Recovery from AKI Following Multiple Wasp Stings: A Case Series

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Summary

Background and objective To observe the outcomes of AKI following multiple wasp stings.

Design, setting, participants, & measurements Eighty-one patients (mean age ± SD, 45.5 ± 14.7 years; 55 men and 26 women; mean Acute Physiology and Chronic Health Evaluation II score, 16.85 ± 2.78) with AKI following multiple wasp stings between 1997 and 2011 were retrospectively analyzed. Data on their demographic characteristics, initial modalities of renal replacement therapy (RRT), urine output, serum creatinine, bilirubin, myoglobin, and other variables were collected. Renal outcomes included complete recovery of kidney function, CKD, and death. Subgroup analysis was performed according to initial modality of RRT in the first 48 hours, including continuous veno-venous hemofiltration (CVVH), intermittent hemodialysis (IHD), and CVVH plus plasma exchange (PE).

Results Of the 75 patients available for follow-up, 7 (9.3%) died, and 8 (10.7%, all in the IHD group) developed CKD. The average RRT time was 18.2 ± 8.4 days, and the average kidney function recovery time was 36.0 (29.0, 41.0) days. Subgroup analysis showed no difference in the mortality rates between the CVVH, CVVH + PE, and IHD groups (8.0%, 7.1%, and 11.1%, respectively; P > 0.99). The recovery time for kidney function was significantly shorter in the CVVH and CVVH + PE groups than in the IHD group (31.9 ± 8.5 days, 28.6 ± 9.4 days, and 41.6 ± 8.1 days, respectively; P < 0.001).

Conclusions This is a large case series report on the outcomes of patients with AKI following multiple wasp stings. Most patients survived with complete recovery of their kidney function. Despite the lack of difference in mortality rates, the patients who began RRT with CVVH and CVVH + PE experienced a better and more rapid recovery of kidney function than those initiated with IHD.


Introduction

Wasps and bees are members of the order Hymenoptera (1). Wasp and bee stings are associated with a wide variety of reactions, ranging from mild local reactions (such as edema, erythema, and urticaria) to fatal systemic complications (such as anaphylactic shock, rhabdomyolysis, AKI, myocardial infarction, acute hepatic failure, and encephalitis) (2–5). AKI is usually caused by intravascular hemolysis, rhabdomyolysis, shock, and the direct toxic effects of the venom; the triad of AKI, hemolysis, and rhabdomyolysis often occurs in patients subjected to multiple wasp or bee stings (6). Renal biopsy usually reveals acute tubular necrosis (5,6), as well as occasional acute interstitial nephritis (7). More than half of the victims who experience multiple wasp or bee stings develop AKI, and most of these patients require intermittent hemodialysis (IHD) or peritoneal dialysis (PD) (4,8–10). The mortality rate of patients who experience AKI due to wasp stings has been reported to be as high as 25% (6). Few large case series have addressed the outcomes of wasp or bee sting–induced AKI, and to our knowledge no studies have focused on the differing modalities of renal replacement therapy (RRT) in these patients. In this study, we analyzed patients with multiple wasp stings at our hospital during a 15-year period who were treated with IHD, continuous veno-venous hemofiltration (CVVH), or plasma exchange (PE) to observe the outcomes of AKI following multiple wasp stings.

Materials and Methods

Patients Data from 103 patients with multiple wasp stings (>50 stings) admitted to West China Hospital of Sichuan University between 1997 and 2011 were included in our analysis. None of the patients had a history of CKD. The diagnosis and staging of AKI were determined according to the 2012 Kidney Disease: Improving Global Outcomes guidelines (11). Among the 103 patients, 81 (78.6%) developed oliguric AKI and received RRT. The clinical course and renal outcomes of these 81 patients were observed; subgroup analysis was performed according to the initial modalities of RRT in the first 48 hours.
Data Collection
Patient demographic characteristics, including age, sex, disease history, and RRT modality administered, were recorded. Important measures, such as mean arterial pressure, urine output, serum creatinine, creatine kinase, lactate dehydrogenase, total bilirubin, myoglobin, electrolytes, and adverse events, were collected.

Observation of Clinical Course and Renal Outcomes
Patients were followed up for at least 3 months. Renal outcomes included a complete recovery of kidney function, CKD, and death. Complete recovery of kidney function was defined as a decrease in the creatinine level to within a normal range with normal urine output. CKD was defined as an estimated GFR of <60 ml/min per 1.73 m² or the occurrence of albuminuria 3 months after the onset of AKI. ESRD was defined as the requirement of maintenance dialysis 3 months after the onset of AKI, and CKD staging was performed according to the 2002 Kidney Disease Outcomes Quality Initiative guidelines (12,13). The recovery time of kidney function, causes of death, and changes in important laboratory measures were also recorded.

