Funnel-web spider bite: a systematic review of recorded clinical cases

Geoffrey K Isbister, Michael R Gray, Corrine R Balit, Robert J Raven, Barrie J Stokes, Kate Porges, Alan S Tankel, Elizabeth Turner, Julian White and Malcolm McD Fisher

ABSTRACT

Objective: To investigate species-specific envenoming rates and spectrum of severity of funnel-web spider bites, and the efficacy and adverse effects of funnel-web spider antivenom.

Data sources: Cases were identified from a prospective study of spider bite presenting to four major hospitals and three state poisons information centres (1999–2003); museum records of spider specimens since 1926; NSW Poisons Information Centre database; MEDLINE and EMBASE search; clinical toxinology textbooks; the media; and the manufacturer's reports of antivenom use.

Data extraction: Patient age and sex, geographical location, month, expert identification of the spider, clinical effects and management; envenoming was classified as severe, mild–moderate or minor/local effects.

Data synthesis: 198 potential funnel-web spider bites were identified: 138 were definite (spider expertly identified to species or genus), and 77 produced severe envenoming. All species-identified severe cases were attributed to one of six species restricted to NSW and southern Queensland. Rates of severe envenoming were: *Hadronyche cerberea* (75%), *H. formidabilis* (63%), *Atrax robustus* (17%), *Hadronyche* sp. 14 (17%), *H. infensa* (14%) and *H. versuta* (11%). Antivenom was used in 75 patients, including 22 children (median dose, 3 ampoules; range, 1–17), with a complete response in 97% of expertly identified cases. Three adverse reactions were reported, all in adults: two early allergic reactions (one mild and one with severe systemic effects requiring adrenaline), and one case of serum sickness.

Conclusions: Severe funnel-web spider envenoming is confined to NSW and southern Queensland; tree-dwelling funnel webs (*H. cerberea* and *H. formidabilis*) have the highest envenoming rates. Funnel-web spider antivenom appears effective and safe; severe allergic reactions are uncommon.

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Funnel-web spiders are the most dangerous spiders in the world and continue to cause severe envenoming in eastern Australia. They belong to the family Hexathelidae: Atracinae and comprise about 40 species in two genera (*Atrax* and *Hadronyche*). Although some species are well known, many have not been formally characterised, and species identification can be difficult. It should be undertaken only by expert arachnologists, using both morphological and distributional attributes.[1,2]

As bites that cause only minor effects are rarely published or correctly attributed to expertly identified spiders, it has been difficult to determine the rate of severe envenoming for different species. For example, the suspected envenoming rate of the Sydney funnel-web spider (*Atrax robustus*) is 10%–25%,[3-6] but this may be confounded by the inclusion of trapdoor-spider bites as non-envenoming bites (as trapdoor spiders are often misidentified as funnel-web spiders[6]), and by publication bias of more severe cases.

Funnel-web spider antivenom was first used in 1981. It is produced against *A. robustus* venom and, based on case reports and small case series, appears effective for severe envenoming.[4,5,7] Although it is assumed to have few adverse effects, there are no large studies of its safety.

Our study was undertaken to:

- investigate the envenoming rate and spectrum of severity of different funnel-web spider species; and
- investigate systematically the use of funnel-web spider antivenom, including dose, efficacy in envenoming by different species, and adverse reactions.

