoAbs in cancer therapy, reviewed all types of monoclonal antibodies-related adverse events (e.g., allergy, immune-related adverse events, cardiovascular adverse events, and pulmonary adverse events), and discussed the mechanism and treatment of adverse events.

To analyze the clinical characteristics of inpatients anaphylaxis and the factors that influenced those characteristics, R. Tang et al. in "Clinical Characteristic of Inpatients with Anaphylaxis in China" collected the patient records from 1990 to 2013 from three highly ranked Chinese hospitals and

retrospectively analyzed the characteristics of 108 inpatients anaphylaxis. The mean patient age was 42 ± 20 years old with a male-to-female ratio of 1 : 1.3. The most common trigger was medications (97/108). The most common clinical manifestations included cutaneous (72.2%), nervous (54.6%), respiratory (52.8%), circulatory (41.7%), and digestive (38.0%) signs and symptoms. Male patients were more likely to experience loss of consciousness. Epinephrine was used as the first-line treatment for 56 cases. Inpatient anaphylaxis was more common in female patients and the number increased gradually during the study period.

Y.-J. Guo et al. in "Analysis of Anaphylactic Shock Caused by 17 Types of Traditional Chinese Medicine Injections Used to Treat Cardiovascular and Cerebrovascular Diseases" described anaphylactic shock following treatment of cardiovascular and cerebrovascular diseases with Chinese herbal injections were described. Their analysis of these reports showed that anaphylactic shock caused by Traditional Chinese Medicine (TCM) injections for the treatment of cardiovascular and cerebrovascular diseases is common but also sometimes fatal. They then proposed the following four suggestions for improving the clinical safety of delivering Chinese herbal injections and reducing the occurrence of allergic shock.

J.-M. Yu in "Diversity of House Dust Mite Species in Xishuangbanna Dai, a Tropical Rainforest Region in Southwest China" enrolled the mite-allergic patients, who visited the Xishuangbanna Dai Autonomous Prefecture Hospital from August 2010 to January 2011 and collected the dust samples from the patients' homes by vacuuming. They isolated the mites in this samples by the flotation method and underdone the morphologically based species determination. In total, 6316 mite specimens of morphologically identifiable species were found in 233 dust samples taken from 41 homes. It showed that the mite family of Pyroglyphidae occupied the highest percentage (96.6%) of the total amount of mites collected, followed by Cheyletidae family (2.0%). The most common adult Pyroglyphidae mites were *Dermatophagoides farinae* (76.5%). The most common mites found besides Pyroglyphidae were *Blomia tropicalis*, *Tyrophagus putrescentiae*, and *Aleuroglyphus ovatus*, which were found in 24.4%, 24.4%, and 7.3% of homes, respectively.

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Review Article

Adverse Events of Monoclonal Antibodies Used for Cancer Therapy

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In 1997, the first monoclonal antibody (MoAb), the chimeric anti-CD20 molecule rituximab, was approved by the US Food and Drug administration for use in cancer patients. Since then, the panel of MoAbs that are approved by international regulatory agencies for the treatment of hematopoietic and solid malignancies has continued to expand, currently encompassing a stunning amount of 20 distinct molecules for 11 targets. We provide a brief scientific background on the use of MoAbs in cancer therapy, review all types of monoclonal antibodies-related adverse events (e.g., allergy, immune-related adverse events, cardiovascular adverse events, and pulmonary adverse events), and discuss the mechanism and treatment of adverse events.

1. Introduction

Engineered monoclonal antibodies (MoAbs) represent a significant addition to the therapeutic armamentarium for a variety of malignancies. Adverse events (AEs) of these new regimens are described to be mild compared with those of classical chemotherapy. Twenty MoAbs are currently registered and approved for the treatment of a range of different cancers. These MoAbs are specific for 11 targets. Five of these molecules are directed against the B-lymphocyte antigen CD20, 3 against human epidermal growth factor receptor 2 (HER2 or ErbB2), 3 against the epidermal growth factor receptor (EGFR), 2 against vascular endothelial growth factor (VEGF), and 1 each against epithelial cell adhesion molecule (EpCAM), CD30, CD52, tumor necrosis factor (ligand) superfamily member 11 (TNFSF11, also known as RANKL), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed death 1 protein (PD-1) and interleukin-6 (IL-6) are summarized in Table 1. Common adverse events (AEs) include allergy (rash, infusion reactions), diarrhea, hypertension, proteinuria, hypothyroidism, and hepatotoxicity. Certain toxicities are caused by on-target, mechanism-associated effects, which can be stratified by whether or not the targets are relevant to response. Other toxicities are off-target and may be caused by immune reactions or toxic metabolites. Here, we review monoclonal antibodies-related AEs and management of patients displaying these reactions.

2. Drug Allergy

Historically, immunologic reactions have been divided into four categories (I to IV) according to the Gell and Coombs system. Drugs are most commonly implicated in type I reactions. These reactions, mediated by IgE antibodies are also known as anaphylactic hypersensitivities and are relatively uncommon after administration of MoAbs. Immediate hypersensitivity may affect a single organ such as the nasopharynx (allergic rhinitis), eyes (conjunctivitis), mucosa of mouth/throat/tongue (angioedema), bronchopulmonary tissue (asthma), gastrointestinal tract (gastroenteritis), and skin (urticaria, eczema) or multiple organs (anaphylaxis). They cause symptoms that range from minor itching and inflammation to death. Symptoms associated with anaphylaxis are shown in Figure 1 [1]. Anaphylaxis has been reported for cetuximab, rituximab, trastuzumab, pertuzumab, obinutuzumab, ofatumumab, tositumomab, and

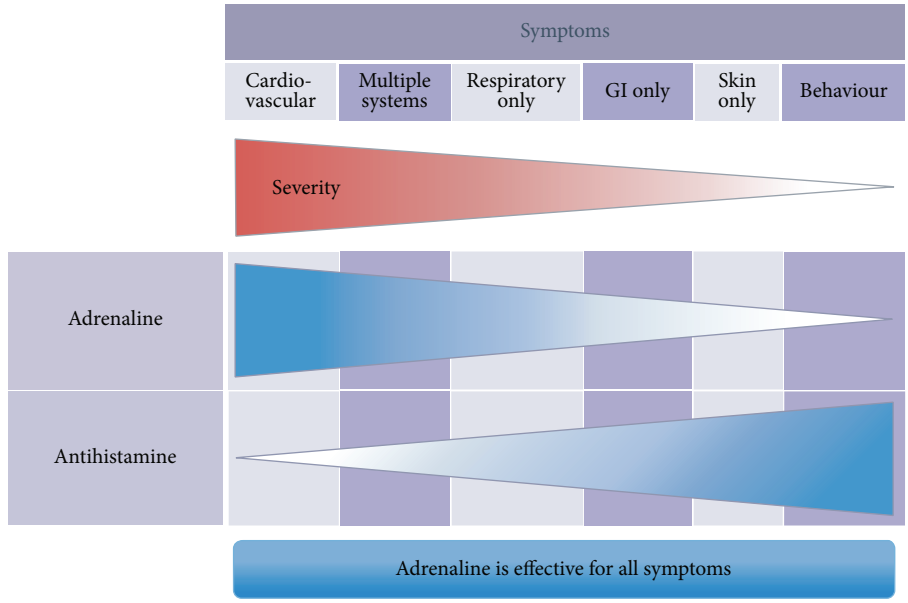
Table 1: Monoclonal antibodies (MoAbs) approved for cancer therapy.

MoAb	Trade name	Target	Type	Indication(s)
Cetuximab	Erbitux	EGFR	Chimeric IgG1κ	HNC and colorectal cancer
Panitumomab	Vectibix	EGFR	Human IgG2κ	Colorectal carcinoma
Nimotuzumab	Nimotuzumab	EGFR	Human IgGh-R3	HNC
Bevacizumab	Avastin	VEGFR	Humanized IgG1κ	Colorectal, renal, lung, and brain cancer
Ramucirumab	Cyramza	VEGFR	Humanized IgG1κ	Gastric or gastresophageal junction cancer
Trastuzumab	Herceptin	HER2	Humanized IgG1κ	Breast cancer, gastric or gastroesophageal junction cancer
Trastuzumabemtansine	Kadcyla	HER2	Humanized IgG1κ	Breast cancer
Pertuzumab	Perjeta	HER2	Humanized IgG1κ	Breast cancer
Alemtuzumab	Campath	CD52	Humanized IgG1κ	Chronic lymphocytic leukemia
Rituximab	Rituxan MabThera	CD20	Chimeric IgG1κ	Chronic lymphocytic leukemia and non-Hodgkin lymphoma
Ofatumumab	Arzerra	CD20	Human IgG1κ	Chronic lymphocytic leukemia
Obinutuzumab	Gazyva	CD20	Human IgG1	CLL
Ibritumomab	Zevalin	CD20	Murine IgG1κ	Non-Hodgkin lymphoma
Tositumomab	Bexxar	CD20	Murine IgG2aλ	Non-Hodgkin lymphoma
Brentuximab Vedotin	Adcetris	CD30	Chimeric IgG1κ	Hodgkin's and anaplastic large cell lymphoma
Ipilimumab	Yervoy	CTLA-4	Human IgG1κ	Melanoma
Catumaxomab	Removab	EpCAM	Rat IgG2b/mouse IgG2a bispecific	Malignant ascites in patients with ePCaM + cancer
Denosumab	Prolia Xgeva	RANKL	Human IgG2κ	Breast cancer, prostate cancer, and giant cell tumors of the bone
Nivolumab	Opdivo	PD-1	Human IgG4	Melanoma
Siltuximab	Sylvant	IL-6	Chimeric IgG1κ	Castleman disease, multicentric (in patients who are HIV negative and HHV-8 negative)

ibritumomab, and these last two MoAbs have also been reported to cause bronchospasm and angioedema [2–6].

A high prevalence of hypersensitivity reactions to cetuximab have been reported in some areas of the United States. In most subjects who had a hypersensitivity reaction to cetuximab, IgE antibodies against cetuximab were present in serum before therapy [7–10]. The antibodies are specific for an oligosaccharide, galactose-α-1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain. The presence of such antibodies is predictive of anaphylaxis, and pretreatment testing would help in minimizing the risk of anaphylaxis associated with cetuximab [11].

2.1. Standard Infusion Reactions (SIR). Nearly all MoAbs share a risk for standard infusion reactions (SIR), but certain drugs (e.g., rituximab, cetuximab, alemtuzumab, ramucirumab, obinutuzumab, and ofatumumab) are associated with a high enough risk to warrant special precautions. The most common symptoms and signs are dyspnea, nausea, headache, and abdominal pain. Most reactions are mild; only approximately 0.3% of patients have serious infusion reactions with features of anaphylaxis (bronchospasm, hypotension, and angioedema). Standard infusion reactions typically develop within 30 minutes to two hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10 and 30% occur during subsequent treatments. Rituximab, obinutuzumab, and trastuzumab induce the highest incidence of SIR. In general, the incidence of MoAb induced IR varies from 15–20% for cetuximab (3% grade 3/4) and 40% for trastuzumab first infusion (<1% grade 3/4) to 77% for rituximab first infusion (10% grade 3/4). Infusion reactions are markedly less common after the initial infusion [12]. The manufacturer reports a frequency of 77, 30, and 14% during the first, fourth, and eighth infusions of rituximab, respectively. The incidence of IR to the humanized MoAbs bevacizumab, panitumumab and nimotuzumabis is significantly lower at <3% (0.2% grade 3/4). The mechanism underlying MoAb-related infusion reactions remain unclear, but most are thought to be related to antigen-antibody interactions precipitating cytokine release [5, 6]. It is the most predictable reaction that occurs with rituximab, and is thought to be caused by the interaction of the drug with the target antigen (CD20) on circulating cells, followed by cytokine release from lymphocytes. Evidence for this mechanism includes the observation that severe and fatal reactions have typically occurred in patients with high numbers of circulating lymphocytes bearing the target antigen [5].



GI, gastrointestinal.

Figure 1: Symptoms associated with anaphylaxis.

2.2. Serum Sickness (A Delayed Type III Allergic Reaction). Serum sickness has been reported with rituximab. Symptoms include fever and arthralgia with a morbilliform skin eruption that often has acral accentuation. The reaction typically develops one to two weeks after treatment and is accompanied by laboratory evidence of complement activation (depressed C3 and C4 levels) and tissue inflammation (elevated erythrocyte sedimentation rate and C-reactive protein) [13]. Chimeric MoAbs have the potential to induce serum sickness. Recently, it has been reported that rituximab-induced serum sickness-like reactions occur in 1–20% of patients [14].

2.3. Treatment

2.3.1. Prevention. Pharmacologic prophylaxis with a histamine H1 receptor antagonist is recommended prior to each infusion of ramucirumab. Pharmacologic prophylaxis with antihistamines and acetaminophen with or without a glucocorticoid is suggested for high-risk agents (i.e., rituximab, first infusion of cetuximab in a patient who resides in a high-risk area and intravenous alemtuzumab). Despite premedication, clinicians must be prepared for an infusion reaction to occur during each drug administration [6, 15].

2.3.2. Mild to Moderate SIR. If the reaction is limited to mild or moderate symptoms of SIR (grades 1 or 2), without features suggestive of anaphylaxis, drug infusion should be temporarily stopped and assessment of airway, breathing, circulation, and mentation should rapidly occur. IV administration of 50 mg of diphenhydramine and 650 mg of acetaminophen may provide symptomatic relief. Once symptoms have resolved, resumption of the drug infusion at a slower rate may permit treatment continuation with close monitoring [6].

2.3.3. Severe SIR or Anaphylaxis. Severe SIR (grades 3/4) or reactions of any severity with any features of anaphylaxis (e.g., generalized urticaria, wheezing, hypotension, and angioedema) require prompt recognition and treatment. Clinical criteria for diagnosing anaphylaxis can be seen in Table 2. Recommendations for emergency management are shown in Table 3 [1]. The first line drug treatment is adrenaline.

2.3.4. Rechallenge. Once the acute event has subsided, the issue of rechallenge must be addressed. Patients with severe infusion reaction or anaphylaxis to cetuximab can be safely switched to pannitumumab. The decision to attempt retreatment depends upon the drug, the severity of the reaction, the cancer being treated, and whether there are reasonable treatment alternatives [5, 6].

2.3.5. Desensitization. Experience with desensitization to MoAbs is relatively limited. At some institutions, these are only performed by allergy specialists [63].

3. Immune-Related Adverse Events (irAEs)

Ipilimumab is a monoclonal antibody that targets CTLA-4, thus unleashing an immune reaction against the tumor. CTLA-4 is a surface protein expressed on activated and

Table 2: Clinical criteria for diagnosing anaphylaxis.

Anaphylaxis is highly likely when anyone of the following three criteria is fulfilled:
(1) acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue, and uvula *and at least one of the following:*
(a) respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, and hypoxemia),
(b) reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, and incontinence);
(2) two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
(a) involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, and swollen lips, tongue, and uvula),
(b) respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, and hypoxemia),
(c) reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, and incontinence),
(d) persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting);
(3) reduced BP after exposure to known allergen for that patient (minutes to several hours):
(a) infants and children: low systolic BP (age specific) or >30% decrease in systolic BP*
(b) adults: systolic BP of <90 mmHg or >30% decrease from that person's baseline

Notes
PEF, peak expiratory flow; BP, blood pressure.
*Low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 × age]) from 1 to 10 years and <90 mmHg from 11 to 17 years.

Table 3: Emergency management: recommendations.

Recommendation	Evidence Level	Grade
First-line intervention: adrenaline		
Adrenaline is potentially lifesaving and must therefore promptly be administered as the first-line treatment for the emergency management of anaphylaxis.	IV	C
Earlier administration of adrenaline should be considered on an individual basis when an allergic reaction is likely to develop into anaphylaxis.	V	D
Adrenaline should be administered by intramuscular injection into the midouter thigh.	I	B
In patients requiring repeat doses of adrenaline, these should be administered at least 5 min apart.	V	D
With inadequate response to two or more doses of intramuscular adrenaline, adrenaline may be administered as an infusion by appropriately experienced intensive care, emergency department, and critical care physicians, with appropriate cardiac monitoring.	IV	D
Second-line interventions		
Trigger of the anaphylaxis episode should be removed.	V	D
Help should be called promptly and simultaneously with patient's assessment.	V	D
Patients experiencing anaphylaxis should be positioned supine with elevated lower extremities if they have circulatory instability, sitting up if they have respiratory distress, and in recovery position if unconscious.	V	D
High-flow oxygen should be administered by face mask to all patients with anaphylaxis.	V	D
Intravenous fluids (crystalloids) should be administered (boluses of 20 mL/kg) in patients experiencing cardiovascular instability.	V	D
Inhaled short-acting beta-2 agonists should additionally be given to relieve symptoms of bronchoconstriction.	V	D
Third-line interventions		
Oral H1- (and H2-) antihistamines may relieve cutaneous symptoms of anaphylaxis.	I	B
Systemic glucocorticosteroids may be used as they may reduce the risk of late-phase respiratory symptoms. High-dose nebulized glucocorticoids may be beneficial for upper airway obstruction.	V	D
Monitoring and discharge		
Patients who presented with respiratory compromise should be closely monitored for at least 6–8 h, and patients who presented with circulatory instability require close monitoring for 12–24 h.	V	D
Before discharge, the risk of future reactions should be assessed and an adrenaline autoinjector should be prescribed to those at risk of recurrence.	V	D
Patients should be provided with a discharge advice sheet, including allergen avoidance measures (where possible) and instructions for the use of the adrenaline autoinjector.	V	D
Specialist and food allergy specialist dietitian (in food anaphylaxis) followup should be organized. Contact information for patient support groups should also be provided.	V	D

regulatory T cells and is upregulated in malignancy [56]. Immune-related adverse events (irAEs) can occur at any point during treatment with ipilimumab, but often first present around the third or fourth dose. The incidence of hypophysitis due to ipilimumab has been reported to range from 0 to 17% in clinical trials, though the mechanism of pituitary injury remains unknown. Other immune-related adverse events include hepatotoxicity, or failure of the thyroid gland (autoimmune thyroiditis), the adrenal gland, and gonadal axis, and enterocolitis, which can be serious or life-threatening (any grade 30%–35%, grade 3–5 diarrhea 5%–8%) [57]. It remains unclear whether the effects result from T cells specifically acting against antigens shared by tumor and normal cells or from the concomitant activation of multiple T cell populations with separate antihost and antitumor activity [64, 65]. Current recommendations include baseline TSH and free T4 and monitoring every 3 weeks during ipilimumab treatment and every 2-3 months following completion. For patients with severe or life-threatening grade 3/4 AEs, treatment with ipilimumab should be permanently discontinued and high doses of corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) are indicated [56].

Radioimmunotherapy (RIT) refers to the use of monoclonal antibodies that are linked to radioisotopes (e.g., yttrium-90). Two drugs have been approved by the United States FDA to be used in treatment of relapsed or refractory CD20 positive, low-grade, follicular, or transformed non-Hodgkin's lymphoma (NHL). Ibritumomabtiuxetan (Zevalin) is a murine anti-CD20 monoclonal antibody conjugated to yttrium-90 [2]. Tositumomab (Bexxar) is a murine anti-CD20 monoclonal antibody conjugated with radioactive iodine-131 [3]. RIT may also lead to hypothyroidism; patients should receive thyroid-blocking medications beginning at least 24 hours prior to tositumomab and continued for 2 weeks after the therapeutic dose. Nivolumab is a humanized monoclonal antibody that targets the PD-1 protein. Immune-related adverse events are the most common side effects, and the skin and gastrointestinal tract are the most often affected organ systems and less frequently hepatic, endocrine, and neurologic events occur [66, 67].

4. Cardiovascular AEs

Cardiac adverse events have occurred with specific MoAbs, including bevacizumab, trastuzumab, trastuzumabemtansine, pertuzumab, ofatumumab, and rituximab [5, 22, 38, 45, 68, 69].

4.1. Hypertension. VEGF plays a key role in the maintenance of vascular homeostasis via mediation of the production of the vasodilator nitric oxide and decrease of vascular resistance through the generation of new blood vessels [68, 70–72]. The overall incidence of bevacizumab-induced hypertension is approximately 12 to 34%, with severe hypertension in 5 to 18%. Hypertension has been proposed to be a clinical biomarker of antitumor activity [73]. The incidence rate of hypertension for ramucirumab was lower than bevacizumab (all grades: 6%; grades 3/4: 8%) [74].

4.2. Arterial and Venous Thromboembolism. An increased risk for arterial thromboembolic events (ATEs) has been linked to the use of bevacizumab and ramucirumab [23, 24, 28, 75]. The overall incidence of bevacizumab-induced thromboembolism is ≤21% (grades 3/4: 15%) and consists of venous thromboembolism (all-grade: 8%; grades 3/4: 5% to 7%) and arterial thrombosis (all-grade: 6%; grades 3/4: 3%). In a pooled analysis of 1,745 patients, of whom 963 were treated with bevacizumab (24% breast cancer), the incidence of thromboembolic events was 4% in patients treated with bevacizumab plus chemotherapy, and 2% in those treated with chemotherapy alone [75]. Ramucirumab-induced arterial thrombosis (including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia) was seen in 2% patients [28].

4.3. Congestive Heart Failure (CHF). A meta-analysis of five randomized trials involving a total of 3,784 metastatic breast cancer patients analyzed the incidence of congestive heart failure (CHF) when using chemotherapy with or without bevacizumab. The incidence of high-grade CHF was 1.6% in patients treated with bevacizumab and 0.4% in patients who did not receive this drug [24]. In NSABP B31, asymptomatic decrease in LVEF occurred in 14% of patients, requiring discontinuation of trastuzumab [22]. Endomyocardial biopsy was performed in a limited number of patients exposed to trastuzumab and demonstrated no significant abnormalities [31]. The incidence of severe CHF in the trastuzumab adjuvant studies is in the range of 1% to 4%. In the Herceptin Adjuvant trial (HERA), with 3.6 years of median followup, all cases of severe CHF occurred during trastuzumab treatment; however, the cardiac performance of the majority of affected patients improved when trastuzumab was withdrawn [32]. The incidence of CHF in older patients treated with trastuzumab is expected to be higher than in the overall population evaluated in large clinical trials [33]. Combining anti-HER2 and anti-VEGF drugs has consequently emerged as an important strategy to optimize the targeted treatment of breast cancer. The bevacizumab plus trastuzumab combination was evaluated in 50 heavily pretreated metastatic breast cancer patients [76]. This combination was associated with a 30% incidence of asymptomatic LVEF decrease, 2% grade 4 LVEF decrease, and 36% incidence of hypertension. In phases I–III of trials of pertuzumab, cardiac dysfunction was seen in 4.5–14.5% of patients with pertuzumab treatment and cardiac dysfunction was usually grade 1/2 [39]. Cardiotoxicity of pertuzumab was usually reported in combination with trastuzumab and no additive cardiotoxicity was reported with addition of pertuzumab to trastuzumab [38]. A phase II study evaluated trastuzumab-DM1 in 107 patients pretreated with anthracyclines, trastuzumab, taxanes, capecitabine, and lapatinib. Reduction in LVEF was observed in two patients [69].