Indication of RRT
Patients were treated with RRT when they had AKI with oliguria (urine output <100 ml in a 6-hour period or <400 ml per day) or complicated by hyperkalemia, metabolic acidosis, or acute pulmonary edema.

Available RRT modalities included IHD, CVVH, and PE. Patients received different RRT modalities mainly on the basis of illness severity. Compared with IHD, CVVH was always performed on patients with more severe symptoms, especially when the AKI was complicated by multiple organ dysfunctional syndromes (MODS). PE was considered when patients had severe hemolysis and rhabdomyolysis.

RRT was stopped when urine output was >1500 ml/d without fluid overload and the serum creatinine level was <3 mg/dl.

Statistical Analyses
Continuous variables were expressed as mean ± SD or as the median (25th and 75th percentiles), as appropriate. Subgroup analysis was conducted according to the initial RRT modalities. One-way ANOVA, the Scheffe test, or the Kruskal-Wallis test was used to make comparisons between groups. Categorical variables were expressed as proportions and were compared using the chi-squared test or Fisher exact test. P values < 0.05 were considered to represent statistically significant differences. All statistical analyses were conducted using SPSS software, version 20.0 (SPSS Inc., Chicago, IL).

Results
General Characteristics
Of the 103 patients with multiple wasp stings, 87 (84.5%) had AKI, and 60 (68.9%) presented with MODS complications. Of the patients who developed AKI, 6 (6.9%) had nonoliguric AKI and recovered without RRT. Of the 81 patients (93.1%; Acute Physiology and Chronic Health Evaluation [APACHE] II score, 16.85±2.78) who received RRT, 6 (2 in the CVVH group and 4 in the IHD group) were lost to follow-up within 3 months from AKI onset. These patients still had impaired kidney function at their last follow-up, and the final outcomes were unknown. Twenty patients (24.7%) started RRT at AKI stage 2; 61 patients (75.3%) at AKI stage 3; and none at AKI stage 1. The important laboratory measures of these patients are listed in Table 1.

General Therapies
Local wounds were washed with normal saline and underwent hydrophilic compress protection. Nutrition support and short-term glucocorticoids were also administered. Blood transfusions were performed as necessary.

Modalities of RRT and Subgroup Analysis
According to the initial RRT modality received, the patients were divided into three groups. (1) CVVH group: CVVH was performed (B. Braun Diapact, Diacap Acute M, 1.5 m²) using predilution bicarbonate replacement fluid at a rate of 30–35 ml/kg per hour with a blood flow rate of 150–200 ml/min. Citrate was considered the first choice for anticoagulation, and low-molecular-weight heparin was used as an alternative when patients had contraindications to citrate, such as severe liver dysfunction or persistent poor tissue perfusion. CVVH was performed for at least 48 hours and then was replaced by IHD when the condition of the patient became stable. (2) CVVH + PE group: In addition to the CVVH and IHD therapies received by the CVVH group, the CVVH + PE group received PE once daily on day 1 and day 2 with a 2000- to 2500-ml exchange volume each time using fresh-frozen plasma. (3) IHD group: IHD was performed (Gambro AK-200 or B. Braun Dialog) three times per week for 4 hours per session using low-molecular-weight heparin or heparin for anticoagulation with a blood flow rate of 200–250 ml/min and a Kt/V ratio of 1.2–1.4.

The subgroup analysis showed no significant differences between the treatment groups with regard to mean arterial pressure, hemoglobin, lactate dehydrogenase, APACHE II score, or AKI stage at the baseline readings, but there were significant differences in the creatinine, total bilirubin, myoglobin, and creatine kinase levels, as well as in the proportion of patients with MODS, between the different treatment groups (Table 1). The average treatment times for the CVVH and CVVH + PE groups were 51.4±18.8 and 49.6±22.1 hours, respectively ($P=0.37$). The IHD group received an average of 12.4±8.4 dialysis sessions.