Menzies School of Health Research, Charles Darwin University, Darwin, NT.
Geoffrey K Isbister, BSc, MD, FACEM, Senior Research Fellow; and Clinical Toxicologist, Newcastle Mater Misericordiae Hospital.
Australian Museum, Sydney, NSW.
Michael R Gray, MSc, PhD, Principal Research Scientist.
NSW Poisons Information Centre, Sydney, NSW.
Corrine R Balit, BPharm, MB BS, Research Pharmacist.
Queensland Museum, Brisbane, QLD.
Robert J Raven, BSc, PhD, Senior Curator (Arachnology).
University of Newcastle, Newcastle, NSW.
Barrie J Stokes, BSc, MMath, Statistician, Clinical Pharmacology.
Gosford Hospital, Gosford, NSW.
Kate Porges, FACEM, Emergency Physician.
Coffs Harbour Base Hospital, NSW.
Alan S Tankel, BSc, FACEM, Director of Emergency Department and Conjoint Senior Lecturer, University of New South Wales, Sydney, NSW.
Tasmanian Museum, Hobart, TAS.
Elizabeth Turner, MAIBiol, Curator, Invertebrate Zoology.
Women's and Children's Hospital and University of Adelaide, SA.
Julian White, MD, FACTM, Associate Professor, and Head of Toxinology.
Royal North Shore Hospital, Sydney, NSW.
Malcolm McD Fisher, MD, FANZCA, FJFICM, Intensive Care Specialist, and Clinical Professor, University of Sydney, NSW.
Reprints will not be available from the authors. Correspondence: Dr Geoffrey K Isbister, Department of Clinical Toxicology and Pharmacology, Newcastle Mater Misericordiae Hospital, Waratah, NSW 2298. gsbite@ferntree.com

METHODS

Data sources

We attempted to identify all known cases of funnel-web spider bite using multiple sources. These included a prospective study of patients with spider bite presenting to the Royal Prince Alfred Hospital, Sydney (NSW) or Royal Darwin Hospital (Northern Territory) (February 1999 to April 2003), or to hospitals served by the Hunter Region Toxicology Service (NSW) (July 2000 to April 2003), as well as people with spider bite contacting the New South

Wales, Queensland or Western Australian Poisons Information Centres (February 1999 to April 2003).[6,8] All people who provided the spider for expert identification were eligible for the study.

Major museums in areas where funnel-web spiders occur were contacted to find specimens responsible for bites, comprising the Australian Museum (1926–2004), Museum Victoria (1980–2004), Queensland Museum (1968–2004), South Australian Museum (1985–2004), Tasmanian Museum (1972–2004), and the Queen Victoria Museum in Launceston (1994–2004). We also contacted arachnologists working outside museums.

We also undertook a systematic review of scientific publications. MEDLINE, OLD MEDLINE (1951–1965) and EMBASE were searched to 14 May 2004 using the terms "Atrax", "Hadronyche", "Atracinae", "Hexathelidae", "Dipluridae" and "funnel-web spider". The reference lists of resulting publications were also searched, and authors were contacted where possible.

In addition, we searched:

- Reports of antivenom use to the manufacturer, CSL Limited, for the period 1994–2003 (earlier reports were published previously[4,9]);
- The database of the NSW Poisons Information Centre for funnel-web spider bites referred to a consultant toxicologist from January 1997 (when a searchable electronic database came into operation) to June 2004 (this database codes funnel-web spider bites only if the diagnosis is clear, and thus is biased to envenoming);
- The database of the Hunter Area Toxicology Service, Newcastle, NSW, for the period 1987 to June 2004;
- Internet sites of major media organisations — the f2 Network (Fairfax Publications) and newstext.com.au (News Corporation) — for the period 1984 to June 2004;
- The Internet using the search engine Google and search term "funnel-web spider bite" to 17 May 2004; and
- Major Australian and international clinical toxinology textbooks.

We also contacted clinical toxicologists appointed to the NSW and Queensland Poisons Information Centres to identify any other unreported bites, envenomings or antivenom uses and to obtain further clinical details of patients they had treated. Clinicians involved in treating patients identified from other sources were also contacted for further information. Cases identified in an ongoing prospective study of funnel-web spider envenoming conducted by the authors, any other cases known to the authors, and cases managed in their hospitals were also included.

Many cases were identified from multiple sources. Date and location of the bite and patient age and sex were compared to avoid duplicating cases.

Data extraction

For all reports of bites and cases where antivenom was used, the following information was extracted, if available: patient age and sex, geographical location, date, whether the spider was collected and identified by an expert arachnologist, species of spider, circumstances and anatomical site of the bite, local and systemic effects, and management (hospital attendance, length of stay and antivenom use, including efficacy and adverse effects).