4.4. Hemorrhage. All VEGF-targeted agents have been associated with an increased risk of hemorrhage. This is most commonly grade 1 epistaxis, though more serious, and in some cases, fatal hemorrhagic events have occurred, including hemoptysis (particularly in patients with squamous cell lung cancer), gastrointestinal bleeding, hematemesis, intracerebral hemorrhage, epistaxis, and vaginal bleeding. The overall risk of major bleeding is approximately 2 to 3%. A total of 12,917 patients from 17 RCTs treated with bevacizumab had a significantly increased risk of cerebrovascular events compared with patients treated with control medication, with a relative risk of 3.28 (95% CI, 1.97–5.48). The risks of CNS ischemic events and CNS hemorrhage were increased compared with control, with relative risk (RRs) of 3.22 (95% CI, 1.71–6.07) and 3.09 (95% CI, 1.36–6.99), respectively. Risk varied with the bevacizumab dose, with RRs of 3.97 (95% CI, 2.15–7.36) and 1.96 (95% CI, 0.76–5.06) at 5 and 2.5 mg/kg/week, respectively [25].

4.5. Treatment. To prevent cardiovascular adverse events, the physician should perform a pretreatment evaluation and screening, including formal risk assessment for potential cardiovascular complications. Preexisting hypertension should be identified and treated before using these agents. Caution and close serial monitoring of LVEF are warranted during therapy with bevacizumab in older adults and those with a history of hypertension, heart disease or anthracycline exposure. Cardiac troponin and amino-terminal fragment B-type natriuretic peptide (NT proBNP) have been the most frequently assessed biomarkers for cardiac injury and will be briefly described. Cardiac troponin is a medium-sized protein that regulates the cardiac contractile elements actin and myosin. The NT proBNP is useful for diagnosing cardiac failure in breathless patients but its utility for identifying subclinical cardiac pathology is unclear [77]. MoAbs should be discontinued for any severe ATE/VTE. Antiangiogenic therapy is associated with impairment of wound healing. It is recommended to withhold ramucirumab treatment prior to surgery. After surgery, clinical judgment dictates when to resume based on adequate wound healing. It is recommended that bevacizumab should be discontinued at least 28 days prior to surgery and should not be reinitiated for at least 28 days after surgery and until wound is fully healed [26, 28].

5. Pulmonary AEs

There are several complications that affect the lungs associated with the use of MoAbs, including interstitial lung disease (ILD), hemorrhage, trachea-esophageal fistula, and thromboembolic disease. Since the mechanisms underlying such lung injuries have generally not been uncovered, any classification on the basis of pathogenesis is difficult. Adverse events can be grouped into 4 main categories: interstitial pneumonitis and fibrosis, acute respiratory distress syndrome (ARDS), bronchiolitis obliterans organizing pneumonia (BOOP), and hypersensitivity reactions. Signs, symptoms, and clinical findings include dyspnea, cough, fatigue, and pulmonary opacities. Because signs and symptoms are generally nonspecific, the diagnosis usually remains one of exclusion [16, 34, 35, 43, 78, 79].

Once again, rituximab is the most implicated MoAb, inducing a heterogeneous spectrum of lung disorders. In 2003, the reported rate of possible drug-induced lung injury was <0.03% from >540,000 exposed patients. BOOP is the most common clinical diagnosis of rituximab-induced lung disease, followed by interstitial pneumonitis, ARDS, and hypersensitivity pneumonitis. Acute or subacute rituximab-induced lung disease, most notably organizing pneumonia, most likely reflects a hypersensitivity reaction to the potentially immunogenic chimeric anti-CD20 antibody. Arguments that support a hypersensitivity reaction include the recurrence and increasing severity of the symptoms from one infusion to the next, occurrence during the third month on average, responsiveness to steroid therapy (delayed onset 15 days after methylprednisolone infusion and favorable outcome with steroid therapy), rash and eosinophilia, BALF lymphocytosis, and histological pattern of organizing pneumonia in many patients [43]. Interstitial lung disease (ILD) has been reported in treatment with cetuximab and transtuzumab [16, 34].

Discontinuation of MoAb is advised in any patient who develops ILD or acute respiratory distress syndrome (ARDS) during treatment. Improvement following treatment with glucocorticoids has been reported; however, the role of glucocorticoid therapy in MoAb-induced pulmonary AEs has not been formally studied [35, 78, 79].

6. Proteinuria/Nephrotic Syndrome

Bevacizumab is associated with proteinuria, though rarely in the nephrotic range (>3.5 g/24 hours) and even more rarely associated with the nephritic syndrome [27, 80, 81]. Hypertension frequently accompanies proteinuria. Proteinuria is usually an asymptomatic event detected only through laboratory analysis. Reports of renal biopsies among patients with proteinuria receiving VEGF-targeted agents are sparse; when reported, the most common causative agent was bevacizumab. Histologic findings include thrombotic microangiography, collapsing glomerulopathy, and isolated reports of cryoglobulinemic and immune complex glomerulonephritis. The overall incidence of mild proteinuria in patients treated with bevacizumab ranges from 21 to up to 63%, but grade 3 or 4 proteinuria (defined as 3+ on dipstick, >3.5 g of protein/24 hours, or the nephrotic syndrome) affects approximately 2% of treated patients. The incidence is not higher in patients who receive shorter bevacizumab infusions (i.e., 10 versus 90 minutes) [82, 83]. The AEs of ramucirumab were lower than bevacizumab, with only 5.1% of patients experiencing proteinuria [28, 74].

Other less common renal problems that have been reported with bevacizumab include acute renal dysfunction and proliferative glomerulonephritis [27, 83].

Temporary cessation of bevacizumab is advised if protein excretion exceeds 2 g in 24 hours, and permanent discontinuation is appropriate for patients who develop the nephrotic syndrome [26].

7. Enterotoxicity

Enterocolitis, colitis, and gastrointestinal perforation (GIP) are common gastrointestinal AEs of MoAbs. In a study of pertuzumab monotherapy in patients with metastatic breast cancer, diarrhea of any grade developed in 48%, but it was severe (grade 3 or 4) in only 3% [39, 40]. A phase III comparison of best supportive care (BSC) with or without panitumumab reported diarrhea of any grade in 21% of patients receiving this MoAb (grade 3: 1%) compared to 11% with BSC alone (none grade 3) [18]. Cetuximab-related diarrhea is generally not severe, and while the rate of diarrhea of any grade was 12.7%, rates of grade 3 or 4 diarrhea in studies of single agent cetuximab have ranged from only 1.5 to 2% [17, 84].

All VEGF targeted therapies, including bevacizumab, can cause gastrointestinal perforation (GIP). GIP has been reported in patients treated with bevacizumab for a variety of malignancies, and has occurred in 0.3% to 2.4% of clinical study patients receiving bevacizumab. It can occur anywhere along the GI tract. Nongastrointestinal fistula formation also has been observed, most commonly within the first 6 months of treatment. Most cases occur within 50 days of treatment initiation. In order to minimize the risk of GIP and fistula formation, at least 28 days (preferably six to eight weeks) should elapse between surgery and last dose of bevacizumab, except in emergency situations [85].

8. Dermatologic/Cutaneous AEs

8.1. Papulopustular Acneiform Eruption. The most common cutaneous reaction pattern with the EGFR inhibitors is a diffuse papulopustular acneiform eruption, which is due to a role of EGFR in maintaining integrity of the skin. It is noted in more than two-thirds of patients receiving any of these agents (cetuximab, panitumumab) [17, 18]. The acneiform eruption is often dose-dependent, and typically begins early, within one week of treatment initiation. The lesions typically occur on the face, trunk, and extremities, sparing the palms and soles. Scaling of the interfollicular skin may also be present. Significant pruritus accompanies the cutaneous eruption in up to one-third of patients. Severity of the acneiform rash (all studies: 76% to 88%; grades 3/4: 1% to 17%; onset: ≤14 days) correlates with treatment response and prolonged survival in colorectal cancer patients treated with cetuximab [86]. In the ASPECCT trial, Grade 3-4 skin AEs occurred in 62 patients (13%) given panitumumab and 48 patients (10%) given cetuximab [19]. The skin AEs of nimotuzumab were very low, with only mild moderate skin rash observed [20].

8.2. Paronychial Inflammation. Paronychia involving the great toe is often the first sign, and secondary bacterial infection (often with *Staphylococcus aureus*) is not uncommon in patients treated with cetuximab [17, 87]. Other less common specific cutaneous reactions include the following: erythematous exanthem caused by cytomegalovirus, Stevens-Johnson syndrome, toxic epidermal necrolysis, and full thickness necrosis, which has been reported in a small number of patients treated with ipilimumab for metastatic melanoma. Treatment options include topical antibiotics, topical corticosteroids, and/or electrodessication for larger lesions. Temporary withholding of the drug is appropriate when the cutaneous complication is serious [57].

8.3. Treatment. Preventive/prophylactic management is recommended: hydrocortisone 1% combined with moisturizer, sunscreen, and doxycycline 100 mg bid for the first 6 weeks. Sunlight may exacerbate skin reactions (limit sun exposure). Treatment include the following: alclometasone 0.05% cream or fluocinonide 0.05% cream or clindamycin 1%, and doxycycline 100 mg bid or minocycline 100 mg daily or isotretinoin at low doses (20–30 mg/day) [88].

8.4. Mucositis/Stomatitis. Mucositis or stomatitis is a frequent oral complication for cetuximab (grades 3/4: 0.9%). It mostly affects the nonkeratinized labial and buccal mucosa, the mucosa of the tongue, of the floor of the mouth, and the soft palate and appears 9–16 days after treatment initiation, as this is the epithelial cell turnover time [17, 86]. Stomatitis has been reported with bevacizumab (grades 1/2: 23%) [89]. Tositumomab has a higher rate of severe mucositis than rituximab (52 versus 18%) [50]. Other dermatologic toxicities include the following: maculopapular, erythematous rash, skinxerosis, pruritus, and Stevens-Johnson syndrome. Changes of the nails include pitting, discoloration, and onycholysis, with partial or complete loss of nails [17, 86, 87].

9. Cytopenia

The most profound side effect of radioimmunotherapy (RIT) is potentially prolonged and significant cytopenia with cell count nadirs ranging from four to nine weeks posttherapy with recovery one to four weeks postnadir. The most common cytopenias are leukopenia and thrombocytopenia, which are easily managed in the majority of patients. RIT causes a transient depletion of B cells for approximately six to nine months. Severe and prolonged cytopenia, including both neutropenia and thrombocytopenia is common [2, 3].

Hematologic events during ofatumumab (CD20-directed MoAb), brentuximab vedotin (CD30-directed MoAb), and alemtuzumab (CD52-directed MoAb) treatment included anemia, neutropenia, and thrombocytopenia. Neutropenia (≥ grade 3: 42%; grade 4: 18%; may be prolonged >2 weeks) and anemia (16%; grades 3/4: 5%) have been reported in treatment with ofatumumab. No patients discontinued the drug due to AEs [45]. Grade 3/4 bone marrow suppression may occur in treatment with brentuximab vedotin, as shown by neutropenia (20%), thrombocytopenia (8%), and anemia (6%) [52–54]. Cytopenia in treatment with alemtuzumab includes the following: lymphopenia (grades 3/4: 97%), neutropenia (77%; grade 3/4: 42% to 64%), anemia (76%; grade 3/4: 12% to 38%), and thrombocytopenia (71%; grade 3/4: 13% to 52%). Serious and fatal cytopenia (including pancytopenia, bone marrow hypoplasia, autoimmune hemolytic anemia, and autoimmune idiopathic thrombocytopenia) has occurred. Single doses >30 mg or cumulative weekly doses

Table 4: Adverse events of 20 MoAbs.

MoAb	Adverse events		Reference
	Systemic	Cutaneous	
Cetuximab	IR; cardiopulmonary arrest; GI; pulmonary toxicity; hypomagnesemia; infection; anaphylaxis	Rash/desquamation; acneiform rash; nail changes; pruritus; paronychial inflammation	[7, 11, 16, 17]
Panitumumab	IR; pulmonary fibrosis; electrolyte depletion; peripheral edema; GI; fatigue	Erythema; acneiform rash; pruritus; nail toxicity; exfoliation; paronychia skin fissures; photosensitivity	[18, 19]
Nimotuzumab	Fever; hypotension; tremor; lymphopenia,	Rash and chills	[20, 21]
Bevacizumab	Hypertension; VTE; ATE; GIP; hemorrhage; wound healing complications; fistula/abscess formation; CHF; IR; proteinurea; necrotizing fasciitis	Exfoliative dermatitis; xeroderma; alopecia	[22–27]
Ramucirumab	Hypertension; IR; ATE; GIP; hemorrhage; wound healing complications; RPIS	Skin rash	[28–30]
Trastuzumab	LVD;CHF; IR; pulmonary toxicity; neutropenia; anaphylaxis/angioedema; anemia; GI	Acne vulgaris; nail disorders; pruritus	[31–35]
Trastuzumabemtansine	Hepatotoxicity; LVD; pulmonary events; thrombocytopenia; neurotoxicity; hypersensitivity; IR; GI	Rash; pruritus	[36, 37]
Pertuzumab	IR; cytopenias; GI; PN; hypersensitivity/anaphylaxis; LVD	Alopecia; rash; paronychia; pruritus palmar-plantar erythrodysesthesia;, xeroderma; pruritus	[38–40]
Alemtuzumab	Cytopenias; IR; infections; immunogenicity; hypotension; hypertension; dysrhythmia; pulmonary events	Urticaria; rash; erythema;	[15, 41, 42]
Rituximab	IR; TLS; PML; renal toxicity; infections; cardiac events; pulmonary events; bowel obstruction/perforation; cytopenias; RA; anaphylaxis; HBr; SS; PML	Paraneoplastic pemphigus; rash; pruritus; angioedema; SJS; TEN	[5, 12–14, 43, 44]
Ofatumumab	IR; cytopenias; intestinal obstruction; PML; HBR; pneumonia; infections; dyspnea; diarrhea; PML; TLS	Rash; urticaria; hyperhidrosis	[45, 46]
Obinutuzumab	IR; hypocalcemia, hyperkalemia, hyponatremia; cytopenias; hepatic toxicity; infection; immunogenicity; HBR; PML; TLS	None	[47, 48]
Ibritumomab	IR; infections; severe cytopenias; immunogenicity; secondary malignancies; extravasation/radiation necrosis	EM; SJS; TeN; exfoliativedermatitis; rash;	[8, 49]
Tositumomab	Anaphylaxis; severe cytopenias; IR; fetal harm; hypothyroidism; secondary malignancies; infection	Rash; pruritus; sweating; dermatitis	[44, 50, 51]
Brentuximab Vedotin	PN; IR; cytopenias; TLS; infectionimmunogenicity; PML; anaphylaxis	SJS; rash; pruritus; alopecia	[52–55]

Table 4: Continued.

MoAb	Adverse events		Reference
	Systemic	Cutaneous	
Ipilimumab	IrAEs; diarrhea; fatigue;	Dermatitis; pruritus; rash SJS; TEN	[56, 57]
Catumaxomab	SIRS; abdominal disorders; CRS; pyrexia; cytopenias	Rash; erythema; pruritus	[58]
Denosumab	Hypocalcemia; hypophosphatemia; embryo-fetal toxicity; ONJ and osteomyelitis; fatigue; dyspnea	Dermatitis; eczema; rash; pruritus	[59, 60]
Nivolumab	Fatigue; diarrhea; lymphopenia	Rash; pruritus; vitiligo	[61]
Siltuximab	GIP; IR; IR/hypersensitivity reactions; elevated hemoglobin levels; infection; diarrhea	Pruritus; skin rash	[62]

CRS, cytokine release syndrome; GI, gastrointestinal symptoms, for example, nausea, diarrhea, vomiting, and constipation; HBR, hepatitis B reactivation; IrAEs, immune-mediated reactions due to T cell activation and proliferation (enterocolitis, hepatitis, dermatitis, neuropathies, and endocrinopathies); IR, infusion reactions; LVD, left ventricular dysfunction; ONJ, osteonecrosis of the jaw; PML, progressive multifocal leukoencephalopathy; PN, peripheral neuropathy; SIRS, systemic inflammatory response syndrome; SJS, Stevens-Johnson syndrome; SS, serum sickness-like reactions; RPIS, reversible posterior leukoencephalopathy syndrome; TEN, toxic epidermal necrolysis;, TLS, tumor lysis syndrome.

>90 mg are associated with an increased incidence of pancytopenia [15, 41, 42, 90].

Treatment should be discontinued for serious hematologic or other serious toxicity (except lymphopenia) until the event resolves [45, 53, 90].

10. Other AEs

Progressive multifocal leukoencephalopathy (PML) due to JC virus infection has been reported with rituximab use, which may be fatal. Cases were reported in patients receiving rituximab. With combination chemotherapy, PML onset maybe delayed, although most cases were diagnosed within 12 months of the last rituximab dose. Clinical findings included confusion/disorientation, motor weakness/hemiparesis, altered vision/speech, and poor motor coordination with symptoms progressing over weeks to months. Cases of reversible posterior leukoencephalopathy syndrome (RPLS) have been reported with VEGF antibodies, which may be fatal. Symptoms of RPLS include headache, seizure, confusion, lethargy, blindness and/or other vision change, or neurologic disturbances. Some of the other less common AEs associated with therapeutic monoclonal antibodies used for cancer therapy include the following: fatigue, vomiting, abdominal pain, anorexia, dysphonia, and peripheral neuropathy [17, 33, 68, 74, 91]. Cetuximab and pannitumumab can induce magnesium wasting resulting in clinically significant hypomagnesemia/hypokalemia and hypokalemia [7, 11, 18].

11. Other MoAbs in Ongoing Clinical Trials

Two anti-PD-1 monoclonal antibodies, pembrolizumab and pidilizumab, have demonstrated activity in initial clinical trials in patients with advanced melanoma. Treatment AEs were manageable. The most common toxicities were fatigue, pruritus, rash, diarrhea, and arthralgia (36, 24, 20, 16, and 16%, resp.). Overall 12% of patients experienced grade 3 or 4 AEs [92, 93]. Anti-PD-1 monoclonal antibodies are currently being evaluated in randomized clinical trials. Clinical activity has been observed with several different anti-PD1-L1 monoclonal antibodies, including BMS-936559, MPDL3280A, BMS-936559, and MEDI4736, which has been evaluated in a dose escalation phase I trial with expansion cohorts in NSCLC, melanoma, and renal cell carcinoma [94, 95]. Further results from these studies are pending.

12. Summary

The panel of MoAbs that are approved by international regulatory agencies for the treatment of hematopoietic and solid malignancies has continued to expand. In this paper, we reviewed currently encompassing a stunning amount of 20 distinct molecules for 10 targets. We provide a brief scientific background on the use of MoAbs in cancer therapy, review all types of monoclonal antibodies-related adverse events (e.g., allergy, immune-related adverse events, cardiovascular adverse events, and pulmonary adverse events), and discuss the mechanism and treatment of adverse events (see Table 4).

Humanized monoclonal antibodies (MoAbs) have unique toxicities that differ from those of traditional chemotherapy. With the rapid development of targeted therapy to cancer, adverse events of MoAbs attract increasing attention. Further research is needed to explore the molecular mechanisms that underlie MoAb-related reactions to accurately identify hypersensitivity reactions and to develop new procedures for predicting AEs during MoAb treatment.

Abbreviations

ADCC: Antibody-dependent cellular cytotoxicity
AEs: Adverse events
ARDS: Acute respiratory distress syndrome
ATE: Arterial thromboembolic event

BALF: Bronchoalveolar lavage fluid
BOOP: Bronchiolitis obliterans organizing pneumonia
BSC: Best supportive care
CHF: Congestive heart failure
CTLA-4: Cytotoxic T lymphocyte-associated protein 4
CLL: Chronic lymphocytic leukemia
EGFR: Epidermal growth factor receptor
EpCAM: Epithelial cell adhesion molecule
FDA: Food and Drug Administration
HNC: Head and neck carcinoma
ILD: Interstitial lung disease
irAEs: Immune-related adverse events
LVEF: Left ventricular ejection fraction
MoAb: Monoclonal antibody
NHL: Non-Hodgkin's lymphoma
NSCLC: Non-small cell lung carcinoma
PD-1: Programmed death 1 protein
RPLS: Reversible posterior leukoencephalopathy syndrome
SIR: Standard infusion reaction
T-DM1: Trastuzumabemtansine
VEGF: Vascular endothelial growth factor
VTE: Venous thromboembolic event.

Disclosure

Mei Guan and Yan-Ping Zhou are co-first authors.

Conflict of Interests

There are no potential conflict of interests to disclose.