Survival and Recovery of Kidney Function
Of the 75 patients available for follow-up, 7 patients died, which corresponded to a mortality rate of 9.3%; the causes of death were acute pulmonary edema ($n=3$), MODS ($n=3$), and acute digestive tract hemorrhage ($n=1$). Kidney function completely recovered in 60 patients (80.0%). Of the 8 patients (10.7%) in the IHD group who developed CKD, 3 were in CKD stage 2, 3 were in CKD stage 3, and 2 developed ESRD. Two of the patients with CKD stage 2–3 presented mild proteinuria (0.5 and 0.7 g/24 hours). The average time required for RRT was 18.2±8.4 days, and it took an average of 36.0 (29.0, 41.0) days for patients to recover kidney function (Table 2).
Group: 11.1%; CVVH group: 8.0%; CVVH + PE group: 7.1%; the mortality rates among the three treatment groups (IHD group: 92.0%; CVVH group: 92.9%; CVVH + PE group: 92.9%; P=0.99). However, compared with the CVVH and CVVH + PE groups, the IHD group experienced a lower rate of complete recovery of kidney function (IHD group: 66.7%; CVVH group: 92.0%; CVVH + PE group: 92.9%; P=0.007). By the 90th day after the onset of AKI, kidney function recovered completely in all of the survivors in the CVVH and CVVH + PE groups. However, in the IHD group, 8 patients (22.2%) developed CKD. Additionally, the total time for RRT treatment was significantly shorter in the CVVH and CVVH + PE groups than in the IHD group (IHD group: 22.6±7.0 days; CVVH group: 14.4±7.2 days; CVVH + PE group: 13.7±8.3 days; P<0.001). Similarly, the time to recovery of kidney function was significantly shorter in the CVVH and CVVH + PE groups (IHD group: 39.0 (36.8, 43.0) days; CVVH group: 32.0 (25.0, 38.0) days; CVVH + PE group: 25.0 (19.5, 32.0) days; P<0.001) (Table 2).

Changes in Biochemical Measures
Serum levels of total bilirubin, myoglobulin, and creatine kinase decreased steadily through the first 7 days of the treatment course, and the serum level of creatinine fluctuated (Figure 1).

Subgroup analysis showed that the IHD group had a higher level of serum creatinine than the other two groups on the 3rd and 7th days after AKI onset (P<0.001) (Table 3). Additionally, the creatinine level rebounded on the 7th day after AKI onset in the IHD group (P=0.002) (Table 3). Although the three groups did not significantly differ in plasma creatine kinase, myoglobulin, and total bilirubin levels on the 7th day after AKI onset (all P>0.05), these values decreased at a faster rate in the CVVH and CVVH + PE groups within the first 3 days of AKI onset relative to the respective baseline levels (Figure 1). Furthermore, total bilirubin decreased more in the CVVH + PE group than in the CVVH group (P=0.007).

Adverse Events
The main complications associated with RRT were arrhythmia, hypotension, and bleeding. No patients required vasopressors before or during RRT.

The IHD group had a higher incidence of hypotension than the other two groups (IHD group, 9 of 40; CVVH group, 0 of 27; CVVH + PE group, 0 of 14; P=0.005). Patients in the CVVH group were most likely to have hypophosphatemia (IHD group, 0 of 40; CVVH group, 7 of 27; CVVH + PE group, 2 of 14; P<0.001), but this symptom improved without additional interventions after the cessation of CVVH. The three groups did not significantly differ regarding other adverse events, such as arrhythmia, hypertension, catheter-related infections, and bleeding episodes.

Table 1. Demographic and clinical characteristics of patients with AKI at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=81)</th>
<th>IHD (n=40)</th>
<th>CVVH (n=27)</th>
<th>CVVH + PE (n=14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45.5±14.7</td>
<td>42.6±15.7</td>
<td>49.1±13.5</td>
<td>47.1±13.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Men/women</td>
<td>55/26</td>
<td>29/11</td>
<td>17/10</td>
<td>9/5</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0.87</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0.38</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>98.9±16.6</td>
<td>96.7±15.4</td>
<td>98.6±18.2</td>
<td>105.9±15.9</td>
<td>0.20</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.07±2.11</td>
<td>9.85±1.73</td>
<td>10.47±2.49</td>
<td>9.93±2.36</td>
<td>0.48</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>25.87±8.12</td>
<td>25.14±8.64</td>
<td>26.82±8.31</td>
<td>26.13±6.04</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Comparisons among the three groups with respect to age, MAP, hemoglobin, white blood cell count, creatinine, total bilirubin, alanine aminotransferase, myoglobulin, creatine kinase, LDH, APACHE II score, time from sting to RRT, and time from admission to RRT were performed using ANOVA. Comparisons among the three groups based on sex, hypertension, diabetes, MODS, and AKI stage were performed using the Fisher exact test. Pairwise comparisons among the three groups with respect to creatinine, total bilirubin, myoglobulin, creatine kinase, and LDH levels were performed using the Scheffe test.
Discussion

This was a large case series report on the outcomes of AKI patients following multiple wasp stings. We found that the incidence of AKI after multiple wasp stings was as high as 84.5%. Eighty percent of the AKI patients were able to achieve complete kidney recovery; however, 9.3% of them died, and 10.7% of them developed CKD.