Data analysis

Envenoming rate

We determined the rate of severe envenoming for bites by expertly species-identified spiders obtained from the prospective study[6] or museum records, as these sources collected consecutive cases. Bites identified from published reports were excluded because of bias to publication of severe envenoming cases, as were individual reports not part of a consecutive series.

Envenoming was classified as:

- *severe,* if three or more features of systemic funnel-web spider envenoming were present (from at least two groups), as defined by:
  - – autonomic effects (diaphoresis, salivation, lacrimation, piloerection, miosis, mydriasis);
  - – cardiovascular effects (hypertension, hypotension, tachycardia, bradycardia);
  - – neurological effects (oral paraesthesia, muscle fasciculations, muscle spasm); or
  - – pulmonary oedema.
- *mild to moderate,* if there were less than three defined features of funnel-web spider envenoming; or regional neurotoxic effects only; or
- *minor or local effects only*.[6]

Although general systemic effects such as vomiting, headache and abdominal pain are common in funnel-web spider bites, they are not sufficiently specific to be included in the definition.

Features of severe envenoming

To determine the time to onset of severe envenoming and frequency of specific clinical effects, we analysed all cases in which a large black spider was seen in the act of biting, and the patient had three or more features of systemic funnel-web spider envenoming, even when the spider was not expertly identified.

Antivenom use

All cases in which the patient received funnel-web spider antivenom were analysed to determine antivenom safety and efficacy. These included cases which were unlikely to be funnel-web spider bites.

Statistical analysis

All analyses were performed using StatsDirect[10] and StatXact[11] computer software. Envenoming rates were compared between species using the Fisher–Freeman–Halton exact test. For descriptive statistics, median and interquartile range (IQR) were used for non-normally distributed data.

RESULTS

We identified 198 cases which were either potential funnel-web spider bites or cases where funnel-web spider antivenom was used:

- 138 cases where the spider was expertly identified, 130 to species level (eight specimens were too immature for species identification); these included 29 cases where antivenom was given;
- 46 cases where antivenom was given on the clinical suspicion of funnel-web spider envenoming, with or without an observed bite by a black spider; these included nine cases which were definitely or probably not funnel-web spider bites (three definite bites by another species [*Namea brisbanensis*, *Missulena bradleyi*, *Misgolas* sp.], one suspected redback spider bite, one bite by another unidentified spider, and four with no history of a bite and unusual clinical features); and
- 14 cases which had the classical features of severe funnel-web spider envenoming but occurred before 1981 (when antivenom became available), and no spider was identified.

The primary sources of the 198 bite reports were:

- 16 from the previously published prospective study;[6]

1 Severity of envenoming in 138 expertly identified funnel-web spider bites reported in different sources

Species†	Common funnel-web name	Museum records			Prospective study[6]			Other*			All bites			
		Minor/ local	Mild/ moderate	Severe	Minor/ local	Mild/ moderate	Severe	Minor/ local	Mild/ moderate	Severe	Minor/ local	Mild/ moderate	Severe	Total
Atrax robustus	Sydney	16	0	3	3	0	1	1	1	18	20	1	22	43
Hadronyche infensa	Toowoomba	5	5	2	1	1	0	0	0	1	6	6	3	15
H. versuta	Blue Mountains	8	0	1	0	0	0	1	0	1	9	0	2	11
H. formidabilis	Northern tree	2	1	5	0	0	0	0	0	2	2	1	7	10
H. venenata	Tasmanian	8	0	0	0	1	0	0	0	0	8	1	0	9
H. cerberea	Southern tree	1	0	2	0	0	1	0	0	4	1	0	7	8
Hadronyche sp. 14‡	Port Macquarie	1	0	1	3	1	0	0	1	1	4	2	2	8
Hadronyche sp. 7	Bermagui	3	2	0	1	0	0	0	0	0	4	2	0	6
Hadronyche sp. 20	Illawarra	1	0	0	0	0	0	4	0	0	5	0	0	5
Hadronyche sp. 11	Hunter Region	2	0	0	0	1	0	0	0	0	2	1	0	3
Other species§		7	3	0	0	0	0	2	0	0	9	3	0	12
Immature¶		6	0	0	2	0	0	0	0	0	8	0	0	8
Total		62	13	14	10	4	2	4	2	27	76	19	43	138