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Research Article

Clinical Characteristics of Inpatients with Anaphylaxis in China

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Objective. To analyze the clinical characteristics of inpatients with anaphylaxis and the factors that influenced those characteristics. *Methods.* Using the patient records from 1990 to 2013 from three highly ranked Chinese hospitals, we retrospectively analyzed the characteristics of 108 inpatients with anaphylaxis (not anaphylaxis admitted). *Results.* The mean patient age was 42 ± 20 years old and male-to-female ratio was 1 : 1.3. The number of patients with anaphylaxis increased gradually, and cases diagnosed after 2005 accounted for 68.5% of the 108 total cases. The most common trigger was medications. The most common clinical manifestations included cutaneous, nervous, respiratory, circulatory, and digestive signs and symptoms. Male patients were more likely to experience loss of consciousness. Multisystem involvement was more likely to develop in patients with low BP, whereas it was uncommon in those with anaphylaxis induced by antibiotics or anesthetics. Epinephrine was used as the first-line treatment for 56 cases. *Conclusions.* Inpatient with anaphylaxis was more common in female patients and the number increased gradually during the study period. The most common trigger was medications. Patients with low BP were prone to having multisystem involvement, whereas the cases of anaphylaxis induced by antibiotics and anesthetics were less likely to involve multiple organ systems.

1. Introduction

Anaphylaxis is a severe and life-threatening allergic reaction that involves multiple organ systems or the whole body and has an incidence rate of 0.05%–2% [1]. Acute episodes are usually attributed to type I hypersensitivity (immediate hypersensitivity) mediated by IgE. The condition can involve the skin, mucosa, respiratory tract, cardiovascular system, and the digestive tract [2]. Anaphylaxis attacks can cause blood pressure to drop within minutes to a few hours and can be lethal if emergency treatment is not provided in a timely manner. In this retrospective study, we review the clinical manifestations and influencing factors of inpatients with anaphylaxis in these 3 well recognized hospitals in Beijing, aiming to help improve early recognition, diagnosis, and treatment of anaphylaxis in clinical practice.

2. Materials and Methods

2.1. Patients. A total of 108 patients were diagnosed with anaphylaxis from 1990 to 2013 at the Peking Union Medical College Hospital (42 cases) and Peking University First Hospital (22 cases) and from 1993 to 2013 at the General Hospital of the Chinese People's Liberation Army (44 cases).

2.2. Methods. In this retrospective study, all existing records were analyzed retrospectively and anonymously. We selected patients by discharge diagnosis codes; those admitted for anaphylaxis were excluded. We summarized the general patient condition, clinical manifestations during attacks, and factors that influenced the manifestations, including the relationships between gender, age, etiology, and underlying diseases with the laboratory and clinical manifestations of anaphylaxis

and among clinical manifestations, the relationship between blood pressure and multisystem involvement. The study had been approved by ethics committee.

Based on the criteria of the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI) [3], anaphylaxis was diagnosed if the patient presented one of the following 3 clinical scenarios: (a) acute onset (minutes to hours) with involvement of the skin and mucosa, as well as airway obstruction, reduced blood pressure, or symptoms of hypovolemia; (b) at least 2 of the following occurring within minutes or a few hours after contact with or exposure to an allergen: cutaneous and mucosal involvement, airway obstruction, a drop in blood pressure, symptoms of hypovolemia, or gastrointestinal symptoms; (c) reduced blood pressure after exposure to an allergen (systolic pressure <70 mmHg in 1–12-month-old infants, <70 mmHg + 2 × age in 1–10-year-old children, <90 mmHg in 11–17-year-old adolescents, or reduced by over 30% compared to the baseline blood pressure).

The clinical presentations of anaphylaxis mainly involve the skin, respiratory tract, digestive tract, circulatory system, and nervous system. Patients were divided into 2 groups, one with at least 3 systems involved and the other with only 1 or 2 systems involved. The blood pressure and laboratory test results obtained during the episodes and during baseline conditions (times when the patients were not experiencing anaphylaxis attacks) were compared. Routine laboratory tests were conducted using an automatic biochemical analyzer and an automatic hematology analyzer.

2.3. Statistical Analysis. The data were all tested for normal distributions. Normally distributed data were expressed as means ± standard deviation, and paired-sample t-tests were applied to compare blood pressure and heart rate during episodes and during baseline conditions. Data that did not fit a normal pattern of distribution were expressed as medians (i.e., P25 and P75). Among independent samples, normally distributed data were analyzed using a t-test and abnormally distributed data were analyzed using a rank-sum test. Constituent ratios were compared using the chi-square test. P values <0.05 represented statistically significant differences.

3. Results

3.1. General Patient Information. The 108 patients in this study were 42 ± 20 years old (range: 3–76 years), including 46 males and 62 females (male-to-female ratio: 1 : 1.3).

Among the anaphylaxis cases, 42 were inpatients from Peking Union Medical College Hospital, 44 were from the General Hospital of the Chinese People's Liberation Army, and 22 were from Peking University First Hospital. Anaphylaxis cases accounted for 0.005% of the 827,791 and 0.003% of the 786,732 inpatients were treated at the Peking Union Medical College Hospital and Peking University First Hospital, respectively, from 1990 to 2013, and 0.006% of the 796970 at the General Hospital of the Chinese People's Liberation Army from 1993 to 2013.

The cases were 7, 15, 11, 30, and 45 during 1990–1994, 1995–1999, 2000–2004, 2005–2009, and 2010–2013, so the incidence was 0.005%, 0.006%, 0.003%, 0.005%, and 0.004%, respectively.

We evaluated the blood pressure and heart rate during anaphylaxis attacks. Baseline blood pressure was recorded for 105 cases. Blood pressure during attacks was recorded for 102 cases, of which 20 were unobtainable (systolic and diastolic pressures were both recorded as 0 mmHg). The systolic pressure decreased from 117.4 ± 13.8 mmHg during baseline conditions to 54.3 ± 31.9 mmHg during episodes ($P < 0.01$) and the diastolic pressure decreased from 71.6 ± 13.6 mmHg during baseline conditions to 33.9 ± 21.4 mmHg during episodes ($P < 0.01$). Baseline heart rate records were available for all of the patients (81 ± 13 bpm), and the heart rates during episodes were recorded for 78 patients (107 ± 38 bpm) and were found to be significantly increased ($P < 0.01$).

The cause of anaphylaxis was unclear for 4 cases (3.7%). In 97 cases (89.8%), anaphylaxis was presumably triggered by medications, specifically antibiotics in 32 cases (29.6%)—including penicillin, ciprofloxacin, cefoperazone sulbactam, cefmetazole, cravit, or cefaclor; contrast media in 18 cases (16.7%); chemotherapy drugs in 12 cases (11.1%)—including L-asparaginase, sulfur hexafluoride, and cisplatin; anesthetics in 8 cases (7.4%); nutritional support in 7 cases (6.5%); blood products in 6 cases (5.6%); antipyretic analgesics in 4 cases (3.7%); Chinese patent medicines in 3 cases (2.8%); a glucocorticoid in 1 case (0.9%); a vaccine in 1 case (0.9%); and other drugs in 5 cases (4.6%). In the remaining 7 cases, the trigger of anaphylaxis was smell in 1 case (0.9%) and food in 6 cases (5.6%), such as steamed bun of Chinese chive, protein powder, peanut, snapping turtle, wheat, and lactic acid milk biscuit. The symptoms of anaphylaxis developed immediately or within 6 hours after allergen exposure.

Twenty-four patients experienced intraoperative anaphylaxis, including 11 during gynecologic surgery, 3 during otorhinolaryngologic surgery, 2 during pancreatic surgery, 2 during urologic surgery, 2 during cardiac surgery, and 1 each during thyroid, ophthalmic, breast, and gallbladder surgeries. Severe allergic reactions to chemotherapy drugs, antibiotics, anesthetics drugs, and nutritional support were detected in 4 cases, including 2 cases caused by blood transfusion, 1 caused by hemostatic drugs, and 1 caused by glucocorticoids. A history of food and/or drug allergies was positively reported in 28 patients and was not reported for the other 80 patients. Eight patients had a history of acute urticaria, bronchial asthma, or allergic rhinitis.

3.2. Clinical Manifestations of Anaphylaxis and Influencing Factors. Clinical manifestations were presented as follows in the 108 patients: 78 developed skin signs (72.2%), mainly rashes, itching, wheals, redness, and swelling; 59 had nervous system signs (54.6%), primarily loss of consciousness and syncope; 57 had respiratory signs (52.8%), mainly shortness of breath, dyspnea, and wheezing in all areas of the lungs; 45

Table 1: Clinical manifestations of anaphylaxis in the inpatients studied [n (%)].

Clinical manifestation	Number (% or percent)
Rash	67 (62.0)
Dyspnea	50 (46.3)
Loss of consciousness	41 (38.0)
Nausea/vomiting	30 (27.8)
Pale face/lip cyanosis	27 (25.0)
Excessive sweating	23 (21.3)
Palpitation	20 (18.5)
Abdominal pain	14 (13.0)
Facial swelling	13 (12.0)
Lung rale	11 (10.2)
Dizziness	11 (10.2)
Convulsion	9 (8.3)
Impalpable pulse	7 (6.5)
Blurred vision	5 (4.6)
Diarrhea/fecal incontinence	4 (3.7)
Coughing	2 (1.9)
Skin peeling	1 (0.9)

had circulatory signs (41.7%), including pale face, palpitation, excessive sweating, lip cyanosis, and dizziness; and 41 had gastrointestinal signs (38.0%), including nausea, vomiting, abdominal pain, diarrhea, and fecal incontinence. Rashes, dyspnea, and loss of consciousness were the most common signs of anaphylaxis (Table 1).

The relationship between gender and the most common clinical manifestations was as follows: the female-to-male ratio of patients who developed rashes was higher than that of patients with no rash (42 : 25 versus 20 : 21, $P < 0.05$), was significantly lower in patients with dyspnea compared with those who did not have dyspnea (23 : 27 versus 39 : 19, $P < 0.05$), and was also significantly lower in patients presenting loss of consciousness compared with those who did not present this sign (18 : 23 versus 44 : 23, $P < 0.05$).

The relationship between blood pressure and the most common clinical manifestations was as follows: blood pressure was unobtainable in 20 cases, of which 11 (55.0%) had rashes and 11 (55.0%) had dyspnea, neither of which were significantly different from the percentages of the patients with obtainable blood pressure (62.9% and 43.8%); of the patients with unobtainable blood pressure, 55.0% experienced a loss of consciousness, which was significantly higher than that in patients with obtainable blood pressure (33.7%, $P < 0.05$).

For multisystem involvement, the clinical manifestations of anaphylaxis mainly involved the skin, respiratory system, circulatory system, digestive system, and nervous system. In the 108 patients, 53 presented signs in at least 3 systems and 55 presented signs in 1 or 2 systems; comparisons between these groups are shown in Table 2.

3.3. Characteristics of Laboratory Test Results during Anaphylaxis. We used paired-sample t-tests to analyze the following characteristics during both baseline conditions and anaphylaxis episodes: white blood cell and neutrophil tests in 53 patients, percentage and absolute count of eosinophils in 35 patients, blood glucose levels in 38 patients, alanine transaminase and total bilirubin levels in 32 patients, creatinine and blood urea nitrogen levels in 40 patients, serum potassium levels in 50 patients, serum sodium levels in 49 patients, serum chloride levels in 47 patients, and serum calcium levels in 36 patients.

As shown in Table 3, both the white blood cell count and the neutrophil percentage increased significantly during episodes of anaphylaxis (both $P = 0.000$), so did the decrease of eosinophil percentage ($P = 0.000$). A significant increase was detected in the blood glucose levels ($P = 0.000$), but not in the alanine transaminase, total bilirubin, creatinine, or blood urea nitrogen levels. Serum potassium and calcium levels both decreased during anaphylaxis ($P = 0.001, 0.040$), while no significant difference was observed for serum sodium or chloride levels.

3.4. Treatment and Prognoses. Patients were mainly treated with epinephrine and glucocorticoids, which alleviated the anaphylaxis condition in minutes or a few days. Epinephrine, glucocorticoids, and antihistamine were received among 56, 94, and 25 patients, respectively. Improvement or recovery was observed in all cases except for 6 deaths (5.6%). In these 6 patients, who were 43 ± 20 years old, 5 had visited one of the 3 hospitals in this study during the previous 10 years, 2 developed anaphylaxis during an operation, and 1 had a history of bronchial asthma. All episodes were triggered by medication, including 2 by antibiotics, 2 by chemotherapy drugs, 1 by a nutritional supplement, and 1 by a glucocorticoid; 6 patients experienced loss of consciousness and 3 patients had multisystem involvement.

4. Discussion

Anaphylaxis is a severe, rapidly progressing, systemic allergic reaction, usually with multisystem involvement, and is life-threatening if not immediately treated. The patients in this study all had acute onset after contact with or exposure to an allergen immediately or within 6 hours and presented with cutaneous, respiratory, circulatory, gastrointestinal, or nervous symptoms and signs. Patients experienced significant drops in blood pressure compared to baseline conditions, leading to a definitive diagnosis of anaphylaxis according to the criteria of the AAAAI, ACAAI, and JCAAI (revised in 2010) [3].

According to Lieberman [1], the incidence rate of anaphylaxis is 0.05%–2%. However, the incidence rate of anaphylaxis among inpatients in the Peking Union Medical College Hospital, the General Hospital of the Chinese People's Liberation Army, and Peking University First Hospital in this study was 0.005%, 0.006%, and 0.003%, respectively. The reason of stable incidence was due to the increasing of inpatient number. The low incidence maybe has relationship with excluding out-of-hospital anaphylaxis. A retrospective study from Bangkok, Thailand, reported only 6% anaphylaxis developed during hospitalization, with estimated incidence

Table 2: Clinical characteristics of anaphylaxis patients with multisystem involvement.

	Multisystem involvement ($n = 53$)	1-2 system involvement ($n = 55$)	P value
Age (yr, $x \pm s$)	40 ± 21	44 ± 19	NS
Systolic BP during anaphylaxis attacks [mm Hg, median (LQ, UQ)]	33 (0, 40)	68 (50, 80)	<0.05
Diastolic BP during anaphylaxis attacks [mm Hg, median (LQ, UQ)]	26 (0, 35)	45 (30, 48)	<0.05
Female : male ratio	28 : 25	34 : 21	NS
Surgical cases	8	16	<0.05
History of allergy	13	15	NS
Antibiotic- or anesthetic-induced anaphylaxis	16	24	<0.05
Food-induced anaphylaxis	5	1	NS

BP: blood pressure; NS: not significant.

Table 3: Routine laboratory test results during baseline conditions and during anaphylaxis attacks.

Test results	N	Baseline condition	Anaphylaxis attack	P value
WBC count ($\times 10^9$/L, $\overline{x} \pm s$)	53	8.2 ± 4.2	13.9 ± 7.6	0.000
Neutrophil percentage (%, $\overline{x} \pm s$)	53	64.3 ± 17.4	78.5 ± 20.0	0.000
Eosinophil percentage [%, median (LQ, UQ)]	35	0.60 (0.01, 2.15)	0.01 (0.00, 0.10)	0.000
Blood glucose (mmol/L, $\overline{x} \pm s$)	38	6.1 ± 2.7	11.8 ± 4.5	0.000
Alanine transaminase [U/L, median (LQ, UQ)]	32	8.4 (6.3, 12.4)	10.1 (6.9, 14.0)	NS
Total bilirubin (mmol/L, $\overline{x} \pm s$)	32	9.6 ± 4.3	10.0 ± 4.4	NS
Blood creatinine (mmol/L, $\overline{x} \pm s$)	40	79.3 ± 39.7	81.2 ± 49.4	NS
Blood urea nitrogen (mmol/L, $\overline{x} \pm s$)	40	6.1 ± 7.9	6.4 ± 8.0	NS
Serum potassium (mmol/L, $\overline{x} \pm s$)	50	4.0 ± 0.4	3.6 ± 0.7	0.001
Serum sodium (mmol/L, $\overline{x} \pm s$)	49	137.8 ± 6.6	138.4 ± 5.4	NS
Serum chloride (mmol/L, $\overline{x} \pm s$)	47	104.2 ± 5.2	104.5 ± 6.3	NS
Serum calcium (mmol/L, $\overline{x} \pm s$)	36	2.27 ± 0.41	2.12 ± 0.48	0.040

WBC: white blood cell.

0.0011% (5/448211) [4]. As Sheikh and Alves [5] and Gupta et al. [6] reported, the incidence rate of anaphylaxis in 2003-2004 was 7 times higher than in 1990-1991. Although the incidence was low and stable, the number of patients with anaphylaxis increases gradually in this 24-year, 3-centre study, with instances of anaphylaxis occurring after 2005 accounting for 68.5% of all cases. The possible mechanisms for the increasing number of inpatients maybe are as follows: the clinicians pay more attention to anaphylaxis, guidelines increase clinicians' understanding of anaphylaxis, and the types of drugs and testing methods are more and more. This time trend reminds us of the urgency of preventing anaphylaxis, along with the need for technical progress in treating episodes.

Women are affected more often than men [7]. In the present study, most of the anaphylaxis patients were female (62/108). The causes maybe are that women have more chance to experience operation, such as induced abortion, Caesarea, or uterine adnexectomy. The systolic and diastolic pressures during anaphylaxis attacks significantly decreased compared to the baseline conditions ($P < 0.01$), which might have resulted from increased vascular permeability or vascular smooth muscle relaxation induced by histamine release [8]. Heart rates were significantly higher during attacks than during baseline conditions ($P < 0.01$), which might be caused by the decrease in the effective blood volume or by accelerated diastolic depolarization of the sinoatrial node induced by histamine-H1 receptor interactions [9].

Identifying the cause of anaphylaxis is crucial for the targeted prevention of episodes, and medications were by far the most common cause [10, 11]. Except for 4 cases in which the cause was unclear, most of the 108 cases of anaphylaxis in this study were triggered by medications, with some episodes occurring during operations. Considering the rapid development and wide use of new drugs, especially antibiotics, and the common practice of prophylactic antimicrobial treatment for patients undergoing an operation, the most common cause of drug-induced anaphylaxis is therefore antibiotics. With the rising incidence of cardiovascular and cerebrovascular diseases and tumors, contrast media, chemotherapy drugs, nutritional support solutions, blood products, and antipyretic analgesics have also become common triggers of anaphylaxis. The mechanisms underlying drug-induced anaphylaxis include both allergic and nonallergic reactions, with the former being IgE-mediated or non-IgE-mediated and the latter including directional release

of mediators by mast cells and basophils, activation of the contact system, disturbances of arachidonic acid metabolism, and recruitment of complement factors, coagulation factors, and fibrinolytic factors. Among these triggers, antibiotics and anesthetics could induce IgE-mediated allergic reactions, contrast media could induce contact system activation and complement-mediated reactions, both anesthetics and contrast media could activate mast cells, and aspirin and nonsteroidal anti-inflammatory drugs could disrupt arachidonic acid metabolism. Given the mechanisms of drug-induced anaphylaxis, tryptase measurements, blood and/or urine histamine tests, and basophil degranulation tests have thus been the primary diagnostic methods for anaphylaxis [12–14]. Among nondrug triggers, food is the most common cause of anaphylaxis and is also the cause of most out-of-hospital anaphylaxis cases [15]. Although the rate of incidence is lower, food-induced anaphylaxis is often not treated as promptly as drug-induced anaphylaxis in inpatients and thus may be more dangerous.

The most common clinical manifestation of anaphylaxis is on the skin, including urticaria and angioedema, which are observed in 85%–90% cases of anaphylaxis; the most common respiratory sign is edema of the upper respiratory tract, observed in 50%–60% cases; 25%–30% cases present gastrointestinal signs, including nausea, vomiting, diarrhea, and cramp-like abdominal pain; 30%–35% cases have dizziness, syncope, and a blood pressure drop; and a few patients present headache, substernal chest pain, or epileptic seizures [9]. Similar frequencies of clinical manifestations were observed in this study, with skin signs being the most common (72.2%), followed by neurological (54.6%), respiratory (52.8%), circulatory (41.7%), and digestive tract (38.0%) signs.

Respiratory signs and loss of consciousness were more often observed in male patients. Because the patients who experience a blood pressure drop are more likely to develop circulatory and neurological signs, lower diastolic and systolic pressures are correlated with a higher possibility of multisystem involvement. Intraoperative anaphylaxis is seldom associated with multisystem involvement, most likely because under general anesthesia the occurrence of anaphylaxis is usually detected based on a blood pressure drop and reduced oxygen saturation, as shown on monitors, or by a wheal-like rash over the torso or limbs observed after removing sterile drapes. Anaphylaxis in these cases is not based on patient-reported chest distress, shortness of breath, dyspnea, abdominal pain, nausea, vomiting, dizziness, or syncope, in contrast to patients with full consciousness.

Increased white blood cell counts, neutrophil percentages, and blood glucose levels were observed in this study in anaphylaxis patients, which is presumably the result of stress and elevated blood catecholamine levels. A reduction in serum potassium levels during anaphylaxis attacks was also noticed, likely because high catecholamine levels would induce potassium transport into the cells and produce a transient decrease in serum potassium [16]. The reduced serum calcium levels observed in this study have not been reported in previous literature. It has been suggested that the reduction in serum calcium levels in severe anaphylaxis patients might be related to suppressed thyroid function, ineffective activated vitamin D, calcium chelators, and hypomagnesemia or be caused by calcium redistribution induced by inflammatory factors [17].

The first choice treatment for anaphylaxis is the timely administration of epinephrine [1, 18, 19]. Only 56 of 108 patients received epinephrine treatment in the study. The cause maybe is that clinicians in the other departments lack understanding about manifestation and treatment of anaphylaxis. So this is the importance of the study. With the progress of medical technology and an improved understanding of anaphylaxis, the mortality rate associated with this condition has been decreasing. Patients with a history of allergic disease or who present with a loss of consciousness and multisystem involvement have a high risk of death. Therefore, it is important to immediately and correctly recognize, diagnose, and treat anaphylaxis based on knowledge of the clinical manifestations and an understanding of the factors that influence anaphylaxis.

This is, as far as we know, the first inpatient anaphylaxis study among three highly ranked hospitals in China. In this study, we had a few limitations, which were lack of tryptase and sIgE detection. Anaphylaxis is a clinical diagnosis that builds on the clinical criteria [20]. Retrospectively the diagnosis may be supported if serum tryptase is elevated within a few hours after the reaction when compared with the patient's baseline levels; however, tryptase levels did not all increase obviously in anaphylaxis [21, 22]. As for sIgE detection, it can be tested for a few antibiotics in this study and allergy knowledge should be updated for doctors in other specialties. Out-of-hospital anaphylaxis maybe more often happened than inpatient anaphylaxis in our three hospitals, so we will take these patients into account in the further study.