Apoidea (bees), Vespoidea (wasps, hornets, and yellow jackets), and Formicidae (ants) are groups of the order Hymenoptera (1). Hymenoptera venoms are complex...
mixtures of biologically active components primarily composed of peptides, enzymes, and amines. Bee venom, which has been studied to a greater extent than the venom of other species within the order Hymenoptera, contains melittin, phospholipase A2 (PLA2), mast cell–degranulating peptide (peptide 401), hyaluronidase, and apamin, among other constituents (1). Melittin, which makes up approximately 50% of the entire bee venom mixture (14), powerfully disrupts cell membranes and has direct toxic effects on renal tubular cells of the host (15–17). Wasp venom does not contain melittin. Instead, wasp venom contains antigen 5 as the main allergen; however, the bioactivity of antigen 5 has not yet been fully determined (1). Victims attacked by wasps or bees can have mild local or regional reactions (e.g., swelling, urticaria, erythema, and pain), as well as severe systemic anaphylactic responses. A description of the stinging insects by their victims, the circumstances surrounding the sting episode, and the local signs of stings can be helpful in differentiating between wasp and bee stings (Table 4) (18–20). Patients with multiple wasp or bee stings could progress to AKI or even MODS. Rhabdomyolysis, hemolysis, and cardiovascular depression caused by venom and direct nephrotoxicity are considered the main mechanisms of bee venom–induced AKI (15,21–23).

In this retrospective study, we found that the mortality rate of AKI following multiple wasp stings was 9.3%, which is lower than that of previous reports, in which patients with AKI following multiple wasp or bee stings were treated with IHD and PD and had a mortality rate between 16% and 25% (6,9,10). Previous studies also showed that, among the patients who survived, 1–3 months was required to recover full kidney function (4,6,8–10,24–26). In our study, the average recovery time of kidney function was shorter in the CVVH or CVVH + PE group than in IHD group, and we believe that this might be partially related to the different RRT modalities used.

In fact, six adult victims of wasp stings who were admitted to our hospital between 1995 and 1996 received PD treatment. Of these patients, one did not return for follow-up, two died, and three developed ESRD. PD was subsequently discontinued in patients with wasp sting–induced AKI in our center. However, in some cases, patients, particularly children, received PD and recovered completely (8,24). Because the number of patients with wasp sting–induced AKI who were receiving PD was limited, we suspect that the selection of patients and the experience of clinical centers could have significantly influenced the outcomes of these cases. In general, the effect of PD in severe AKI remains controversial (27), and the role of PD in patients with multiple wasp stings will require further investigation. In this study, we found that >80% of patients with multiple wasp stings developed AKI, >90% of whom required RRT; these results are consistent with those of recent case studies (9,10). However, we reported a mortality rate of 9.3%, which is low relative to the 18.0% (2 of 11 patients) (9) and 16.3% (7 of 43 patients) (10) rates reported in earlier studies. Although the number of patients included in these studies was limited and some patients were stung by different species of wasps and bees, making direct comparisons of the severity of sickness more difficult, we believe that the lower mortality rate in our study could be partially related to the more diversified RRT modalities used.

Mortality did not significantly differ among the IHD, CVVH, and CVVH + PE groups, which could be partially due to the limited number of patients. Although there were no significant differences in the APACHE II scores between any of the groups, patients who received CVVH or CVVH + PE presented higher levels of total bilirubin, myoglobin, and creatine kinase, which indicated that these patients experienced more severe rhabdomyolysis and hemolysis. In addition, there were larger proportions of patients with MODS in the CVVH and CVVH + PE groups than in the IHD group. Notably, the patients who developed CKD all belonged to the IHD group (8 of 36 [22.2%]). A previous study (10) that included 43 patients with AKI after being stung by Africanized bees showed that only 41.7% of patients had normal kidney function at their last follow-up (average duration of follow-up, 25.2 ± 18.3 days). In our study, 66.7% of the patients in the IHD group achieved complete kidney function recovery by the 90th day of follow-up, but these patients experienced a much longer recovery time for kidney function than those in the CVVH and CVVH + PE.
groups. Therefore, patients administered continuous RRT seemed to have a better and more rapid kidney recovery than patients who received IHD. The reasons for this observation are unclear, but we think that this difference could be partially related to the more stable internal environment and smoother fluid balance control experienced by the patients who were administered continuous RRT. Patients in the IHD group received dialysis three times per week, and these patients experienced more episodes of intradialytic hypotension, which could have induced kidney ischemia.