* Other sources comprised scientific publications (27), NSW Poisons Information Centre database (2), referrals to author M M F (2), newspaper reports (1), and ongoing prospective study of snake and spider envenoming (1). † All belong to the genera *Atrax* or *Hadronyche*.
‡ *Hadronyche* species 14 and 15 were combined because of their taxonomic similarities.
§ Other species were *Atrax* sp. 1 (Bega funnel-web: one case with local effects, one mild–moderate effects), *Atrax* sp. 2 (Batlow funnel-web: one local, one mild–moderate effects), *H. modesta* (two local effects), *Hadronyche* sp. 9 (Gippsland funnel web; one mild–moderate effects), *H. adelaidensis, H. valida, Hadronyche* sp. 2 (Alpine funnel web), *Hadronyche* sp. 3 (South-west slopes funnel web), *Hadronyche* sp. 4 (Monaro funnel web) (each with one case with local effects).
¶ Although definitely identified as members of the Hexathelidae: Atracinae, eight spiders were too immature to be identified to species level.

- 89 from records of specimens at the Australian Museum (64), Queensland Museum (16), Tasmanian Museum (8) and Museum Victoria (1);
- 43 from the MEDLINE and EMBASE searches (13 case reports and series[3,4,6-8,12-19] in 185 publications) and from reference lists and textbooks (a further 12 reports[5,20-29]).
- 50 from other sources: CSL antivenom reports (14), NSW Poisons Information Centre (9); the media (6); Hunter Area Toxicology Service (5); ongoing national prospective study of snake and spider envenoming (3) and other reports from authors (13).

Species-specific rates of envenoming

The species responsible and severity of envenoming for the 138 expertly identified funnel-web spider bites are shown in Box 1. There were 43 cases of severe envenoming, attributed to six species — the southern tree (*Hadronyche cerberea*), northern tree (*H. formidabilis*), Sydney (*Atrax robustus*), Port Macquarie (*Hadronyche* sp. 14), Toowoomba or Darling Downs (*H. infensa*), and Blue Mountains (*H. versuta*) funnel-web spiders. Rates of severe envenoming by these species are shown in Box 2. Rates varied significantly ($P = 0.02$; Fisher–Freeman–Halton exact), from 11% for the Blue Mountains funnel-web spider to 75% for the southern tree funnel-web spider.

Female spiders were responsible for 17 of the 138 expertly identified bites: *A. robustus* (7), *H. infensa* (5), *H. versuta* (2), *H. modesta* (1), *Hadronyche* sp. 14 (1) and unknown *Hadronyche* sp. (immature speciment) (1). Effects were local in 14 cases, and mild envenoming in three (all *H. infensa*).

Bites in which the spider was expertly identified as a funnel-web spider occurred in all eastern states and territories: NSW (108), Australian Capital Territory (1), Queensland (16), Victoria (3), Tasmania (9), and South Australia (1). However, cases of severe envenoming were confined to NSW and southern Queensland.

Features of severe envenoming

A total of 77 cases were classified as severe funnel-web spider envenoming: 43 expertly identified cases, and another 34 in which a large black spider was seen biting but was not expertly identified, and the patient had three or more features of severe funnel-web envenoming. Thirty-two of these 77 cases (42%) were in children. The median number of cases of severe envenoming for 1981–2004 was 2 per year (IQR, 1–3; range, 0–7). Most cases occurred between November and March.

The 77 cases comprised:

- 13 deaths (all before the introduction of antivenom in 1981), seven in children;
- 16 non-fatal bites before antivenom introduction (10 with species identification and 6 with non-expert identification of a Sydney funnel-web spider); and
- 48 cases treated with antivenom.