5. Conclusion

In conclusion, the anaphylaxis inpatients studied in the 3 hospitals were more common in female patients. The number of inpatients with anaphylaxis exhibited a rising trend over the study period. During anaphylaxis attacks, the patients presented significantly decreased blood pressure and increased heart rates. The most common causes were drugs, especially antibiotics. The most common clinical manifestations were skin signs; respiratory, neurological, circulatory, and gastrointestinal signs were also common. Male patients were more prone to develop respiratory signs and lose consciousness. The patients presenting a drop in blood pressure during anaphylaxis attacks were more likely to have multisystem involvement, whereas those patients with anaphylaxis induced by antibiotics or anesthetics were less likely to have multisystem involvement.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Rui Tang, Han-Yi Xu, and Ju Cao have the same contribution in this paper.

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Research Article

Diversity of House Dust Mite Species in Xishuangbanna Dai, a Tropical Rainforest Region in Southwest China

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Purpose. To survey the species diversity of home dust mites (HDM) in Xishuangbanna, a tropical rainforest region in Southwest China. *Methods*. From August 2010 to January 2011, mite-allergic patients and healthy controls were invited to participate. Dust samples from the patients' homes were collected, and mites in the samples were isolated. Permanent slides were prepared for morphologically based species determination. *Results*. In total, 6316 mite specimens of morphologically identifiable species were found in 233 dust samples taken from 41 homes. The result shows that the mite family of Pyroglyphidae occupied the highest percentage of the total amount of mites collected, followed by Cheyletidae family. The most common adult Pyroglyphidae mites were *Dermatophagoides* (*D.*) *farinae*, *D. pteronyssinus*, and *D. siboney*. The most common mites found from other families were *Blomia tropicalis*, *Tyrophagus putrescentiae*, and *Aleuroglyphus ovatus*. Four main allergenic dust mite species *D. farinae*, *D. pteronyssinus*, *D. siboney*, and *Blomia tropicalis* were found to be coinhabiting in 6/41 homes. *Conclusion*. The HDM population in homes in Xishuangbanna, a tropical rainforest region in Southwest China, has its own characteristics. It has rich dust mite species and the dust mite densities do not show significant variation across seasons.

1. Introduction

Presently, approximately 10 million Chinese children suffer from asthma and about 50 million Chinese adults have allergic rhinitis [1–6]. In the past ten years, the allergic diseases have increased in prevalence all over the world and have become a public health problem [5–7]. Various kinds of allergens can lead to allergic diseases. Among these allergens, home dust mites have been considered as the major source of allergen and more than 50% of allergic diseases in clinics are attributed to them [8]. Therefore, research of HDM region distribution may help in allergic diseases' prevention and treatment [9].

China is large, and its climate varies from tropical zone to cold temperate zone. It is evident that the predominant allergenic mite species differ across diverse regions of China [10–13]. For example, in Northern China region (Beijing), the predominant species were *D. farinae*, *D. pteronyssinus*, and *D. siboney*. In Central China region (Shanghai), the predominant species were *D. pteronyssinus, Hirstia domicola*, and *Glycyphagus privatus*. In Southern China region (Guangzhou), the predominant species were *D. pteronyssinus*, *D. farinae*, and *B. freemani*. In Guangxi province, a subtropical region in Southern China, the predominant species were *D. farina* and *D. pteronyssinus*. These surveys of the distribution of domestic mites in China have been conducted mostly in the densely populated and highly industrialized central cities of China. Wide use of air-conditioner in industrialized cities may be related to growth of dust mites.

There are no reports about HDM surveys in tropical rainforest area of China. In the present study, to improve our understanding of the national epidemic of allergic diseases in China, we investigated the distribution of HDM in Xishuangbanna Dai, P.R. China, which is a special city in a

tropical rainforest biome. We compared mite distributions in Xishuangbanna area homes between its rainy and dry seasons and compared the seasonal distributions in Xishuangbanna and in Beijing [10, 11].

2. Materials and Methods

2.1. Study Groups and Allergy Tests. The survey subjects included a case group and a control group. The case group consisted of 31 homes of patients who were admitted to Xishuangbanna Dai Autonomous Prefecture Hospital and diagnosed by specialists with mite-related allergic diseases between August 2010 and January 2011. Their diagnoses were based on comprehensive considerations about disease history, symptoms, signs, skin prick test results, and serum sIgE test results. The case group only included homes where patients had positive skin prick test results from *D. farinae* and *D. pteronyssinus* (ALK Denmark skin prick test solution) and sIgE positivity of at least 2 classes (d1 and d2 from Phadia, Sweden). The control group consisted of 10 homes without any mite-allergic patients selected via the same diagnostic procedure. In accordance with Good Clinical Practice, we acquired their permission to collect their house dust. The patient information was anonymized. The Institutional Review Board of Peking Union Medical College Hospital approved the study protocol.

2.2. Dust Collection Methods. Dust samples were collected with a 1200 W vacuum attached securely to an ALK Dust Trap (ALK. Copenhagen, Denmark) with a vacuum hose and O-ring and a measuring device to define 1 m^2 of collection area or a scale. The filter dish was removed carefully to prevent dust spillage. Each collection dish was covered with a lid, sealed, and labeled with date and place information. The vacuum nozzle was stored vertically to prevent dust from falling out after vacuuming. The nozzle was rinsed and dried before being fitted with a new filter dish for collection of the next sample.

Collection sites were locations where mites survive and breed easily (i.e., pillows, quilts, sheets, sleeping pads and mattresses, sofas, rugs, and carpet floors). Collections were made by placing the vacuum nozzle over a defined 1 m^2 area for 3 minutes. Samples were collected from the entire selected surface. The collection time was shortened to 2 minutes for places with surface area less than 1 m^2 (such as pillows, sofas, and rugs).

All dust samples were collected and prepared by two researchers (Qing-Hua Luo and Yu-Ling Zhou). For each sample, a record of which collection device and filter plate were used, the collection location, and other related information such as the family's living conditions was kept. Dust samples were transported to the lab in Xishuangbanna. Whenever possible, the mites within the samples were isolated immediately; otherwise, they were stored frozen at −20°C for later isolation [10, 11].

2.3. Isolation, Storage, and Identification of Mites. The flotation method was used to extract mite bodies from the dust samples. Isolated mite specimens were stored in 70% alcohol. For convenient morphological species identification of individual mites, permanent slides were prepared using Hoyer's Medium and observed under a light microscope. Species were identified in accordance with the morphological characteristics described by Krantz and Walter and other related information [10, 11, 14–16].

3. Data Analysis

The mite-positive rate of samples was calculated as follows: positive rate is positive sample number/total sample number × 100%. The number of mites in each mite species within each sample was counted, and the percentage of each species relative to the total mite counted for each sample was calculated. All mite bodies were counted, whether they were alive, dead, or physically damaged. Mite density was calculated for each sample as follows: mite density is total number of mites detected/weight of isolated dust (in g). If the number of mite species obtained from the same location at different time points differed, the average number was used for the distribution calculations. The Xishuangbanna HDM data obtained in this study were compared to analogous data from a study conducted in Beijing during the same time span from December 2008 to January 2010 ($n = 38$ homes) [10, 11].

Rank sum tests for two independent samples (Mann-Whitney U test) were used to compare mite density data between Xishuangbanna and Beijing. A Chi-square test of two independent samples was used to compare the prevalence of mites between Xishuangbanna and Beijing. A row mean score differ statistic was used to compare the dust mite densities between the case and control groups. Statistical analysis was conducted with statistical software SPSS 13.0. A statistical level of $\alpha = 0.05$ was considered significant for two-tailed tests.

4. Results

4.1. Characterization of Dust Mite Population and Distribution. A total of 233 dust samples were collected from 41 homes in the Xishuangbanna area between August 2010 and February 2011. Mites were detected in 186/233 samples (79.8%) and 40/41 homes (97.5%). In total, 6,349 live, intact mites in various development stages were detected. They were distributed among 877 slides. Species identification was possible for 6316/6349 of the mites. This group of 6316 identified specimens (the damaged remains of dead mites were not identified) included mites spanning 23 species in 15 genera, representing 12 families belonging to 3 orders of Acari. Notably, the four main allergenic HDM including *D. farinae*, *D. pteronyssinus*, *D. siboney*, and *Blomia (B.) tropicalis* were found together, for the first time in China, in 6/41 homes. Additionally, 40 individual insects (class Insecta, order Psocoptera) were identified; they included two barklice species (family Liposcelididae) of the same genus (Table 1).

The numbers and percentages of individual arachnids and insects of particular species are reported in Table 1, together with the numbers and percentages of dust samples and homes

Table 1: Composition of mites and insects in house dust in Xishuangbanna area.

Species	Sampled homes[a,b] (n = 41)		Samples[b] (n = 233)		Mites[c] (n = 6349)	
	Number	%	Number	%	Number	%
Acari	40	97.56	186	79.83	6316	99.48
Astigmata	40	97.56	183	78.54	6157	96.98
Pyroglyphidae	40	97.56	182	78.11	6102	96.11
D. farinae	40	97.56	167	71.67	4001	63.02
D. pteronyssinus	38	92.68	126	54.08	1128	17.77
D. siboney	20	48.78	39	16.74	101	1.59
Nymph	38	92.68	126	54.08	818	12.88
Larva	19	46.34	27	11.59	54	0.85
Acaridae	14	34.15	19	8.15	34	0.54
T. putrescentiae	10	24.39	16	6.87	28	0.44
A. ovatus	3	7.32	3	1.29	6	0.09
Glycyphagidae	13	31.71	16	6.87	19	0.30
B. tropicalis	10	24.39	16	6.87	19	0.30
Histiostomatidae	2	4.88	2	0.86	2	0.03
Oribatida	5	12.20	8	3.43	26	0.41
Haplochthoniidae	5	12.20	8	3.43	25	0.39
Unidentified	1	2.44	1	0.43	1	0.02
Prostigmata	27	65.85	54	23.18	123	1.94
Cheyletidae	27	65.85	54	23.18	123	1.94
Mesostigmata	5	12.20	8	3.43	10	0.16
Blattisociidae	3	7.32	6	2.58	8	0.13
Laelapidae Berlese	2	4.88	2	0.86	2	0.03
Insecta	10	24.39	12	5.15	33	0.52
Liposcelididae	6	14.63	6	2.58	22	0.35
Unidentified	6	14.63	7	3.00	11	0.17
Total number identified	40	97.56	186	79.83	6349	
Total number collected	41		233			

[a]Homes with more than one sample were regarded as the same home. [b]The percentages of homes and samples were calculated with total number collected as the denominator. [c]The percentage of individual specimens was calculated with total number identified as the denominator.

positive for particular species. The Pyroglyphidae family was most prevalent among the mite species detected (96.6%), followed by Cheyletidae (2.0%). The small minority of non-Pyroglyphidae mites isolated were composed of Prostigmata (57.1%), Acaridae (16.3%), Oribatida (12.0%), other Astigmata (10.4%), and Mesostigmata (5.2%).

Among the predominant Pyroglyphidae mites, most were adults (85.7%), followed by nymphs (13.4%) and larvae (0.9%). *D. farinae* made up more than three quarters (77.0%) of the adult Pyroglyphidae mites (Table 1), including 1483/4001 (37.1%) males and 2518/4001 (62.9%) females. *D. pteronyssinus*, the second most prevalent Pyroglyphidae, constituted about a fifth of the adult Pyroglyphidae mites (21.6%), including 511/1128 (45.3%) males and 617/1128 (54.7%) females. *D. siboney* ranked a distant third (1.9%), including 49/101 (48.5%) males and 52/101 (51.5%) females.

The detailed counts and percentages of mites of the particular species of mites observed are reported in Table 1. Briefly, the order of mite specimen prevalence overall was *D. farinae* ≫ *D. pteronyssinus* ≫ *D. siboney* > *Tyrophagus putrescentiae* > *B. tropicalis* > *Aleuroglyphus ovatus*. The distribution of homes positive for each of these species followed a similar order, except that *T. putrescentiae* and *B. tropicalis* were found in an equal number of homes. Hence, although most of the aforementioned species were present in low numbers, relative to *D. farinae*, they were widespread in Xishuangbanna area homes.

Multiple mite species were often found within homes and within dust samples. Among the 41 surveyed homes, 2 homes had eight species of mites, 1 had seven species, 2 had six species, 6 had five species, 14 had four species, 11 had three species, 3 had two species, 1 had one species, and only 1 home had no mites. The predominant mite species was *D. farinae* in most of the homes (33/41; 80.5%) and *D. pteronyssinus* in about one-sixth of the homes (7/41; 17.1%). In homes with duplicate collection, the predominant mite species did not change. Generally, the predominant mite species within each sample constituted greater than 70% of the mites observed in that sample, and species predominance was consistent across samples from homes that were sampled more than once.

Table 2: Comparisons of the mite density in case homes versus control homes.

Group (number of samples)	Mite density, number of samples (%)		
	Low[a]	Medium[b]	High[c]
Case (n = 192)	110 (57.3%)	59 (30.7%)	23 (12.0%)
Control (n = 41)	21 (51.2%)	12 (29.3%)	8 (19.5%)

[a] ≤100 mites/g dust. [b]100–500 mites/g dust. [c] >500 mites/g dust.
Note: the value of row mean score differ test was 1.2184 and the P value was 0.2697, which indicated that there were no differences in the mite densities between case and control homes.

4.2. Mite Density Comparisons between Seasons and Regions. Domestic mite densities in Xishuangbanna area are shown by season in Figures 1(a)–1(d). We found the mean mite density for 18 sites was 171.7 mites/g in wet season and 111.1 mites/g in dry season, respectively (Figure 1(a)). Although the mean mite density in wet season was higher than that in the dry season, this difference was not significant ($P = 0.103 > 0.05$) after Wilcoxon signed rank test by two paired samples for these two seasons. Also, we found there were no statistical differences in mite density for both *D. farinae* (Figure 1(b)) and *D. pteronyssinus* (Figure 1(c)) after paired t-test between wet season and dry season ($P = 0.311 > 0.05$ for *D. farinae* and $P = 0.091 > 0.05$ for *D. pteronyssinus*). In addition, the mite density for *B. tropicalis* in wet season was higher than that in dry season ($P = 0.02 < 0.05$) (Figure 1(d)).

The mite densities and positivity rates in the Xishuangbanna area differed markedly from analogous data for samples collected in the Beijing area (December 2008 to January 2010) [4, 5], revealing a significant geographical variation in mite populations ($P < 0.001$). The positive detection rate (positive sample number/total sample number) for domestic mites was higher in Xishuangbanna (79.8%) than in Beijing (64.6%; $P < 0.001$).

4.3. Domestic Mite Density in Case versus Control Groups. As reported in detail in Table 2, we found no differences in mite densities between the case group (homes of patients with mite allergies) and the control group (homes of healthy controls) ($P = 0.2697 > 0.05$). The two groups had similar representations of low-density (≤100 mites per g of dust), medium-density (≤100 mites per g of dust), and high-density (>500 mites per g of dust) samples, as well as similar densities overall (Table 2).

5. Discussion

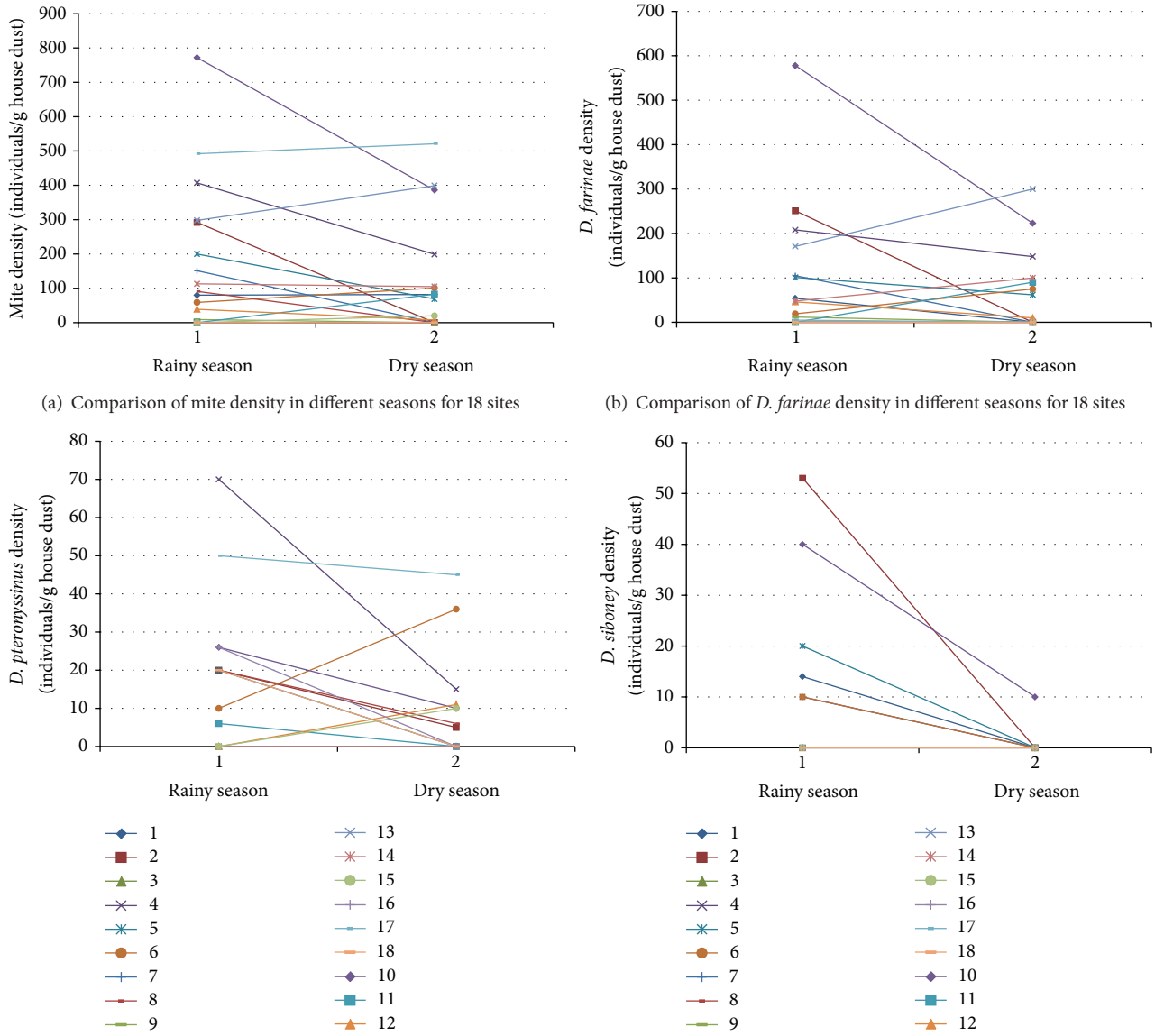
The present results confirm that home dust mites exist in Xishuangbanna area. We found that *D. farinae* was the most prevalent mite species in Xishuangbanna home dust samples, as is the case in Beijing [10, 11]. In contrast, the most prevalent mite species observed in Taiwan [17] and Hong Kong [18], cities which have latitudes similar to Xishuangbanna area, were *D. pteronyssinus* and *B. tropicalis*, respectively. This difference may be due to the difference of the environment and climate. For example, Xishuangbanna is inland and tropical, whereas Taiwan and Hong Kong are coastal and subtropical. Interestingly, a similar dissociation of cites at similar latitudes was found between Italy and the USA, where *D. farinae* and *D. pteronyssinus* were found to be the predominant mite species, respectively [19, 20].

The factors affecting the distribution and abundance of mite species are quite complex, involving not only geographical factors such as latitude, seasonality, climate, rainfall, altitude, and distance from a coast, but also household factors such as neighborhood location, building age and materials, house orientation, ventilation and thermal systems, family economic conditions, surrounding foliage, types of furnishings, and number of occupants and their smoking status and health habits [21–24]. It is clear that the concentration of mite allergens in houses is influenced by multiple factors related to climate, housing design, and the behavior of the occupants. In the current study, for the domestic mite density, there was little seasonal effect and no difference between the houses of mite-allergic patients with asthma or allergic rhinitis and those of healthy controls. This may be caused by the special climate of the region. In a consistently humid and warm climate, mite exposure is likely to be present in all houses.

D. siboney and *B. tropicalis*, which were also detected in this survey, albeit at lower amounts, are major allergen culprits in some subtropical and tropical regions. For example, *D. siboney* is the predominant mite allergen in Cuba [14] and Puerto Rico [15], whereas *B. tropicalis* is the predominant mite allergen in Singapore [25], Malaysia [26], the Philippines [27], Taiwan [17], and Hong Kong [18]. Although *D. pteronyssinus, D. siboney*, and *B. tropicalis* were minor species in Xishuangbanna in terms of percentage of dust mites observed, relative to *D. farinae*, they were detected commonly. Indeed, for the first time, *D. farinae, D. pteronyssinus, D. siboney*, and *B. tropicalis* were found to be coinhabiting. Further study is needed to elucidate the importance of these minor mite species in allergic disease in Xishuangbanna and other tropical regions.

Mite densities and positive detection rates were significantly lower in Beijing than in Xishuangbanna, perhaps due to their different geographical and climate characteristics and the large difference in latitude between the two areas. Indeed, it is not surprising that dust mites would be present in large numbers in tropical areas, such as Xishuangbanna, with mild temperature changes and a high relative humidity, which are optimal conditions for growth of the dust mites.

We observed no differences between the homes of mite-allergic people (case group) and homes of nonallergic people (control group) in terms of overall mite densities, nor in terms of numbers of homes with low, medium, or high densities of mites. Experts at an international seminar regarding mites and asthma held in 1988 reached a consensus that mite density of more than 100 mites per g of dust is a risk factor for sensitization and development of asthma (our cut-off between low- and medium-density samples) and that a mite density of more than 500 mites per g of dust is a risk factor for development of acute asthma attacks in mite-allergic patients (our cut-off between medium- and high-density samples). These cut-off values were used in our case versus control comparisons because they have been accepted indicators in mite research internationally for the last two decades [28]. The fact that there were no differences between mite densities



(a) Comparison of mite density in different seasons for 18 sites

(b) Comparison of *D. farinae* density in different seasons for 18 sites

(c) Comparison of *D. pteronyssinus* density in different seasons for 18 sites

(d) Comparison of *D. siboney* density in different seasons for 18 sites

Figure 1: Comparisons across the seasons of total mite (a), *D. farinae* (b), *D. pteronyssinus* (c), and *D. siboney* (d) densities at 18 sites.

in the case versus control groups underscores the notion that mites are free-living organisms whose living patterns are independent of human beings, while also arguing against the perspective that allergic patients' symptoms are due to higher-than-average mite levels in their homes. We consider that the allergic diseases are associated with both of the complex environmental elements and the individual genetic characteristics rather than a single factor such as the home dust mite density.