Moreover, hemolysis and rhabdomyolysis play a pivotal role in multiple wasp or bee sting-induced AKI. Compared with IHD, CVVH and/or PE may have provided a more effective clearance of some toxins with a large molecular weight. Myoglobin (17,800 D), the “secondary toxin” produced by rhabdomyolysis following wasp and bee stings, could be cleared by CVVH, which has sieving coefficients that range from 0.23 to 0.60 (28,29). Most of the components of wasp and bee venoms are also large molecules, which makes these components subject to clearance by CVVH (Table 4) (30). The main component of bee venom is melittin, which is a 2800-D water-soluble polypeptide, each peptide of which consists of 26 amino acid residues (31), and PLA2, which has a molecular mass of 14,500 D and is also water soluble (32). Antigen 5 and phospholipase A1 (PLA1), the chief components of wasp venom, have even larger molecular masses of 23,000 and 43,000 D, respectively (30). Theoretically, CVVH could remove these toxins more effectively than conventional 4-hour, standard-flux IHD. Unfortunately, our study provides no direct evidence regarding the effect of RRT on removing wasp or bee venom components, and future studies should investigate this possibility.

Although the mechanism remains unclear, myoglobin, creatine kinase, and total bilirubin decreased faster in the CVVH group, and this effect appears to have been exaggerated by PE. PE has proven effective in patients who have ingested poison and been bitten by a snake (33), but the evidence of the efficacy of PE in patients with wasp or bee stings is limited (34,35). We believe that PE is advantageous in clearing the venom components, the secondary toxic agents, and the inflammation mediators in circulating blood (36), but future studies should explore the optimal initiation time and frequency of PE.

Some studies have shown that earlier RRT interventions could improve the outcomes of patients with severe AKI (37–39). However, in our study, 75.3% of the patients in our study did not receive RRT until they reached stage 3 AKI. This delay in the initiation of RRT may arise partially because most wasp attacks occurred in the countryside or mountainous areas, requiring extra time for the transport of patients from local clinics to hospitals capable of performing RRT. We also noted that all 7 patients who did not survive died within 72 hours after admission, which may suggest that earlier RRT intervention could be beneficial for AKI patients following multiple stings. However, this observation needs to be confirmed in future studies.

This study has some limitations. The study was a retrospective analysis, and the number of patients was limited. The selection of RRT modalities was generally dependent on the experience of the physician in charge and was based on the general condition of the patient and various laboratory measures. Six patients were lost to follow-up in this study, which might, to some extent, overestimate the survival rate. However, the comparison of complete recovery of kidney function rate would probably still show a trend in favor of the CVVH or CVVH + PE group even if none of the six patients recovered kidney function. Furthermore, the selection of RRT modality could have been influenced by many factors beyond the severity of patient illness, such as the financial status of patients. Further larger prospective studies are needed to confirm our results.

In conclusion, this is a large case series report on the outcomes of patients with AKI following multiple wasp stings. Most patients survived with complete recovery of their kidney function. Despite the lack of difference in mortality rates, the patients initiated with CVVH and CVVH + PE experienced a better and more rapid recovery of kidney function compared with those initiated with IHD.

Disclosures
None.

### Table 4. Differences between wasp and bee stings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bees</th>
<th>Wasps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body shape</td>
<td>Fuzzy</td>
<td>Smooth</td>
</tr>
<tr>
<td>Food</td>
<td>Nectar and pollen</td>
<td>Insects and sweet substances (e.g., sap, nectar, soft drinks, and cans)</td>
</tr>
<tr>
<td>Circumstances of sting incidents</td>
<td>Usually near flowers or a beehive</td>
<td>Near, for example, open soft drink cans; when performing outdoor activities that disturb their nests</td>
</tr>
<tr>
<td>Type of sting</td>
<td>Sting only once, usually with a stinger (with barbs) in the skin</td>
<td>Sting repeatedly, normally without a stinger (without barbs) in the skin</td>
</tr>
<tr>
<td>Medically important components in venom (references 30–32)</td>
<td>Melittin (2.8 kD)</td>
<td>Antigen 5 (23 kD)</td>
</tr>
<tr>
<td></td>
<td>PLA2 (14.5 kD)</td>
<td>PLA1 (34 kD)</td>
</tr>
<tr>
<td></td>
<td>Hyaluronidase (39 kD)</td>
<td>Hyaluronidase (38 kD)</td>
</tr>
<tr>
<td></td>
<td>Acid phosphatase (43 kD)</td>
<td></td>
</tr>
</tbody>
</table>

PLA2, phospholipase A2; PLA1, phospholipase A1.
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