Detailed information on clinical effects was available for 59 cases (Box 3). Time to onset of symptoms was known for 42 cases of severe envenoming and ranged from 8 to 175 minutes (median, 28 min; IQR, 15–45 min). Two patients had onset after 2 hours; both had a pressure immobilisation bandage applied, and in one of these, symptoms occurred on release of the bandage.[14] The use of pressure immobilisation bandages was recorded in 44% of cases since it was first recommended in 1980.[30]

Antivenom safety and efficacy

Antivenom was given to 75 patients, including 29 with expertly identified funnel-web spider bites, and nine who definitely or

2 Rate of severe envenoming for the six most medically important species of funnel-web spider

Species	Common name	No. of bites*		Severe envenoming rate (95% CI)
		Severe	Total	
H. cerberea	Southern tree	3	4	75% (19%–99%)
H. formidabilis	Northern tree	5	8	63% (24%–91%)
Atrax robustus	Sydney	4	23	17% (5%–39%)
Hadronyche sp. 14	Port Macquarie	1	6	17% (0–64%)
H. infensa	Toowoomba	2	14	14% (2%–43%)
H. versuta	Blue Mountains	1	9	11% (0–48%)

* Expertly identified bites identified from the prospective study or museum records; other sources were excluded because of the potential for bias to severe cases.

probably had not been bitten by a funnel web spider. Patients included 6 infants, 22 children aged 2–15 years, two pregnant women and two women who were breastfeeding. The median dose of antivenom was three ampoules (IQR, 2–5; range, 1–17).

Adverse effects were seen in three of the 75 patients, all adults:

- a severe systemic reaction with hypotension which occurred 1 hour after administration of four ampoules of antivenom and responded to subcutaneous adrenaline; the patient was given two more ampoules of antivenom for ongoing envenoming without further adverse effects;
- itchiness and throat tightness occurring within hours of administration of three ampoules of antivenom which responded to promethazine and salbutamol; and
- serum sickness presenting 7 days after administration of five ampoules of antivenom.[20]

There were no adverse effects in infants, children or pregnant women administered antivenom. The rate of severe allergic reactions was therefore 1 in 75 (1.3%; 95% CI, 0–7%).

Among the nine patients who had no evidence of a funnel-web spider bite but received antivenom, one died. This patient's condition initially appeared to respond to antivenom, but had no history of spider bite, and no spider was found.

A complete response to the antivenom was reported in 28 of 29 patients (97%) with expertly identified funnel-web spider bites and information on antivenom response. Complete responses to antivenom were seen in patients bitten by the six funnel-web species that caused severe envenoming and by one patient bitten by *Hadronyche* sp. 7, which caused moderate envenoming.[4]

The median hospital stay among patients who survived severe envenoming was 1.8 days for those treated with antivenom (95% CI, 1.3–3.7 days) versus 3.5 days for those who were not treated with antivenom (95% CI, 2.6–9.4 days; $P = 0.02$ by Mann–Whitney test).

DISCUSSION

This study has better defined the range of the most dangerous funnel-web spider species and their envenoming rates. We found that species which caused severe envenoming were restricted to NSW and southern Queensland. The study also identified 75 patients who received funnel-web spider antivenom, with a rate of severe adverse effects less than 2%, and complete responses in more than 90% of those with expertly identified funnel-web spider bites, including patients bitten by the six most dangerous species.

We found apparent differences in envenoming rates between species: the Sydney funnel web spider had a rate of severe envenoming of 17%, while the southern and northern tree funnel web spiders had much higher rates (over half of cases). These findings are not consistent with results of *in vitro* venom studies, which suggested similar toxicity for venom of 10 *Atrax* and *Hadronyche* species, including some not found to cause envenoming in our study.[31] The latter may be due to the limited number of bites by these spiders. Alternatively, the difference in envenoming rates may be due to differences in spider size, fang length, behaviour and ability to inject venom, rather than in venom toxicity. Determination of the envenoming rate is limited by the small number of cases and differences in the data sources. Ideally, a large prospective multicentre study would provide more accurate rates.