In conclusion, the present study showed that the HDM population in Xishuangbanna area has its own characteristics. It has rich dust mite species. Four main allergenic dust mite species including *D. farinae, D. pteronyssinus, D. siboney*, and *Blomia tropicalis* were found to be coinhabiting. Compared to Beijing area, the dust mite densities in Xishuangbanna area did not show significant variation across seasons. Primary investigation showed that there were no differences in mite densities between the homes of mite allergies and the healthy controls in this area.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Efficacy of Sublingual Immunotherapy with *Dermatophagoides farinae* Extract in Monosensitized and Polysensitized Patients with Allergic Rhinitis: Clinical Observation and Analysis

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Aim. To investigate differences in the efficacy of sublingual immunotherapy with *Dermatophagoides farinae* drops in monosensitized and polysensitized allergic rhinitis patients. *Methods*. The patients enrolled in the study were treated for more than one year by sublingual immunotherapy (SLIT) using *Dermatophagoides farinae* drops and were divided into a monosensitized group ($n = 20$) and a polysensitized group ($n = 30$). Total nasal symptom scores of patients before and after SLIT were analyzed to evaluate the curative effect. The phylogenetic tree of dust mite allergens as well as other allergens that were tested by skin prick test was constructed to help the analysis. *Results*. There was no significant difference in the efficacy of SLIT between dust mite monosensitized and polysensitized patients. *Conclusions*. Both dust mite monosensitized and polysensitized patients could be cured by SLIT using *Dermatophagoides farinae* drops. This study provides a reference for the selection of allergens to be used in immunotherapy for polysensitized AR patients.

1. Introduction

Allergic rhinitis (AR) is a global health problem that seriously affects patients' daily life [1]. Epidemiological data indicates that AR and asthma are the same airway disease. There is a great desire for treatments of AR that can also prevent and control the occurrence and progress of bronchial asthma [2]. Some studies have shown that patients with reactivity to multiple allergens accounted for a large proportion of the allergic population [3–5] and reactivity to house dust mite (HDM) is the most prevalent allergen seen in the patients with asthma and AR [6]. Treatments for AR include avoidance, symptomatic treatment, and allergen immunotherapy. Allergen-specific immunotherapy (ASIT) is currently the only available treatment able to moderate the typical symptoms of AR [7]. However, conventional subcutaneous ASIT requires 30 to 80 injections in three to five years, which leads to poor compliance by the patients. In contrast, sublingual immunotherapy (SLIT) offers a noninvasive, nonpainful, and more convenient treatment. We analyzed the differences in the curative effect of treatment with dust mite SLIT between monosensitized and polysensitized patients in order to help us build a foundation for further development of representative allergen-specific immunotherapy.

2. Materials and Methods

2.1. Study Population. All patients who consulted the Allergy Department in the Second Affiliated Hospital of Guangzhou Medical University between January 2008 and August 2012

were consecutively enrolled. The inclusion criteria were as follows: (1) aged between 4 and 60; (2) diagnosed with moderate to severe dust mite AR through medical interviews and clinical symptoms by allergists according to criteria described by Allergic Rhinitis and its Impact on Asthma (ARIA) [8]; (3) having positive skin prick test (SPT) to dust mite allergens; (4) having dust mite specific IgE higher than 0.35 kU/L; (5) having duration of SLIT at least one year; (6) willing to accept follow-up evaluation and stop the treatment for 1 to 2 years; (7) not having acute or chronic sinusitis, organic nasal disease, nonallergic autoimmune disease, malignant tumor, chronic infection, or mental disorder. Written informed consent was obtained from all subjects. According to the results of the SPT and allergen-specific IgE antibodies, patients were divided into two groups that were either monosensitized to dust mite only or polysensitized to dust mite as well as other allergens.

2.2. Skin Prick Test. SPT was performed by trained nurses on the volar aspect of the subjects' forearms with 50 mg/mL to 200 mg/mL of inhalant allergen extracts using standard procedures. None of the patients had taken medications that might interfere with SPT two weeks before the test. SPT was performed using the following inhalant allergen extracts prepared in a sterile environment followed by toxicity and potency evaluation according to an in-house standard protocol as described [9]: 67 mg/mL animal dander (duck, chicken, rabbit, porcine, and goose), 50 mg/mL spring pollen (*Acacia confusa* Merr., pine tree, cedar, *Broussonetia papyrifera*, *Myrica rubra*, Chinese Mulberry, and *Livistona chinensis*), 50 mg/mL summer pollen (maize, *Casuarina equisetifolia*, *Melia azedarach*, and *Eucalyptus camaldulensis*), 50 mg/mL autumn pollen (*Mallotus apelta*, *Humulus scandens*, mugwort, *Vitex negundo,* and *Sesbania cannabina* Pers.), 50 mg/mL winter pollen (*Melaleuca leucadendra* and *Bauhinia blakeana* Dunn.), 50 mg/mL spiny amaranth (*Amaranthus spinosus* L.) pollen, 50 mg/mL cockroaches, 50 mg/mL moths, 50 mg/mL bees, 67 mg/mL silk, 50 mg/mL mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), 200 mg/mL house dust, 67 mg/mL padding, 67 mg/mL cat hair, and 67 mg/mL dog hair. Buffer solution was used as a negative control and 10 mg/mL histamine dihydrochloride (ALK-Abello, Hørsholm, Denmark) was used as positive control concurrently with SPT. Each drop of allergen extract solution was approximately 15 μL and was pricked onto the skin with a sterile lancet (ALK-Abello, Hørsholm, Denmark). The distance between the location of the positive control and the locations of the allergen extracts was more than 4 cm. SPT results were recorded after 15 min and the wheals were outlined and transferred to paper with transparent tape. The mean wheal diameter (MD) was calculated according to the formula $(D + d)/2$, where D was the largest longitudinal diameter and d was the largest transverse diameter. The mean value of the wheals was calculated and considered positive if at least 3 mm in diameter.

2.3. Determination of Allergen-Specific Antibodies. Serum allergen-specific IgE antibody was measured using the ImmunoCAP technology-UNICAP 100 (Pharmacia AB Diagnostics, Uppsala, Sweden). A positive result was defined as ≥0.35 kU/L.

2.4. Evaluation of Nasal Symptoms. Nasal symptoms were recorded before and after the therapy using questionnaires and a total nasal symptoms score was calculated [10] (Table 1). The therapy effectiveness was calculated for each patient as (the symptom score before therapy − symptom score after therapy) × 100%/symptom score before therapy. The patients were discriminated into three classes according to their therapy effectiveness: therapy effectiveness being more than 65% was regarded as markedly effective, 65%~26% effective, and less than 26% ineffective.

2.5. Sublingual Immunotherapy. The treatment course was at least 12 months and was performed with *Dermatophagoides farinae* drops (Figure 1). The concentration of *Dermatophagoides farinae* drops number 1 to number 5 was 1 μg/mL, 10 μg/mL, 100 μg/mL, 333 μg/mL, and 1000 μg/mL, respectively. These drops include increasing therapeutic doses and a maintenance dose. Number 1 to number 4 were the increasing doses and number 5 was the maintenance dose for patients above 14 years of age. For patients under the age of 14, number 1 to number 3 were the increasing doses and number 4 was the maintenance dose. Daily doses of drops number 1 through number 3 were administered as 1, 2, 3, 4, 6, 8, or 10 drops every 7 days, followed by maintenance doses using 3 drops of number 4 and number 5. Drops were instructed to be kept under the tongue for 2 min before being swallowed.

2.6. Statistical Method. Qualitative data were analyzed using statistical software SPSS 13.0 (SoftPol, IBM, USA). The Kruskal-Wallis (KW) test was used for analysis of differences in curative effects. Statistical significance was assumed at $P < 0.05$.

2.7. Phylogenetic Tree of Der p 10. Amino acid sequences of Der p 10 and other homological allergens were searched in UniprotKB (http://www.uniprot.org/). Identity comparison was made with ClustalX 1.83 and the phylogenic tree was generated by MEGA 4.1.

3. Results and Discussion

3.1. Symptom Scores. 50 patients were enrolled after screening and all of them lived in an urban environment. The curative effects of patients treated with sublingual immunotherapy for more than 1 year were analyzed. 22 of 50 patients reported markedly effective relief of symptoms, 15 cases reported effective relief, and 13 cases reported ineffective relief, with a total of 74% of patients reporting a relief of their symptoms (markedly effective + effective).

3.2. Distribution of Sensitized Patients to Specific Allergens. After combining their medical records with clinical manifestations, SPT, and serological testing results, patients were divided into two groups: monosensitized to only dust mite or polysensitized to multiple allergens. We found that 30 of the 50 patients (60%) were polysensitized to a variety of allergens other than dust mite. Accordingly, we further

Table 1: Standards of symptom score of allergic rhinitis.

Symptom score	Sneeze*	Rhinorrhoea#	Rhinobyon	Rhinocnesmus
1	3~5	≤4	Conscious inspiratory	Intermittent
2	6~10	5~9	Intermittent	Formication but supportable
3	≥11	≥10	Mostly breathing through mouth	Formication and insupportable

*The number of continuous sneezes. #The number of times blowing nose per day.

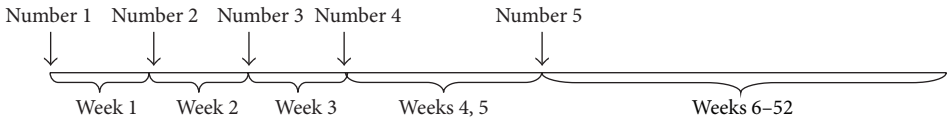

Figure 1: Dosage regimen of SLIT using *Dermatophagoides farinae* drops. Drops number 1 to number 3 with daily doses of 1, 2, 3, 4, 6, 8, or 10 drops were administered for the first three weeks, followed by daily maintenance doses using 3 drops of number 4 or number 5 in the following two weeks and after the 6th week, respectively.

Table 2: Skin prick tests results*.

Allergen species	Positive cases	% positive in polysensitized patients	% positive in all patients
Dust mite	30	100.0	100.0
Animal dander	16	53.0	32.0
Spring pollen	10	33.0	20.0
Summer pollen	13	43.0	26.0
Autumn pollen	15	50.0	30.0
Winter pollen	21	70.0	42.0
Amaranth thorn	13	43.0	26.0
Cockroach	25	83.0	50.0
Moth	15	50.0	30.0
Honey bee	13	43.0	26.0
Silk	19	63.0	38.0
House dust	11	37.0	22.0
Padding	7	23.0	14.0
Cocoon filament	7	23.0	14.0
Cat hair	12	40.0	24.0
Dog hair	9	30.0	18.0

*The other 20 patients are only allergic to dust mite based on the results of skin prick test.

analyzed the rate of positive sensitivity of these patients to other allergens (Table 2). The most common positive allergens were cockroach (83.0%), winter pollen (70.0%), and silk (63.0%). In consideration of potential cross-reactivity between dust mite and other allergens [11], we further analyzed whether SLIT with *Dermatophagoides farinae* drops was able to elicit the same effectiveness in polysensitized patients as in monosensitized patients.

3.3. Comparison of SLIT Effectiveness between Monosensitized and Polysensitized Patients. Differences in the efficiency of SLIT with *Dermatophagoides farinae* drops between monosensitized patients and polysensitized patients (Table 3) were analyzed. Based on $\alpha = 0.05$, there was no significant difference in curative effects between the two groups ($P > 0.05$), which meant that SLIT with *Dermatophagoides farinae* drops improved nasal symptoms to a similar degree in both monosensitized and polysensitized patients. In a previous study, Malling et al. [12] performed immunotherapy using a single species grass vaccine and demonstrated that it was equally effective in polysensitized and monosensitized subjects.

3.4. Cross-Reactivity Analysis of Dust Mite Allergen. 83% of the polysensitized patients allergic to dust mite were also allergic to cockroach (Table 2). Previously, many researches have reported that dust mite allergen is highly cross-reactive with other allergens. Therefore, we considered the cross-reactivity of dust mite allergen with other allergens during our analysis. Here, we used bioinformatics methods to explore common identities among dust mite, cockroach, silk, and other allergens. The phylogenetic tree of dust mite major allergen Der p 10 and other allergens showed that identity between Der p 10, silkworm allergen Bomb m 7, and cockroach allergen Bla g 7 had reached 80% (Figure 2), and the identity between Der p 10 and moth allergen Lon o 7 was 65%. FAO/WHO experts on the allergenicity of foods [13] advise that cross-reactivity between food allergens has to be considered when there is more than 35% identity in the amino acid sequence of the allergens, using a window of 80 amino acids and a suitable gap penalty. To a certain degree, this advice might be applicable to aeroallergens like Der p 10. Because of the high amino acid identity with other aeroallergens, Der p 10 could be cross-reactive with some other inhaled allergens, which could lead to the high positive rate to cockroach, silk, and moth seen in dust mite sensitized patients.

Data from 11,355 subjects in the first European Community Respiratory Health Survey showed that 16.2% to 19.6% were monosensitized patients and 12.8% to 25.3% were polysensitized [3]. Although polysensitized patients were a large proportion of the survey, immunotherapy cannot be performed in response to every positive reaction to allergen preparations as some positive results are caused by cross-reactivity. Fortunately, our study showed that immunotherapy with house dust mite extract was equally effective in the AR subjects who were sensitized to multiple allergens when compared with the monosensitized subjects. Ciprandi et al. [14–16] have also published several reports on the use

Table 3: Curative effect analysis of polysensitized and monosensitized patients.

Group	Curative effect			H_C value	$\chi^2_{0.05,1}$	P value
	Markedly effective	Effective	Ineffective			
Monosensitized	9 (45%)	7 (40%)	4 (20%)	0.1890	3.841	0.663
Polysensitized	13 (43%)	8 (27%)	9 (30%)			
Total	22	15	13			

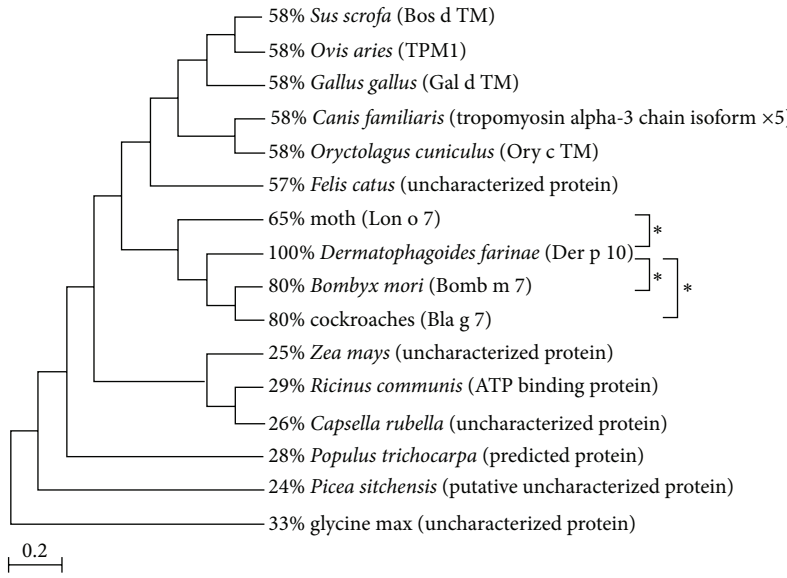

Figure 2: The phylogenetic tree (N-J method) and amino acid identity between Der p 10 and other allergens used for SPT.

of primarily single allergen SLIT in polysensitized subjects and concluded that single allergen SLIT was safe and effective in polysensitized patients. However, a placebo effect was not considered in our study, which could potentially have caused a 1.3% increased response to SLIT according to the research [17] and, thus, double-blind placebo-controlled trials will be performed in our further studies.

In this study, we found that most dust mite sensitized patients also reacted to winter pollen, silkworm, cockroach, and moth. We further explored the relationship between dust mite allergen and other allergens using a phylogenetic tree, which showed a high identity between dust mite major allergen Der p 10 and silkworm, cockroach, and moth allergens. Therefore, we concluded that this cross-reactivity among dust mite, silkworm, cockroach, and moth allergens played a critical role in the development of AR. Dust mite extract used for immunotherapy was composed of more than 20 different house dust mite (HDM) allergens including major allergens Der p 1, Der p 2, and Der p 10. Many researchers have reported that Der p 10, one of the tropomyosin derivatives, has a high cross-reactivity with other tropomyosin allergens (Bla g 7, Pen a 1, etc.) [18–20], but in some regions such as American inner cities, France, and Italy this is rare [21, 22]. One possible explanation might be that the factors that influence cross-reactivity between mite allergens and other tropomyosin allergens are complicated and that dietary habits, living environment, and genetics all play a role in the development of multiple sensitivities and could affect therapeutic and assay results.

Resch et al. reported [23] that the patients who were positive in Der p 10-IgE tests were generally sensitive to many other allergens and, thus, Der p 10 might be a diagnostic marker for HDM allergic patients who are not sensitive to Der p 1 and Der p 2 but react to other HDM allergens. In addition, Bronnert described IgE to Der p 1, Der p 2, and Der p 10 as the markers for HDM allergy [24]. Immunotherapy with representative allergens based on cross-allergenicity is the tendency and using Der p 1, Der p 2, and Der p 10 as immunotherapy vaccines represents an attractive treatment option, especially for polysensitized patients.

4. Conclusion

In this study, we determined that SLIT with *Dermatophagoides farinae* drops in polysensitized house dust mite AR patients showed improvements in nasal symptoms comparable to that seen in monosensitized patients.

Conflict of Interests

The authors report no conflict of interests.

Authors' Contribution

Chen-Xia Xu and Miao-Lian Zhang contribute equally.

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Review Article

Analysis of Anaphylactic Shock Caused by 17 Types of Traditional Chinese Medicine Injections Used to Treat Cardiovascular and Cerebrovascular Diseases

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Several reports describing anaphylactic shock following treatment of cardiovascular and cerebrovascular diseases with Chinese herbal injections were described. Our analysis of these reports showed that anaphylactic shock caused by traditional Chinese medicine (TCM) injections for the treatment of cardiovascular and cerebrovascular diseases is common but also sometimes fatal. Therefore, we proposed the following four suggestions for improving the clinical safety of delivering Chinese herbal injections and reducing the occurrence of allergic shock. First, patients with cardiovascular and cerebrovascular diseases are at high risk, so they should only be given TCM injections after a doctor's diagnosis and approval. Second, people in allergic groups can suffer anaphylactic shock, so vigilance is important in the treatment of all age groups, although even more caution should be exercised when treating children or elderly people. In fact, TCM injections may not be appropriate for those age groups, so that they should be carefully considered before treatment. Third, no significant gender differences have been noted in patients with anaphylactic shock, so all patients should be carefully monitored, irrespective of gender. Fourth, the timeframe in which different drugs cause anaphylactic shock varies; thus, patients should be observed as long as possible.

1. Introduction

In recent years, traditional Chinese medicine (TCM) injections have been widely used in the clinic for the treatment of many conditions, including hypertension, coronary heart disease, diabetes, nephrosis syndrome, rheumatoid arthritis, fracture, and cervical degenerative disease. However, a new dosage form of TCM injections has changed the traditional route of administration, while still retaining the characteristics of TCM. This new form works more quickly and effectively in treating certain disease [1], especially for cardiovascular and cerebrovascular disease, digestive system disease, respiratory system disease, tumor, and so on. It is found that compound Danshen, Honghua, Shuxuetong, Ginkgo biloba, ligustrazine, *Erigeron breviscapus*, Ciwujia, Mailuoning, Ge Gensu, and Dan Hong injection have obvious advantages in the treatment of coronary heart disease, angina, and acute cerebral infarction [2]. Recently, with the increased incidence of cardiovascular and cerebrovascular diseases, the usage of TCM injections has increased each year due to its clinical efficacy. However, despite the effectiveness of TCM injections in treating some diseases, its toxicity has been of concern as it can induce adverse drug reactions (ADRs), such as allergy including anaphylactic shock, a common side effect. Therefore, the toxicity of TCM injections should be recognized and, as such, be carefully utilized.

Allergy occurs when the immune system develops specific antibodies against an exogenous antigen (allergen) that results in an exaggerated response toward a substance that is normally harmless, thereby causing tissue damage. Anaphylactic shock is a severe, systemic allergic reaction to a specific allergen that occurs due to acute peripheral circulatory failure. It is rapid in onset and can be fatal if not treated quickly. The clinical manifestations of anaphylactic shock include heart palpitations, chest tightness, laryngeal obstruction, dyspnea, pale or cyanotic complexion, chills, sweating, cold perception in the limbs, weak pulse, drop in blood pressure, loss of consciousness, coma, convulsions, incontinence, and

even sudden cardiac death. China's National Center for Adverse Drug Reaction listed the top 10 TCM injections that caused serious side effects. Of these, seven types were responsible for the most cases of anaphylactic shock and included Shenmai injection, Xuesaitong injection, *Salvia miltiorrhiza* injection, compound Danshen injection, Shengmai injection, Xueshuantong injection, and Mailuoning injection. Mailuoning injection caused 64 cases of anaphylactic shock. In addition, between January 1, 2011 and December 31, 2011, the National Drug Adverse Reaction Monitoring Center received a total of 1500 ADR case reports from Mailuoning injection, of which 189 cases were severe. Compound Danshen injection caused 53 cases of anaphylactic shock. On March 24, 2009, the Ministry of Health and China's State Food and Drug Administration jointly issued an urgent notice requesting the immediate termination of the usage, selling, and production of compound Danshen injection from Taizhou Tianrui Pharmaceutical Company. Ciwujia injection caused 33 cases of anaphylactic shock, with the most severe cases occurring after October 5, 2008. Subsequent investigation showed that these serious ADRs were caused by drug contamination.

Since these drugs have similar pharmacological effects, their common characteristics may cause ADRs. However, these injections also have specificity, as they have distinct chemical compositions [1]. In 2009, the article has reported serious anaphylaxis caused by nine Chinese herbal injections used to treat common colds and upper respiratory tract infections [3]. Also, another article has reported anaphylactic shock and lethal anaphylaxis caused by *Houttuynia cordata* injection for antibacterial and antiviral therapy [4]. So far, there is no study on anaphylactic shock caused by traditional Chinese medicine injections used to treat cardiovascular and cerebrovascular diseases. In order to further explore the characteristics underlying the ADRs to TCM injections and to provide evidence that may ensure the safe and effective clinical usage of TCM injections, we studied the general pattern and characteristics of anaphylactic shock caused by TCM injections.

2. Cases

In this report we analyzed 316 articles, collected from medical journals published in China between 1980 and 2013 that described cases of anaphylactic shock caused by herbal injections for cardiovascular and cerebrovascular diseases. A total of 17 different types of herbal injections were described in these reports. Collectively, 350 episodes of anaphylactic shock and 10 deaths were reported (summarized in Table 1). All 10 lethal anaphylaxis incidences occurred following intravenous injection (IVI). Among the 350 anaphylactic shock cases, 4 patients (1.14%) were administered intramuscular injections (IMI), and 346 patients (98.86%) were given IVI. Patient age ranged from 9 to 97 years. Of the 350 patients who suffered anaphylactic shock, 5 were children under the age of 18, 108 were between 19 and 45 years of age, 104 were between 46 and 59 years of age, 132 were over 60 years of age, and 1 patient was a pregnant woman. The studies included a total of 169 females and 181 males. The interval between herbal injection and time of anaphylactic shock ranged from 3 s to 2.5 h. The patients in these studies were those who were hospitalized for cardiovascular and cerebrovascular diseases. When allergic reactions to herbal injections occurred, all patients were immediately taken to the emergency department (Table 1).

3. Analysis

3.1. Shenmai Injection. Shenmai injection can be used for the treatment of shock, coronary heart disease, viral myocarditis, chronic cor pulmonale, and neutrophils to reduce. It also can improve the immune function of tumor patients and reduce the adverse reaction caused by chemotherapy. Shenmai injection mainly contains ginseng, *Ophiopogon japonicus*, the active components of ginseng saponin, flavones, and trace ginseng polysaccharides. These components can stimulate the body to produce antibodies, resulting in adverse ADRs. In addition, the improper use of red ginseng can cause severe ADRs, such as psychiatric and neurological symptoms, arrhythmia, gastrointestinal bleeding, or even death [5]. It is possible that the pathogenesis of red ginseng is due to component structural changes and modifications that occur after preparation of red ginseng and *Ophiopogon japonicas*; however, further studies are needed to validate this theory. The content of *Ophiopogon japonicus* in Shenmai injection is significantly lower than that of *Panax* species, so more studies have focused on ginseng (species of the genus *Panax*). Ginsenosides Rb1, Rb2, Rc, Rd, Re, Rg1, and *Ophiopogon in* D are the active and main components of Shenmai injection. Test results after Shenmai injection showed that the blood concentration of ginsenoside Rb1 was relatively high, but those of ginsenoside Rg1 and ginsenoside Re were low. Ginsenosides Rg1 and Re were rapidly distributed and eliminated *in vivo*, but ginsenoside Rb1 was slowly metabolized *in vivo*. The efficacy of ginsenoside Rb1 may be related to the fact that it has a long half-life of up to 47 h [6], so the anaphylactic shock caused by Shenmai injection may be mainly due to ginsenoside Rb1.

3.2. Ciwujia Injection. Ciwujia injection contains several active components, including Eleutheroside, isofraxidin glycosides, Ding Xiangdai, Hyperoside, and *Acanthopanax senticosus* polysaccharide. These components can dilate blood vessels, increase coronary blood flow, increase myocardial oxygen consumption, improve blood circulation, and increase appetite. It has been difficult to determine the main component that causes anaphylactic shock, and it may be caused by the active components themselves or impurities in the drug preparation.

As aforementioned, anaphylactic shock is a serious, potentially life-threatening allergic response. Ciwujia injection contains various active polymers, and once administered directly into the blood stream intravenously, this exogenous antigen stimulates the immune system and causes an allergic reaction. No significant relationship has been found between Type I allergic reactions and drug concentration and dosage, indicating that allergic reactions are associated with drug quality and the active components or

Table 1: Patients who suffered anaphylactic shock after being treated with 17 types of traditional Chinese medicine injections for cardiovascular and cerebrovascular diseases.

Serial number	Chinese herbal injections	Constituents	Number of cases	Distributions of ages*	Sex	Mode of delivery	Onset of symptoms	Distributions of onset*	Timely rescue	Number of deaths
1	Shenmai injection	(1) Red ginseng (2) *Ophiopogon japonicus*	39	0/22/11/6	26 F, 13 M	36IVI*, 3IMI*	10 s–1 h	8/25/6/0/0	Yes	0
2	Ciwujia injection	Ciwujia stem and leaf extracts	33	0/11/14/8	15 F, 18 M	33IVI	3 min–2.5 h	1/15/13/3/1	Yes	0
3	Salvia miltiorrhiza injection	*Salvia miltiorrhiza* extract	9	0/5/2/2	3 F, 6 M	9IVI	1 min–30 min	2/4/3/0/0	Yes	0
4	Tanshinone IIA sodium sulfonate injection	*Salvia miltiorrhiza* extract; main components: Two terpene quinone compounds	5	0/0/1/4	3 F, 2 M	5IVI	2 min–30 min	0/1/4/0/0	Yes	0
5	Dan Hong injection	(1) *Salvia miltiorrhiza* extract (2) Safflower extract	4	0/2/0/2	3 F, 1 M	4IVI	1 min–40 min	0/3/1/0/0	Yes	0
6	Breviscapine injection	*Erigeron breviscapus* extract	11	0/2/4/5	3 F, 8 M	11IVI	3 min–2 h	0/2/6/3/0	Yes	0
7	Erigeron injection	*Erigeron breviscapus* extract: phenolic constituents Main component: wild Baicalin, total caffeic acid ester	6	0/0/0/6	4 F, 2 M	6IVI	10 min–1.5 h	0/1/4/1/0	Yes	0
8	Compound Danshen injection	(1) *Salvia miltiorrhiza* extract (2) Dalbergia extract	53	0/19/18/16	23 F, 30 M	53IVI	10 s–2 h	5/30/15/3/0	Yes	5 death, 1 fetal death
9	Puerarin injection	(1) Puerarin extract (2) *Propylene glycol*, water for injection	23	0/1/11/11	8 F, 15 M	23IVI	2 min–2 h	1/2/18/2/0	Yes	2
10	Safflower injection	Safflower extract Main components: safflower yellow pigment, safflower quinone, glycoside, carthamin, new carthamin	27	0/7/10/11	15 F, 12 M	27IVI	2 min–1 h	1/16/10/0/0	Yes	0
11	Mailuoning injection	Honeysuckle, *Achyranthes* root, *Dendrobium*, Xuan Can	64	1/19/15/29	30 F, 34 M	64IVI	10 s–50 min	11/40/13/0/0	Yes	2
12	Shengmai injection	Red ginseng, *Ophiopogon japonicus*, *Schisandra chinensis*	16	0/2/5/9	7 F, 9 M	16IVI	10 s–30 min	3/10/3/0/0	Yes	0
13	Shuxuetong injection	Leech and earthworm	6	0/1/3/2	4 F, 2 M	6IVI	5 min–1.5 h	0/3/2/1/0	Yes	0
14	Xingnaojing injection	Musk, borneol, turmeric, *Gardenia*	17	2/7/3/5	4 F, 13 M	17IVI	3 s–45 min	1/12/4/0/0	Yes	0

Table 1: Continued.

Serial number	Chinese herbal injections	Constituents	Number of cases	Distributions of ages*	Sex	Mode of delivery	Onset of symptoms	Distributions of onset*	Timely rescue	Number of deaths
15	Xuebijing injection	Extracts: safflower, Radix Paeoniae Rubra, Rhizoma Chuanxiong, Radix *Salviae miltiorrhizae*, Radix *Angelicae sinensis* Main component: safflor yellow A	12	2/7/2/1	7 F, 5 M	12IVI	2 min–10 min	0/12/0/0/0	Yes	0
16	Xuesaitong injection	Total saponins of three-seven byproducts, main components: Ginsenoside Rb1, Ginsenoside Rg1, three-seven, Ginsenoside R1	21	0/3/5/13	13 F, 8 M	20IVI, 1IMI	2 min–1.5 h	1/11/8/1/0	Yes	0
17	Xueshuantong injection	Three-seven root extracts, main components: Ginsenoside Rg1, Ginsenoside Rb1	4	0/0/2/2	1 F, 3 M	4IVI	3 min–1 h	0/2/2/0/0	Yes	0
	Total		350	5/108/106/132	169 F, 181 M			34/189/112/14/1		

*Distributions of ages: number of children (≤18 years)/number of youth (19–45 years)/number of middle-aged (46–59 years)/number of aged cases (≥60 years).
*Distributions of onset: within 1 min/between 1 min to 10 mins/between 11 mins to 60 mins/between 61 mins to 120 mins/over 120 mins.
IVI: intravenous injection.
IMI: intramuscular injection.
The references of the cases are in the support material.

impurities in the drug preparation [7]. It has been reported that patients with drug allergies are more susceptible to anaphylactic shock from Ciwujia injection; thus, before treatment, patients should be asked to detail their history of drug sensitivity [8]. In addition, patients with idiosyncratic reactions should be banned from taking this drug [9].

3.3. Salvia miltiorrhiza (Danshen) Injection. *Salvia miltiorrhiza* can dilate coronary artery, increase the blood volume, improve myocardial ischemia, promote myocardial ischemia or injury recovery, and reduce the myocardial infarction scope. It also can fight against thrombosis, regulate blood lipid, inhibit the formation of atherosclerotic plaques, and protect liver cells and gastric mucosa. It also has anti-inflammatory and antiallergic effect. The mechanism underlying the allergic reaction to *Salvia miltiorrhiza* injection is unclear; however, there are two possibilities. First, tanshinone and acid crystals in the *Salvia miltiorrhiza* injection may bind to plasma proteins and have sufficient immunogenicity to cause an allergic reaction. Second, the active components of *Salvia miltiorrhiza* injection are caffeic acid ester derivatives that polymerize to form orthodihydroxy compounds. It is similar to the structure of tannin and also binds to plasma proteins [10]. It has been reported that the anaphylactic shock caused by *Salvia miltiorrhiza* injection was related to the drug concentration. Specifically, two cases [11] of anaphylaxis occurred upon administration of 24 g *Salvia miltiorrhiza* using 250 mL low molecular weight dextran for an intravenous drip at 30 drops/min. However, when the *Salvia miltiorrhiza* concentration decreased to 10 g, no cases of anaphylactic shock occurred. Therefore, it appears that allergic shock was caused by the high density of the drug. *Salvia miltiorrhiza* can slow the heart rate and dilate blood vessels. At high concentrations, excessive doses, and fast drip rates, its concentration in the bloodstream increases rapidly to dilate small blood vessels and decrease blood pressure. Therefore, in the clinic, input concentration, velocity, and dose of *Salvia miltiorrhiza* should be tightly controlled, particularly in patients with bradycardia, to avoid the occurrence of severe ADRs [12]. In addition, *Salvia miltiorrhiza* combined with low molecular weight dextran has a larger probability of causing anaphylactic shock. Low molecular weight dextran functions as a blood volume expander but also has mild anticoagulant effects. At the same time, *Salvia miltiorrhiza* can promote blood circulation to remove blood stasis and increase the number of mast cells. After combining *Salvia miltiorrhiza* with low molecular weight dextran, the extracellular fluid moves from the blood vessels into the tissue, and the mast cells release chemical mediators such as histamine and serotonin. These chemical mediators can cause muscle spasms and increase vascular permeability. Furthermore, the antigenicity of dextran can stimulate the body to produce antibodies, resulting in anaphylactic shock. The residual ethanol in the Danshen injection can undermine the dextran precipitates and destroy colloidal solution, causing drug degeneration. Thus, *Salvia miltiorrhiza* should not be combined with low molecular weight dextran for intravenous administration [13]. The same to Danhong injection and Compound Danshen injection those contain Danshen.

3.4. Tanshinone IIA Sodium Sulfonate Injection. Tanshinone IIA is derived by sulfonation of the water-soluble substance Tanshinone IIA sulfonate. Tanshinone IIA is derived from phenanthrene-quinone, which is isolated from *Salvia miltiorrhiza*. Tanshinone IIA sodium sulfonate can increase coronary flow, inhibit platelet aggregation and antithrombotic ischemia, reduce myocardial infarct size, and so on [14]. Tanshinone IIA increases water solubility by sulfonation, so Tanshinone IIA sodium sulfonate has high solubility in water. However, because Tanshinone IIA sodium sulfonate is susceptible to hydrolysis, the soluble components are separated from the insoluble ones; therefore, Tanshinone IIA sodium sulfonate injection has slight precipitate particles during long-term storage that can cause allergic reactions in the body. In fact, reports have shown that anaphylactic shock is caused by the small amount of impurities and resin remnants that remain after the extraction process.

3.5. Danhong Injection. Danhong injection can be used for antiatherosclerosis, inhibit platelet aggregation, and protect vascular endothelial cells. The main components of Danhong injection are *Salvia miltiorrhiza* and safflower. The mechanism by which Danhong injection induces anaphylactic shock is similar to that of *Salvia miltiorrhiza*. Safflower injection may contain pollen protein, which can cause anaphylactic shock [10]. Because Danhong injection contains *Salvia miltiorrhiza*, it should also not be combined with low molecular weight dextran. This was proven when a patient in one case report suddenly succumbed to anaphylaxis after being administered an intravenous drip of Danhong combined with 250 mL low molecular weight dextran [15]. Danhong injection has certain drip specifications. For example, patients with heart conditions can receive Danhong injection at a rate of ~30–40 drops/min, but for other adults, an injection rate of 60 drops/min is suitable; the injection rate for children varies according to age and physical circumstances. The intravenous drip rate can greatly affect the incidence of ADRs, so the doctor should carefully control drip speed and closely observe the patient's reaction. Danhong injection has a safe medication dose range and must be used in accordance with the drug dosage given in the instructions. Patients can take Danghong injection at ~20–30 drops/min for 1-2 times per day. Danghong should be diluted with 5% glucose (100–500 mL) for injection. Some patients with allergic shock may be related with solvent. Yuan and Zhao [10] reported that one patient, aged 83, due to the eyes of ischemic optic nerve disease in hospital, with a history of hypertension, cerebral infarction, and myocardial infarction, with no history of adverse drug reaction, suffered anaphylactic shock when he/she accepted Dan Hong injection 20 mL with 0.9% NS 250 mL intravenous drip on day 8. Therefore, except special condition, the user of Danhong injection should be strictly in accordance with the drug instructions.

3.6. Breviscapine Injection. Breviscapine injection contains flavonoids, scutellarin, and the *Erigeron* 60 hormone, although scutellarin is the main component. Scutellarin can inhibit the intrinsic coagulation system, promote the activity of plasmin, reduce platelet count, and inhibit platelet aggregation. Flavonoids in acidic environments are easy to precipitate; therefore, breviscapine is stable in 0.9% NaCl or 5% glucose for injection. In addition, the pH should not be less than 4.2 or it will crystallize, leading to an increase in the number of particles and subsequent allergic reactions. Breviscapine injection is a pure TCM preparation with a complex composition.

3.7. Erigeron Injection. Erigeron injection is composed of *Erigeron breviscapus* extracted with sterile water solution made of phenolic compounds. *Erigeron* injection esters mainly contain scutellarin and coffee. It is commonly used for the treatment of ischemic stroke, coronary heart disease, and angina pectoris due to the fact that it promotes circulation and removes stasis. The literature has reported that *Erigeron breviscapus* solution is weakly alkaline (pH 7.0–7.5). When the pH is low, *Erigeron breviscapus* solution can easily crystallize, thereby increasing the number of insoluble particles. In addition, when glucose is used as the solvent for *Erigeron breviscapus* injection, there is an increase in the number of insoluble particles, whereas the number of particles is much lower when 0.9% NaCl is used as the solvent. In these studies, 5% glucose was used as the solvent in most patients, although the instructions stated that the solvent should be 0.9% NaCl. He and Lei [16, 17] reported that three patients with the use of 10% glucose or 5% glucose as solvent showed the symptoms of anaphylactic shock.

The insoluble particles may be the main cause of allergic shock, so 0.9% NaCl should be used as the solvent in the clinic. Although there did not appear to be a significant correlation between drug dose and anaphylactic shock, some patients were injected with up to 100 mL *Erigeron breviscapus*, which is two times more than the instructions specified. In particular, elderly people had poor tolerance and were more likely to suffer from ADRs.

3.8. Compound Danshen Injection. Compound Danshen injection is composed of Danshen extract and *Lignum dalbergiae* odoriferae extract. *Salvia miltiorrhiza* can scavenge free radicals and resist lipid peroxidation; *Dalbergia* can reduce lipid peroxidation injury. *Dalbergia* and *Salvia miltiorrhiza* have synergistic effects and can decrease heart rate, act as a sedative, and cause hypnotic and transient hypotension. The mechanism underlying allergic reactions induced by *Salvia miltiorrhiza* is similar to that of compound Danshen. Long-term toxicity studies of *Salvia miltiorrhiza* have shown that if it is infused too quickly, a fall in blood pressure will occur, which can easily cause anaphylactic shock [18]. Compound Danshen has an injection pH range of 4 to 6.5. The number of insoluble particles greatly increased when compound Danshen was mixed with 0.9% NaCl for injection at an alkaline pH. This increases the chance that a patient will suffer from an ADR. Most patients infused at a drip speed of 85 drops/min suffered from anaphylactic shock, which often occurred as quickly as a few seconds after injection. Thus, aninfusion rate of 30 drops/min is more appropriate. Importantly, patients should be closely observed for at least 15 min after injection, as patients cannot adjust the drip speed themselves. If the patient suffers from an ADR, the nurse should immediately close the valve and report to the physician. Compound Danshen causes mild vasodilatation; if the concentration is too high or if it is infused too quickly, the blood concentration of the drug will increase rapidly in a short period of time, causing blood vessel dilatation due to small decreases in blood pressure and bradycardia, which can lead to anaphylactic shock. Therefore, the input velocity and drug concentration must be tightly controlled with compound Danshen injection [19].

3.9. Puerarin Injection. Puerarin injection can dilate coronary and cerebral blood vessels, improve myocardial systolic function, inhibit platelet aggregation, reduce blood viscosity, and improve microcirculation. Anaphylactic shock mostly occurred in patients who were continuously using Puerarin, which belongs to I type allergic reaction. The patients recovered a few days after drug treatment was terminated and they received antiallergy medication. Anaphylactic shock may have been caused from impure substances in Puerarin resulting from drug preparation, which induced antigenicity [20].

Additionally, Puerarin itself or its byproduct may have decomposed by drug metabolism and then may have combined with a protein carrier to form a hapten carrier complex, resulting in an immune response. Puerarin injection mainly contains flavonoid glycosides but also contains small amounts of daidzein, daidzin, and other effective components of TCM. These components or impurities in the formulation can serve as antigens or haptens and cause anaphylactic shock. Puerarin is an isoflavone compound with low solubility. Isoflavones as strong planarity molecular are arranged closely between the molecule and another one, so it is difficult to dissolve in water. In order to increase the solubility of Puerarin, 50% propylene glycol was added to the injection as a solvent. Propylene glycol can degrade to produce pyruvic acid, lactic acid, acetic acid, and other allergens in certain conditions, which can cause vascular stimulation in patients and symptoms of fever. In addition, propylene glycol can directly cause the dissolution of red blood cells. Studies have shown that the number of particles in TCM injections is significantly greater than that in Western medicine intravenous injections. Puerarin injection, as a TCM preparation, may produce insoluble particles that cannot be metabolized in the body, resulting in allergic reactions [21].

If Puerarin injection is used as a treatment over a long period of time, toxic effects can be caused by drug accumulation. Most cases of anaphylactic shock resulted from the continuous use of Puerarin, unlike the anaphylactic shock caused by penicillin. Most people who suffered from an allergic reaction had no history of drug allergies; however, doctors should still ask patients to detail their personal and family histories of drug allergies before treatment, and patients with drug

allergies should use Puerarin carefully. Patients who suffered from an ADR following Puerarin injection recovered within a few days of drug withdrawal and antiallergy medication. Before allergic shock occurred, patients had adverse reactions such as fever and chest tightness. When this occurs, doctors should immediately terminate the drug and treat the patients' symptoms.

The use of Puerarin should be strictly controlled, especially in elderly patients. Patients' blood routine, liver, and kidney function should be monitored, and treatment should not be for too long as the intermittent use of Puerarin can easily induce the production of antibodies. Large doses of medication can trigger immune complexes to cause tissue injury, and subsequent use of the medication will cause memory cells to respond quickly, leading to serious ADRs. Sun [22] reported that one patient, aged 58, with coronary heart disease, showed suddenly palpitations, shortness of breath, sweating, cold extremities, and other symptoms of anaphylactic shock 30 minutes after the intravenous drip of Puerarin on day 8. Therefore, we suggest a treatment schedule of 1 course for 1 week, which should be repeated after 1 week. This course of treatment will significantly reduce the risk of ADRs. Since Puerarin is a vasodilator, the patient's full medical history should be taken into account before it is administered [23].

3.10. Safflower Injection. Safflower injection is a TCM injection of safflower extract. It has many functions, such as scavenging free oxygen radicals, inhibiting platelet aggregation, and reducing vascular resistance and dilation of the coronary artery. Previous studies indicated that the excessive use of safflower injection can increase the number of insoluble particles, which can result in anaphylactic shock. Excessive use can also increase the liquid concentration, such that, at the same drip speed, patients are more susceptible to ADR due to the increase in pharmacological effects. The drug instructions recommend using 5% and 10% glucose (~250–500 mL) as the dilution solvent. Lu and Ye [24] reported that one patient, aged 63, suffering lumbar disc herniation, with history of cephalosporin allergy, appeared dizziness, chest tightness, shortness of breath, clammy skin, and other symptoms of anaphylactic shock when accepting intravenous injection of safflower injection +0.9% Sodium Chloride Injection 10 minutes later. In the first medication, compatibility and stability tests showed that as the pH of the solvent increased, the number of insoluble particles significantly increased as well. Thus, it is better to not combine safflower with 0.9% NaCl for injection [25].