Severe envenoming was not reported for female funnel-web spiders, consistent with previous findings that most female funnel-web spiders have less potent venom than male spiders. However, there were no reported bites by female tree funnel-web spiders, which have been shown *in vitro* to be highly venomous.[31] Antivenom was effective in people bitten by all six dangerous species, consistent with results of *in vitro* antivenom studies.[31]

The onset of severe envenoming is rapid, with deaths reported within an hour.[29] In our study, the median time to onset of envenoming was 28 minutes, with only two cases having onset after 2 hours, both with a pressure immobilisation bandage or tourniquet applied. This suggests that patients are highly unlikely to develop

3 Frequency of clinical effects (95% CI) in severe cases of funnel-web spider envenoming where comprehensive information was available

Clinical effect	Adults ($n = 36$)	Children ($n = 23$)	Total ($n = 59$)
Autonomic			
Diaphoresis	83% (67%–94%)	70% (47%–87%)	78%
Increased salivation	44% (28%–62)	43% (23%–66%)	44%
Piloerection	25% (12%–42)	39% (20%–61%)	31%
Lacrimation	17% (6%–33%)	4% (0–22%)	12%
Pupillary changes	36% (21%–54%)	26% (10%–48%)	32%
General systemic			
Agitation	44% (28%–62%)	52% (31%–73%)	47%
Vomiting	33% (19%–51%)	52% (31%–73%)	41%
Headache	14% (5%–29%)	4% (0–22%)	10%
Abdominal pain	8% (2%–23%)	13% (3%–34%)	10%
Cardiovascular			
Hypertension	81% (64%–92%)	65% (43%–84%)	75%
Hypotension	14% (5%–29%)	4% (0–22%)	10%
Tachycardia	53% (36%–70%)	70% (47%–87%)	59%
Bradycardia	11% (3%–26%)	9% (1%–28%)	10%
Neurological			
Oral paraesthesia	44% (28%–62%)	13% (3%–34%)	32%
Fasciculations	67% (49%–81%)	35% (16%–57%)	54%
Muscle spasm	19% (8%–36%)	13% (3%–34%)	17%
Coma/unconsciousness	0% (0–10%)	22% (7%–44%)	8%
Pulmonary oedema	44% (28%–62%)	70% (47%–87%)	54%

envenoming after 2 hours, but, until this is confirmed by prospective studies, it is important to observe patients with suspected funnel-web spider bites for 4 hours.

The rarity of severe funnel-web spider envenoming (a median of two cases annually in the past 10 years, when data collection was most complete) has made it difficult to evaluate the efficacy and safety of funnel-web antivenom. Sutherland suggested in 1992 that about 50 patients had been treated with antivenom in the first decade of its availability,[9] with nine in the first 3 years.[4] We report use of antivenom in 75 patients over 23 years, including infants, children, and pregnant and breast-feeding women, with only one severe immediate allergic reaction and one delayed reaction (serum sickness) (< 2% for each), both in adults. Although the study may have underestimated the rate of delayed reactions, it is unlikely to have underestimated early reactions.

We found no confirmed deaths after funnel-web spider bite since the antivenom was introduced. Antivenom completely reversed the effects of clinical envenoming in 97% of expertly identified cases. This confirms previous clinical reports[12,13,15] and results of animal research[31] suggesting that the antivenom, which is produced against *A. robustus* venom, is effective against *Hadronyche* spp. We also found that use of funnel-web spider antivenom appeared to reduce length of hospital stay after envenoming, consistent with the finding of a previous prospective study in a single hospital.[5] This supports the continuing use of funnel-web spider antivenom as the mainstay of treatment for severe funnel-web spider envenoming, despite the lack of a controlled trial.

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COMPETING INTERESTS

Associate Professor White is employed by the Women's and Children's Hospital, Adelaide, which is paid by CSL Ltd to provide a consultant clinical toxinology service for users of CSL antivenom and venom detection products.

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