ADRs induced by safflower injection involve multiple systems of the human body. Foreign antigens combine with antibodies in the material, leading to an abnormal immune reaction that may be due to the safflower injection or due to patients' specific allergies. The elements of safflower injection are complex and contain Safflor yellow and safflower glucoside. Antigens or haptens injected or transfused directly into the bloodstream can cause allergic reactions. In particular, when yellow pigment combines with sugar in the body, it forms a semiantigen. Hapten combines with the material in the red blood cell surface to form an antigen. Then, the antigen acts on the mast cells of target cells (laryngeal, tracheal, and bronchial) to produce IgE antibodies to cause allergic reactions. Some patients previously used safflower and produced specific antibodies in their bodies. In those cases, the intravenous drip of safflower injection acted as an allergen that activated the intracellular enzyme release of active substances, such as histamine like, causing an allergic reaction [26].

Safflower injection may contain pollen protein, which can cause anaphylactic shock. Therefore, we advised manufacturers to improve the purification process of safflower injection and try to remove impurities and pollen protein [27].

3.11. Mailuoning Injection. Mailuoning injection is a compound preparation that contains *Achyranthes* root, Radix Scrophulariae, *Dendrobium*, and honeysuckle. Mailuoning functions to clear away heat, nourish Yin, promote blood circulation, and remove blood stasis. The main components of honeysuckle are chlorogenic acid and isochlorogenic acid. Chlorogenic acid is an allergen that can cause allergic reactions, although it does not cause allergic reactions when being orally prepared [28]. *Achyranthes*, Radix Scrophulariae, *Dendrobium*, and honeysuckle in Mailuoning injection are from nature. People who had contact with or used these drugs previously will be sensitive to them. Therefore, the majority of allergic reactions will occur on first drug use [29]. Mailuoning injection is prepared by chemical extraction; however, due to extraction methods, its purity is not guaranteed. In addition, during the preparation process, manufacturers add solubilizing agent, stabilizer, and other additives to improve the solubility and stability of the active components of Mailuoning injection. These additives can cause allergic reactions. For example, the use of polysorbate 80 as a solubilizing agent for TCM injections correlated with the occurrence and severity of ADRs.

3.12. Shengmai Injection. Shengmai injection contains ginseng, *Ophiopogon japonicus*, and *Schisandra chinensis*. Red ginseng is a type of ginseng, with ginsenoside being as the active component. Ginsenoside can adjust blood pressure, improve circulation, and promote metabolism and protein synthesis. The active component of *Ophiopogon japonicus* is *Maidong saponin*. The active component of Fructus Schisandra is Schisandrin. The effect of Shengmai injection is determined by the interaction of the 3 components, and there are many reasons that it can lead to ADRs.

Some possible reasons that Shengmai injection may cause anaphylactic shock include the fact that the treating physician may not fully understand the indications of Shengmai injection. For example, fracture of diaphragm fibers can be caused by Shengmai injection. Second, the physician may not ask patients about their personal and family history of drug allergies before administering the drug. This will cause some patients with drug allergies, food allergies, or chronic bronchial asthma to receive Shengmai injection, leading to ADRs. Third, some doctors may give patients an excessive dose of medication. The usage and dosage of Shengmai injection are specified as follows: 1 intravenous drip of

20–60 mL diluted with 5% glucose (250–500 mL). However, in some cases, the doctors gave an intravenous drip of 80–100 mL, which is more than the prescribed maximum dose of 60 mL. Fourth, the doctor may choose an inappropriate infusion solvent, which could lead to anaphylactic shock, although this theory needs to be further researched. Lastly, if Shengmai is infused too quickly, anaphylactic shock can occur [30]. Zhang [31] reported that 3 patients by intravenous of Shengmai injection 100 mL + 0.9% Sodium Chloride Solution 250 mL showed allergic shock symptoms in 5 minutes.

Since the majority of patients suffered allergic shock for the first time after Shengmai injection, and the majority of cases (13/16, 81.25%) occurred within 10 min after administration, we can conclude that allergic shock induced by Shengmai injection leads to an immediate allergic reaction. However, the components that cause anaphylactic shock are still unclear, although we speculate that ginsenoside may be the underlying culprit [32]. Only red ginseng Shengmai injection, all the effective components were determined. The effective components of *Ophiopogon japonicus, Schisandra*, have no quantitative determination. The quality of TCM injection cannot be guaranteed due to imperfect quality standards. Thus, additional studies are needed to strengthen the quality standard and to establish a method for determining the active components of specific drugs. This would most likely reduce the occurrence of ADRs.

3.13. Shuxuetong Injection. Extracts of the leech and earthworm are the active components of Shuxuetong injection. These extracts contain hirudin, earthworms, earthworm enzyme, and other antithrombotic substances. Hirudin is found so far the strongest thrombin specific inhibitor. It can reduce the activity of thrombin, block the formation of fibrin, prevent hemostatic response and platelet activation response induced by thrombin, and reduce platelet activity, exerting its anticoagulant effect. This enzymatic system expresses the tissue type plasminogen activator, which has strong fibrinolytic activity. Thus, ADRs may be associated with these protein components [33]. To prepare Shuxuetong injection, large molecules, such as amino acids, peptides, and mucopolysaccharides, are removed using a filter [34]. The molecular weight of the remaining polysaccharides, polypeptides, and amino acids with physiological activity is about 5800 Da and should be less than 1% of the Shuxuetong injection material. However, small amounts of residual polymer protein may cause ADRs [35]. Although the mechanism by which ADRs occur following Shuxuetong injection remains unclear, there are two characteristic possibilities. First, the protein constituents contained in leech and earthworm may have sensitizing effects. Second, Shuxuetong injection has anticoagulant and antithrombotic pharmacological activities and improves blood rheology. Improvements in technology may lead to improvements in drug purity, thereby reducing the occurrence of ADRs [36].

3.14. Xingnaojing Injection. Xingnaojing injection has detoxicating, cooling blood, and restoring consciousness effect. Xingnaojing injection is composed of musk, borneol, turmeric, and gardenia. Protein, fatty acids, and other molecules can be used as antigens in the body to stimulate the immune system to produce antibodies. The antibody attaches to mast cells, which then become sensitized. When mast cells are exposed to the same antigen, the antigen reacts with antibodies on the surface of mast cells, after which the mast cells release particles into the surrounding media [37]. Stimulation of the immune system can lead to an allergic reaction. The blood capillaries expand and their permeability increases, and the respiratory system, cardiovascular system, and skin and mucous membranes change to induce anaphylactic shock. The possibility of allergies induced by musk is great, possibly because musk is animal drugs [38].

3.15. Xuebijing Injection. Xuebijing injection mainly contains safflower, chuanxiong, and *Salvia*. Xuebijing injection can improve circulation, reduce infection and injuries induced by bacterial endotoxin, reduce the inflammatory response, and inhibit the formation of granuloma. During the process of extraction, there are many problems such as low purity and a large amount of residue. At the same time, the active components of safflor yellow A can enter the bloodstream and stimulate the body to produce antibodies or sensitized lymphocytes. Thus, when the allergen enters the body again, an allergic reaction will occur [39].

Manufacturers need to further improve the production process and quality of their products to strengthen the quality control of Xuebijing injection, which will reduce the occurrence of ADRs. The body is in a state of stress after an operation. The number of peripheral blood phagocytes increases, enhancing the immune system. This makes the body susceptible to allergic reactions.

3.16. Xuesaitong Injection. Xuesaitong injection is composed of panaxnoto ginseng extracted from *Panax pseudoginseng*. It can dilate cerebral vessels, inhibit platelet aggregation, and have antiatherosclerosis, antithrombosis, and antiarrhythmia activities. The elements of *Panax notoginseng* are complex, containing more than 20 kinds of saponin-active material and 17 kinds of trace elements, protein, vitamins, and polysaccharides.

There are four other possible causes of allergic reactions due to Xuesaitong injection. First, *Panax notoginseng* is the main component of Xuesaitong. It is not stable in aqueous solution, easily precipitates when stored, and directly affects the quality of the drug. Second, the dilution solvent for Xuesaitong is ethanol, so patients with alcohol allergies are banned from taking Xuesaitong injection. Third, Xuesaitong mixed with NaCl forms insoluble particles. Fourth, the occurrence of allergic shock correlates with the condition of the patient [40].

3.17. Xueshuantong Injection. Similar to Xuesaitong injection, Xueshuantong injection is composed of *Panax notoginseng* extracted from *Panax pseudoginseng*, with the main ingredients of ginsenoside Rg1 and Rb1. It can promote blood circulation, remove blood stasis, expand blood vessels, and improve microcirculation. The ADRs caused by

Xueshuantong injection may be due to some factors. First, patients with personal or family histories of allergies are more susceptible to ADRs. Second, *Panax notoginseng* is the active component of Xueshuantong injection and can stimulate the immune system.

4. Discussion

The cases of anaphylactic shock caused by different drugs varied greatly. The abovementioned data and examples showed that doctors should pay more attention to the drug that frequently causes anaphylactic shock. The first reason that anaphylactic shock occurs is because TCM injection components are complex. They are composed of organic compounds, such as pigment, tannin, starch, protein, and other ingredients in colloidal form, which can stimulate the body's immune system and produce antibody-sensitized T lymphocytes to induce hypersensitivity [41]. Second, allergic shock correlates with the temperature and humidity of transportation and storage. In addition, TCM injection is unstable; if storage conditions do not meet certain requirements, the amounts of harmful components and unstable particles will increase, causing anaphylactic shock [42]. Third, the TCM injection with the cosolvent, stabilizer, and possible allergens may activate the H1 receptor of the skin tissue, causing histamine release and an increase in body reactivity [43]. The poor drug quality and insoluble particles are the main reasons underlying the occurrence of ADRs, so nurses must observe the medicine to ensure that it has no liquid crystals, turbidity, or sedimentation.

People of any age can suffer anaphylactic shock induced by TCM injection. The age distribution in studies was such that 5 cases of allergic shock appeared in patients under the age of 18, 108 cases were in patients aged 19 to 45, 106 cases were in patients aged 46 to 59, and 132 cases were in patients over 60 years old. ADRs occurred in patients of all ages, but the largest number of cases (350, 67.43%) was in patients above 45 years old. According to the data, Tanshinone IIA sodium sulfonate, *Erigeron* injection, Shengmai injection, and Xuesaitong injection (over 50% of those treated) were more likely to cause the elderly (>60 years old) to suffer anaphylactic shock. This may be because the elderly are susceptible to a variety of cardiovascular and cerebrovascular diseases with frequent usage of the injection. The more drug they were administered, the more likely they were to suffer an ADR. In addition, individual doses in elderly patients cause different degrees of decline in organ function. Compared to youth, the elderly have different sensitivities and drug tolerance and are thus prone to drug accumulation. However, to a surprising extent, there was a significant proportion of young people who suffered ADRs. This occurred for two main reasons. First, young people often have a good physique and are thus easily ignored by doctors. Second, youth take medications more frequently than other ages because of physical maturity. Otherwise, persons under the age of 18 are relatively fewer, mainly because this group accounted for a small proportion of total population taking TCM injection. Doctors should exercise precaution when treating minors as they are still in the growth stage, and their liver and kidney functions and some enzyme systems have not matured. In conclusion, before selecting TCM injections for treatment, doctors should ask about patient to detail their personal and family medical and drug allergy history. In addition, doctors should exercise caution when treating elderly people, children, and other special groups, such as patients with a history of drug allergies.

In general, there were no significant differences in gender with regard to anaphylactic shock; therefore, for the most part, doctors can equally consider the treatment of male and female patients with cardiovascular disease with TCM injection. However, some drugs did have gender-specific effects. For example, females were more prone than males to suffer anaphylactic shock after Shenmai injection and Xuesaitong injection, whereas males were more susceptible to anaphylactic shock after taking Breviscapine injection, Puerarin injection, and Xingnaojing injection.

Among the 350 people in the described studies, only 4 took TCM injection by IMI; the other patients were treated by IVI. At the same time, the ten death cases were received intravenously. Although IVI has a fast curative effect, treatment is more difficult when anaphylactic shock occurs. To reduce the incidence of anaphylactic shock, doctors should fully understand the drug indications, usage, dosage regimen, and route of drug administration. The drug should be administered orally, followed by IMI, with the final choice of drug administration by IVI or infusion. Use of Chinese herbal injections should be restricted to treatment of severe diseases or critical cases [1]. In addition, the patient should be prohibited from blindly taking a large dose and undergoing treatment for a long period of time, especially with IVI.

Together, the data showed that anaphylactic shock usually occurred between 3 sand 2.5 h, although there were some differences, depending upon a patient's fitness level, pathological state, genetic makeup, and drug sensitivity. In addition, TCM injections can more easily cause allergies when they are given as macromolecules; thus, this is the form that makes patients more susceptible to ADRs. Based on the abovementioned two reasons, the time of occurrence of anaphylactic shock differed between patients. Thus, the length of time that a patient should be monitored should be adjusted to suit that individual and in accordance with the type of drug administered. For example, patients who were administered Shenmai injection, *Salvia miltiorrhiza* injection, Dan Hong injection, compound Danshen injection, Mailuoning injection, Shengmai injection, or Xingnaojing injection suffered anaphylactic shock within 1 min. So, doctors need to pay close attention to patients who are treated with these drugs that cause immediate hypersensitivity. In addition, the appropriate emergency measures need to be immediately taken when serious ADRs occur. Patients who were administered Ciwujia injection, Breviscapine injection, compound Danshen injection, and Puerarin injection suffered anaphylactic shock after more than 2 h; thus, with these drugs, patients need to be observed for an extended period time. During the course of treatment, the drip rate should be strictly controlled, and the patient should be closely observed. Once an ADR occurs, treatment should be terminated, and the appropriate measures should be taken. I suggest that the patients should be observed more

than two hours. The patients may leave after two hours, if they have no discomfort.

5. Conclusions

Based on the analyses of the aforementioned studies, we suggest the following. The first suggestion is for pharmaceutical enterprises. Chinese herbal injections should be approved by the SFDA according to the results of double-blind randomized controlled clinical trials [1]. Although TCM injections can cause allergic shock and other serious ADRs, instructions on how to use these drugs are rarely mentioned. In addition, some TCM injection instructions are not standardized, are poorly written, and lack information and warnings about possible clinical toxicities and side effects [44]. Therefore, pharmaceutical companies should equip TCM with detailed instructions, including possible ADRs and contraindications.

The second suggestion is for pharmaceutical supervisory and administrative departments. The ADRs caused by TCM injection are multifaceted, with diverse clinical manifestations. The production of TCM injection is extracted according to the theory of TCM and a precise process. The essence of TCM is Bianzhenglunzhi. According to Bian zheng lun zhi, the patient's health situation can be treated holistically. Holistic approaches may have their merits, especially in terms of promoting optimum health [3]. Therefore, the use of Chinese medicines should be guided by TCM theory and, in particular, should be according to the syndrome differentiation treatment principle. Doctors should not simply and blindly follow instructions, without allowing for differences between individual patients. They should pay attention to different diseases that have the same symptoms or one disease that has different symptoms, thereby achieving the goal of reasonably applying the principle to TCM injections [44]. This requires doctors to strictly master the application method of the drug and to build upon their knowledge of ADRs caused by TCM injections. In order to improve public safety, doctors should take measures to avoid the occurrence of ADRs to the extent possible.

The third suggestion is for the pharmacy department and pharmacists. Pharmacists must check prescriptions, especially those for TCM injections, to reduce the occurrence of repeated drug use, drug overuse, and irrational drug use. In addition, information on TCM injections, contraindications, and ADRs should be obtained and collected. Any observed ADRs should be reported to the hospital in a timely manner. Drug consultation services should be accessible that will provide accurate medical information to patients, thereby ensuring the reasonable, effective, and safe use of medication. In addition, clinical pharmacists should do ward rounds of the wards together with physicians for the purpose of strengthening the clinical supervisory activities and guiding the proper clinical use of the medications [45].

Fourth, it is important for patients to detail their personal and family history of allergies before being administered TCM injection. Patients who are allergic to medication should be closely observed after injection, and if any ADR occurs, doctors should immediately terminate drug administration [13].

All things considered, TCM injection has a unique role in medical practice, as it not only has the common advantages of injection, but also retains the characteristics of TCM. As a new dosage form of TCM, TCM injection has the advantages of being effective and accurately dosed compared with other TCM dosage forms, especially in treating the seriously ill. Importantly, TCM injection has overcome the inconvenience and difficulty in boiling process. The naysayers of this drug have brought great attention to the ADRs caused by TCM injection due to its complex composition, incomplete preparation process, and lack of rigorous evaluation of clinical efficacy. In order to maximize the effectiveness of this treatment and to reduce the associated ADRs, regulators are seeking to more strictly monitor and reevaluating these drugs and improve the relevant laws and regulations. Medical personnel should also cooperate with regulatory authorities to monitor and report ADRs and to take active preventative measures to reduce or avoid the occurrence of severe ADRs, thereby ensuring drug safety to the public [44].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Yu-Jiao Guo and De-Wang Wang contributed equally.

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Review Article

Artemisia Allergy Research in China

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Artemisia is the most important outdoor allergen throughout China. It can cause allergic rhinitis, asthma, or both of them. Since it was verified as an allergenic pollen in 1960, it was identified two times in the Chinese National Pollen Survey (1984, 2009). The first oral immunotherapy double-blinded trial for *Artemisia* pollen asthma research was conducted in China in 1989 and published in 1990. 40 years since that study, there have been many published research reports on Chinese *Artemisia* allergy. This review summarizes the information regarding the discovery of *Artemisia* as an allergenic pollen, pollen account, epidemiology, allergen components, immunological changes in hay fever patients, natural course from rhinitis to asthma, diagnosis, and immunotherapies in China.

1. Introduction

Artemisia species, or mugwort, is an anemophilous genus included in the Compositae family. Mugwort plants produce high pollen grain quantities [1–4]. This plant is characterized by a huge production of small pollen grains that can be transported for several hundreds or even thousands of kilometers by large air masses. The occurrence of *Artemisia* species is associated with dry or slightly moist habitats and full exposure to light, which are important components of steppes [5].

Pollen from the various *Artemisia* species is one of the most frequent and serious pollinosis causes in many parts of the world [5–9]. The genus *Artemisia* includes 57 species in Europe [10] and 187 species in China [11]. In this review, we summarize *Artemisia* allergy research in China.

2. Discovery of *Artemisia* as an Allergenic Pollen

In the 1950's, Professor Ye in ENT Department of Peking Union Medical College Hospital (PUMCH) had finished his allergy practice training in Johns Hopkins Hospital in USA and learnt that ragweed was the main allergenic pollen in autumn in Europe and United States. He found that many allergy patients showed negative reaction with ragweed prick skin test. Confusingly, there were too many allergic rhinitis patients visiting his clinic every autumn. After then, Ye [12] found that there was a type of weed, *Artemisia annua*, that grew widely in North China. Further, they found that the most abundant pollen count dates were September 4, August 24, and September 5 in 1962, 1963, and 1972, respectively. The allergic patient numbers and their symptom severities were related to the local pollen counts. By a nasal challenge test with *Artemisia annua* extract, this study verified that *Artemisia annua* is a major outdoor allergen source in North China.

To clarify the allergenicity of the nonpollen containing components of the plant, they collected and extracted *Artemisia annua* leaves and stems before the pollination period in 1987 [13]. They showed that the pollen-free plant extracts did have in vivo allergenic activities.

3. *Artemisia* Allergic Rhinitis and Airway Hyperresponsiveness

To study the relationship between *Artemisia* allergic rhinitis and airway hyperresponsiveness, Ma et al. [14] chose 50 *Artemisia* hay fever patients and 20 normal controls. Each of these subjects was separately engaged with a skin test with

Artemisia annua extract. All 50 patients had an intensely positive reaction to the *Artemisia annua* pollen skin test, but all of the controls were negative. Additionally, they conducted a bronchial provocation test (BPT) with a 1 : 100 (w/v) *Artemisia annua* pollen dilution. Before and after the BPT, they separately tested the forced expiratory volume in first second (FEV1) and serum eosinophil cationic protein (ECP) levels. They concluded that patients with *Artemisia* allergic rhinitis not only had chronic inflammation in their nose mucosa that resulted from an allergic reaction but also had chronic bronchial inflammation, leading to airway hyperresponsiveness (AHR). Their results also reveal that most patients with allergic rhinitis have AHR (76%).

4. Features of Pollen Prevalence

4.1. National Pollen Surveys. From 1984 to 1989, Ye [15], at PUMCH, led the first national pollen survey in mainland China. They found that *Artemisia* pollen could be counted in each province in mainland China (Figure 1). At the same time, they got *Artemisia* pollen count data from many Chinese cities in 1988 autumn (Table 1). In 2009, Yin, at the same allergy department, led the second national epidemic allergy study from 100,000 populations in 18 provinces and cities in mainland China, and that data will be published soon.

4.2. Other Pollen Count Studies. During the periods that occurred between 1983 and 1986 and between 1999 and 2007, daily airborne pollen monitoring was performed by the gravitational method, using Ye's sampler at the top of the Peking Union Medical Hospital Outpatient Department Building, Beijing, China. He et al. [16] found that *Artemisia* was the most abundant airborne pollen and showed that it was produced over the longest period within a year, from the beginning of July until the end of September. The *Artemisia* levels were followed by *Humulus* pollen levels. Similar reports were conducted with the Durham gravity method in Xi An city (northwestern region of China) [17] in the 1980's and in Wuhan city (central region of China) in the 1990's [18]. From March 31, 2001–April 1, 2002, pollen counts were evaluated in Nanchang city (central region of China). Additionally, Xie et al. [19] found that the highest airborne presence (the percent of total yearly pollen counts) was from *Ambrosia* (35.73%), followed by *Pinaceae* and *Artemisia* (11.94%).

The Burkard volumetric trap was used to sample airborne pollen in Beijing city from August 1, 2007 to October 10, 2007. Yao [20] determined that (1) *Artemisia* and *Humulus* (including *Cannabis sativa* L.) were the main airborne pollen types observed during August and September in Beijing city, which accounted for 31% and 51% of the total pollen levels, respectively; (2) the *Artemisia* pollen season was from August 8th to October 8th; (3) the daily peak mugwort pollen concentration was 267 grain/m^3, with an average of 71 g/m^3; and (4) 88.5% of the outpatients that suffered from hay fever or asthma during the Autumn season were allergic to *Artemisia*. This was the first time that the Burkard volumetric sampler was employed for *Artemisia* and *Humulus* concentration monitoring in Beijing city.

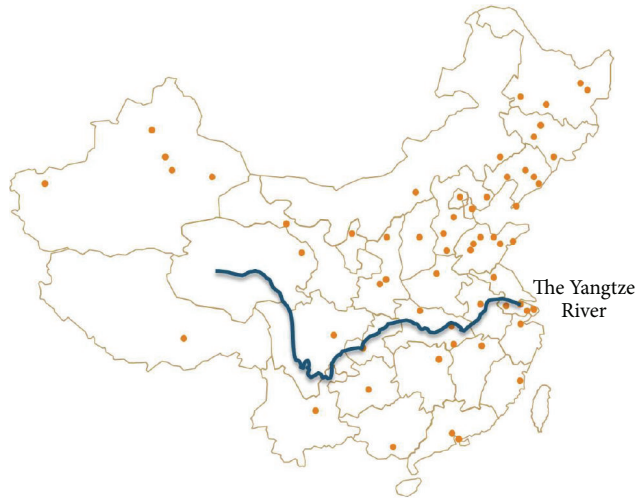

Figure 1: Distribution of *Artemisia* pollen in China.

In 2005, Qiao et al. [4] published a color atlas of airborne pollens and plants that are prevalent in China. In this book, the main *Artemisia* species on the China mainland were described, which included *Artemisia argyi* Levl. Et Vant., *Artemisia sieversiana* Willd., *Artemisia annua* L., *Artemisia capillaris* Thunb., and *Artemisia lavandulaefolia* DC.

5. Epidemiology of *Artemisia* Allergy

A cross-sectional survey was performed that included 6,304 patients who suffered from asthma and/or rhinitis in 17 cities across China [21]. These patients completed a standardized questionnaire that determined their respiratory and allergy symptoms. They also underwent skin prick tests with 13 common aeroallergens. The overall prevalence of the positive skin prick responses was 11.3% for *Artemisia vulgaris*, 6.5% for *Ambrosia artemisiifolia*, 3.5% for mixed grass pollen, and 2.2% for mixed tree pollen. The severity of rhinitis and asthma was significantly correlated with the skin reactivity index to *Artemisia vulgaris* and *Ambrosia artemisiifolia* and to *D. pteronyssinus*, *D. farinae*, and *Blomia tropicalis* ($P < 0.001$). The main pollen and spore families in Beijing are *Artemisia genus*, *Ambrosia genus*, Chenopodiaceae, and Gramineae. They can reach approximately 307,000 grains of pollen/1000 m^3 of air in August [6].

A total of 215,210 tests with the ImmunoCAP system were assayed in the past three years in the PUMCH Allergy Department, which is the largest allergy department in China, and 76% were inhalant allergens. Among these allergens, the three most prevalent allergens were *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, and *Artemisia* [22].

Many studies had been done about *Artemisia* pollen survey and its relationship with allergic diseases in China. The authors showed that *Artemisia* pollen was the most

Table 1: *Artemisia* pollen season distribution in Chinese cities (July–October), unit: grain.

Province	City	July	August	September	October
Beijing	Beijing*	85	1773	1492	186
Tianjin	Tianjin*	107	632	631	42
Hebei	Baoding*	81	778	1852	185
Hebei	Shijiazhuang*	42	282	590	164
Shanxi	Taiyuan*	52	3203	1518	26
Shanxi	Yuncheng*	0	81	581	972
Inner Mongolia	Hohhot*	1071	1639	1088	152
Inner Mongolia	kerqinzuoyihou*	467	1156	896	25
Liaoning	Shenyang*	72	1330	327	39
Liaoning	Dalian*	72	554	802	169
Jilin	Changchun*	822	1620	210	5
Jilin	Tonghua*	6	385	171	6
Heilongjiang	Harbin*	14	1977	139	99
Heilongjiang	Jiamusi*	2	2178	47	24
Heilongjiang	Qiqihar*	18	1748	43	22
Shandong	Ji'nan*	31	421	1936	131
Shandong	Qingdao*	96	106	319	86
The Ningxia	Yinchuan*	377	2805	533	101
Shaanxi	Xi'an*	8	256	1132	431
Gansu	Jiuquan*	5	24	8	5
Qinghai	Xining*	49	1048	1673	84
Xinjiang	Urumqi*	10	711	1555	196
Xinjiang	Hami*	21	34	68	75
Tibet	Lhasa*	1325	1817	549	93
Henan	Zhengzhou*	28	35	836	249
Hubei	Wuhan#	23	37	221	61
Hubei	Xiangyang#	3	1150	1194	354
Anhui	Hefei*	3	62	24	8
Sichuan	Chengdu*	16	114	28	3
Shanghai	Shanghai#	8	7	207	64
Jiangsu	Nanjing#	2	71	643	35
Jiangsu	Suzhou#	0	0	58	13
Zhejiang	Hangzhou#	0	0	0	6
Jiangxi	Nanchang#	2	52	1050	45
Fujian	Fuzhou#	0	53	77	48
Guizhou	Guiyang#	0	1	1	0
Yunnan	Kunming#	23	13	97	324
Hunan	Changsha#	0	0	56	27
Guangdong	Guangzhou#	0	0	14	20
Guangxi	Nanning#	0	3	226	156

*Cities in north of the Yangtze River; #Cities in south of the Yangtze River.

allergenic pollen in northern part area of Yangtze River in China (Figure 2) [23–64].

A total of 1,144 subjects (aged from 5 to 68) from June to October 2011 underwent intradermal testing using a panel of 25 allergen sources [65]. Of the 1,144 subjects, 170 had positive intradermal reactions to pollen and 144 donated serum for IgE testing from these 170 subjects. The positive intradermal response prevalence to *Artemisia sieversiana, Artemisia annua, Ambrosia artemisiifolia*, and *Humulus scandens* pollen was 11.0%, 10.2%, 3.7%, and 6.6%, respectively. Among the intradermal positive subjects, the specific IgE antigen prevalence to *Artemisia vulgaris* was 58.3%, to *Ambrosia artemisiifolia* was 14.7%, and to *Humulus scandens* was 41.0%. The specific IgE antigen prevalence to the Art v 1 allergen was 46.9% and to the Amb a 1 allergen was 11.2%. The correlation between the presence of IgE antibodies that were specific to *Artemisia vulgaris* and to the Art v 1 antigen was very high. Subjects with *Ambrosia*

Figure 2: *Artemisia* pollen was the most allergenic pollen in north part area of Yangtze River in China (with skin test or sIgE blood test).

artemisiifolia specific IgE also had *Artemisia vulgaris* specific IgE but with relatively high levels of *Artemisia vulgaris* IgE antibodies. There were no correlations between the presence of IgE antibodies that were specific to *Humulus scandens* and *Artemisia vulgaris*. They concluded that the specific IgE antibody correlations suggest that pollen allergens from *Artemisia* and *Humulus* are independent sources for primary sensitization.

6. *Artemisia* Allergens

In 1992, Ou [66] purified the major allergen, A2c, from a wild *Artemisia* sieversiana extract. Its molecular weight was 31 kDa, and its pI was 5.3 kDa and 6.35 kDa. We verified this finding by evaluating the components of wild *Artemisia sieversiana* allergen extract with two-dimensional electrophoresis analyses [67].

To isolate and identify the *Artemisia argyi* and *Artemisia apiacea* pollen, Yang et al. [68] precipitated *Artemisia argyi* and *Artemisia apiacea* pollen extract with saturated ammonium sulfate and then evaluated it with SDS-polyacrylamide gel electrophoresis (SDS-PAGE). They identified the major and minor allergens by western blot analysis. Specifically, they found more than twenty protein bands and 9 allergens in the *Artemisia argyi* pollen extract. The major allergens were 62 kDa, 43 kDa, and 38 kDa. Similarly, in the *Artemisia apiacea* pollen extract, there were 11 allergens. The major allergens were 43 kDa and 38 kDa. The pollen from both species shares many allergens. Unique allergen protein bands in each of the pollen allergens were also identified.

Wu [69] analyzed *Artemisia* and ragweed extract antigens with SDS-PAGE and western blot analysis. They found that there were 13 bands between 18 kDa and 100 kDa in the *Artemisia* extract and 5 bands between 18 kDa and 63 kDa in the ragweed extract. Additionally, cross-reactivity between the *Artemisia* and ragweed extracts existed in the 18 kDa protein.

7. Immunological Characteristic in *Artemisia* Hay Fever Patients

7.1. The Th1 and Th2 Balance. Qiu et al. [70] collected tonsil lymphocytes in *Artemisia* pollen allergic patients and nonatopic people with a lymphocyte separation medium and incubated these cells with *Artemisia* pollen antigen. They found that the levels of IL-4 and IL-5 in the tonsil lymphocytes of the *Artemisia* pollen allergic patients were higher than those in the nonatopic controls after they were stimulated with this specific antigen, but the levels of IFN-γ were lower than those in nonatopic controls ($P < 0.01$). Obvious proliferation for the levels of IL-4 and IL-5 was observed in the allergic group after lymphocytes were stimulated with the specific antigen ($P < 0.01$), but there were no significant changes in the control group. The authors demonstrated that cytokines from Th cells of tonsil lymphocytes from *Artemisia* pollen-allergic people after they were specifically stimulated by *Artemisia* pollen antigen became imbalanced, indicating that Th1 drifts to Th2.

7.2. Basophils. With 119 hay fever patients who were allergic to *Artemisia* and 30 nonallergic patients, Zhang et al. [71] found that basophil numbers (mucosal mast cells) in the nasal mucosa as well as nasal eosinophil numbers increased during the pollen season and decreased during the nonpollen season. They concluded that basophils in the nasal mucosa and nasal eosinophils were related to stimulation by *Artemisia* in hay fever patients.

7.3. ICAM-1. Eleven patients with *Artemisia* allergic rhinitis were evaluated by Wang et al. [72]. Among them, 8 were studied during pollen season and 3 were studied outside of pollen season. Intercellular adhesion molecule-1 (ICAM-1) was detected on nasal epithelial cells by reverse transcription polymerase chain reaction (RT-PCR). The results showed that ICAM-1 was detectable in all of the pollen season samples. However, during the nonpollen season, 2 of the 3 samples were negative and 1 was positive (this subject was also positive to house dust). It was suggested that ICAM-1 is detectable on nasal epithelial cells during exposure to specific allergens (*Artemisia*).

7.4. HLA-DR. To investigate whether susceptibility or resistance to *Artemisia* allergic rhinitis is associated with HLA-DRB alleles or not, Xing [73] tested the frequency distribution of HLA-DRB alleles in 41 patients with *Artemisia* allergic rhinitis (AR) and in 41 healthy controls from Beijing, China, using PCR-SSP (sequence-specific primer polymerase chain reaction). The frequency of HLA-DRB1* 0301.2 and HLA-DRB4* 0101 was lower in the AR subjects than the controls (2.44% versus 17.07%, $P < 0.05$; 29.27% versus 51.22%, $P < 0.05$). They showed that the HLA-DRB1* 0301.2 and HLA-DRB4* 0101 alleles might confer protection against AR.

To determine whether alleles at one or more of the HLA loci were associated with *Artemisia* pollen hypersensitivity in allergic rhinitis patients, Xing et al. [74] also tested the frequency distribution of the HLA-DQA1 and DQB alleles

in 41 patients with allergic rhinitis (AR) and in 41 healthy controls from Beijing with PCR-SSP. They demonstrated that the frequency of HLA-DQA1* 0201 and DQB1* 0602 was lower in the AR subjects than the controls (24.39% and 4.88% versus 46.34% and 26.83%, resp.) and the frequency of DQA1* 0302 was increased among the AR patients (58.54% versus 14.63%). They concluded that the HLA-DQA1* 0201 and DQB1* 0602 alleles might confer protection against AR and that DQA1* 0302 may be an *Artemisia* pollen hypersensitivity susceptibility factor.

8. The Natural Course from Rhinitis to Asthma

A total of 1,096 patients with autumnal pollinosis, which excluded those with typical seasonal rhinitis or asthma symptoms but with positive skin tests and serum IgE specific to dust mites and fungi, included 511 with pure allergic rhinitis and 585 with allergic rhinitis complicated with asthma. These subjects underwent inhalant allergen skin tests, evaluations for serum IgE specific to autumnal pollens, and a questionnaire survey. Yin et al. [75, 76] found that the average onset age of the allergic rhinitis patients induced by autumnal pollens was 27.9 years, and this age was significantly younger than that of the allergic asthma patients (32.6 years, $P < 0.001$). Out of the 1,120 patients, 1,096 (97.9%) had allergic rhinitis, 602 (53.8%) had asthma, 507 (45.3%) only had allergic rhinitis, and 10 (0.9%) only had allergic asthma. Among the 1,096 allergic rhinitis patients, 585 (53.4%) suffered from seasonal asthma. Among the 602 asthma patients, 585 (97.2%) suffered from seasonal rhinitis and 183 of the 602 patients (30.8%) needed emergency treatment. The authors showed that autumnal pollens are very important inducers of asthma during the autumn season in northern China and that almost half of the patients with autumnal pollen allergic rhinitis develop seasonal allergic asthma within 9 years [75–77].

From July 1 to October 31, 2006, Wen also observed 18 patients with only allergic rhinitis and 31 patients with allergic rhinitis and asthma [77]. The authors reported that there was a significant correlation between the *Artemisia* pollen count and the scores for night and daytime asthma symptoms, PEF, and diurnal variation in PEF (rs = 0.762, rs = 0.682, rs = −0.649, rs = −0.596, rs = 0.549, $P < 0.001$). It was also concluded that *Artemisia* pollen could trigger autumnal asthma in northern China.

9. Diagnostic

To evaluate the value of intradermal skin test (IDT) and serum sIgE detection in diagnosing *Artemisia* sensitivity, 1,150 patients with autumnal rhinitis or asthma were evaluated by experienced physicians. These subjects then underwent IDT with a 1 : 1,000 dilution of (W/V) *Artemisia annua* extract [78]. Then, all patients were examined for *Artemisia* sIgE (w6). The diagnostic standards were established based on the IDT and sIgE results. A reference standard was established according to the typical history and symptoms and a wheal with a diameter ≥ 5 mm and a sIgE level ≥ 0.35 kU(A)/L; a wheal with a diameter ≥ 10 mm alone; or a sIgE level ≥ 0.70 kUa/L alone. When using the reference standard as the criteria, the IDT had better sensitivity (96.2%), specificity (74.2%), positive predictive value (+PV, 93.5%), negative predictive value (−PV, 85.7%), and efficiency (91.6%) than using the sIgE ≥ 0.35 kUa/L alone as the IDT criteria. Additionally, the sIgE detection had better sensitivity (97.6%), specificity (94.9%), +PV (98.7%), −PV (91.1%), and efficiency (97.0%) than using wheal diameter ≥ 5 mm alone as the sIgE detection criteria. The IDT false positive and sIgE detection rates decreased from 35% and 22.7% to 25.6% and 5.1%, respectively, when using a wheal diameter ≥ 10 mm or sIgE ≥ 0.70 kUa/L as the positive criteria.

It was showed that IDT and sIgE detection were well correlated with each other in diagnosing *Artemisia* pollinosis, whereby both of them had the possibility of being false positive, but IDT had a higher false positive rate than sIgE detection. The IDT and sIgE detection false-positive rates can be decreased by increasing the positive criteria to a higher grading criterion.

Sera from 50 weed pollen-induced allergic rhinitis patients were tested for specific serum IgE reactivity against allergenic *Artemisia* extracts (*Artemisia vulgaris*, Art v) and single Art v 1 or Art v 3 allergens [79]. Sera from 88% of the patients demonstrated a positive specific IgE reactivity to Art v, and of these, 82% were positive to Art v 1. The authors found that specific IgE reactivity towards the major mugwort allergen, Art v 1, was a good indicator for Art v sensitization.

10. Immunotherapy

10.1. Intradermal Immunotherapy. A one-year controlled trial for an immunotherapy was conducted in 50 *Artemisia* sensitive hay fever patients (treatment group) [80]. From October 1985 to July 1986, all of the treatment group patients received regular *Artemisia* pollen allergen extract injections over one year, which totaled 30,000 protein nitrogen units (PNU). For these patients, the symptom score indices of the post-treatment 1986 pollination season were compared with those from the pretreatment 1985 season and also with the scores of a similar group of 30 *Artemisia* sensitive patients treated only with symptomatic medications during the 1986 season (control group). The 1986 symptom scores for the treatment group were significantly improved, and the effective rate was 78%. An immunological study with the human basophil degranulation test (HBDT) showed a significant decrease in degranulation reactions after immunotherapy. Moreover, the decline in the HBDT positive rate in the treatment group was significantly greater in the patients with improved symptoms than the patients with unchanged symptoms. No difference was observed in basophil degranulation in those patients tested with a pollen-free plant extract, which was not applied in the immunotherapy. The results suggested that immunotherapy could induce basophil desensitization and that the induction might be allergen specific. Basophil desensitization may play an important role in immunotherapy mechanisms.

10.2. Oral Immunotherapy. In 1989, eighteen asymptomatic *Artemisia* pollen asthma patients with normal pulmonary functions were selected for a double-blinded oral immunotherapy trial [81]. Each patient had a positive *Artemisia* pollen extract skin test and also had a positive bronchial challenge response to the same extract. The patients were randomly assigned to an active treatment or a placebo group and received intensive oral administration of *Artemisia* pollen extract over a 50-day course. The nine patients who received the active treatment ingested a cumulative dose of 396,652 PNU and showed a significant decrease in serum-specific IgE antibodies ($P \leq 0.05$) and a significant reduction in bronchial sensitivity to the same extract ($P \leq 0.01$). The changes in these two variables correlated well. The nine patients who received the placebo showed no significant changes in serum-specific IgE or bronchial sensitivity to the *Artemisia* pollen extract. Follow-ups for two cases with the same extract showed that the reductions in serum-specific IgE as well as bronchial sensitivity induced by oral immunotherapy were maintained for 3 months.

Clinically, sublingual immunotherapy (SLIT) that uses allergen extracts effectively alleviates allergic rhinitis and asthma symptoms. Ma et al. [82] hypothesized that the oral administration of a high dose of allergen extracts imitates SLIT and may prevent IgE-related responses in allergic diseases. In this study, they investigated the effects of the oral administration of mugwort (*Artemisia*) pollen (MP) allergen extracts on allergen-induced inflammation and airway hyperresponsiveness (AHR) in an allergic mouse model. After the administration of MP drops containing Art v 1 and Art v 4 extracts derived from MP specifically in MP-sensitized mice, the effects of the MP drops on AHR, inflammatory cell accumulation, cytokine production in the bronchoalveolar lavage fluid and lung tissue, and serum IgE and IgG levels were investigated. The results indicated that the MP drops not only prevented AHR in response to methacholine in a dose-dependent manner but also significantly reduced the total serum and allergen-specific IgE levels. All of the maximal effects were achieved at a dose of 100 μg/(kgd) and were comparable to the effects of dexamethasone at a dose of 0.5 mg/(kgd). Furthermore, the oral administration of the MP drops dose dependently elevated allergen-specific serum IgG2a levels, reduced total and allergen-specific IgE levels, and normalized the imbalance between the Th1 cytokine IL-12 and the Th2 cytokines IL-4 and IL-5. Finally, the oral administration of the MP drops significantly reduced goblet cell hyperplasia and eosinophilia in the MP-sensitized allergic mouse model. These sets of data suggest that the MP drops effectively improve specific allergen-induced inflammation and AHR in MP-sensitized and MP-challenged mice and provide the rationale for the clinical use of MP drops in specific allergen-induced asthma. Currently, a Stage I clinical SLIT trial for *Artemisia annua* L. was permitted by the Chinese Food and Drug Administration for one Chinese pharmaceutical company (http://www.sfda.gov.cn/WS01/CL0001/).

11. Summary

Artemisia pollen is a major important outdoor allergen in China. It has been verified as an allergen by nasal challenge and bronchial provocation tests, and these allergens have been shown to occur not only in its pollen but also in its leaves and stems. Two national allergenic pollen surveys have been conducted in China. The main allergenic *Artemisia* species in mainland China were recorded and described by color photos. Immunological changes from *Artemisia* pollen-allergic subjects were studied, including Th1 and Th2 balance, basophils, HLA-DR, and ICAM-1.

Artemisia pollen can trigger not only allergic rhinitis but also asthma alone or both of them. Almost half of the patients with autumnal pollen allergic rhinitis developed seasonal allergic asthma within 9 years. IDT and sIgE detection are well correlated with each other in *Artemisia* pollinosis diagnoses. Specific IgE reactivity towards the major mugwort allergen Art v 1 is a good indicator for Art v sensitization. In 1989, asymptomatic *Artemisia* pollen asthma patients were selected for a double-blinded oral immunotherapy trial. Recently, a Stage I clinical SLIT trial for *Artemisia annua* L. was permitted by the Chinese Food and Drug Administration for one Chinese pharmaceutical company. *Artemisia* immunotherapy could induce the desensitization of basophils, and basophil desensitization may play an important role in immunotherapy mechanisms.

Abbreviations

AHR:	Airway hyperresponsiveness
ECP:	Eosinophil cationic protein
HBDT:	Human basophil degranulation test
LTP:	Lipid transfer protein
ICAM-1:	Intercellular adhesion molecule-1
IDT:	Intradermal skin test
MP:	Mugwort pollen
PUMCH:	Peking Union Medical College Hospital
SDS-PAGE:	SDS-polyacrylamide gel
SLIT:	Sublingual immunotherapy
FEV1:	The forced expiratory volume in first second.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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