

## Does soybean intravenous lipid emulsion therapy reduce time to recovery faster than ClinOleic therapy in cats with permethrin toxicosis?

A Knowledge Summary by

**Shadira Gordon** DVM MPVM<sup>1\*</sup>

<sup>1</sup> University of California, Davis, One Shields Ave, Davis, CA 95616

\* Corresponding Author ([dsgordon@ucdavis.edu](mailto:dsgordon@ucdavis.edu))

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ISSN: 2396-9776

Published: 04 Nov 2021

in: The *Veterinary Evidence* journal Vol 6, Issue 4

DOI: <https://doi.org/10.18849/ve.v6i4.469>

Reviewed by: Jacqueline Renee Cole (BSc BVetMed MRCVS)  
and Merran Govendir (BVSc PhD MEd MANZCVSc  
FHERDSA)

Next Review Date: 10 Oct 2023

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### PICO question

Is soybean oil-based intravenous lipid emulsion (IVLE) therapy more effective than olive oil-based (ClinOleic IVLE therapy) for reducing time to recovery in cats with permethrin toxicosis?

### Clinical bottom line

### Category of research question

Treatment

### The number and type of study designs reviewed

Five case reports and one randomised clinical trial

### Strength of evidence

Weak

### Outcomes reported

Soybean oil-based and ClinOleic IVLE therapies can be used safely as adjuvant treatments to reduce time to recovery in cats with permethrin intoxication. However, the evidence collected suggests that soybean oil-based IVLE therapy is faster than ClinOleic to reduce time to recovery after permethrin toxicosis

### Conclusion

The overall findings showed that the average recovery time after soybean oil-based IVLE therapy between patients with permethrin intoxication was 8.5 hours and the average time to recovery after olive oil-based emulsions (ClinOleic therapy) was 39 hours. This may suggest that soybean oil-based formulations are a better option for reducing the recovery time in cats after permethrin toxicity. Dermal decontamination, supportive care, muscle relaxers, and anticonvulsant drugs are examples of recommended treatments before the administration of any intralipid therapies and must be used based on the clinical signs of each patient

### [How to apply this evidence in practice](#)

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

### Clinical Scenario

A 4 year old spayed female domestic short-haired cat presents to your emergency room with seizures and hypersalivation. The owners described the first episode of seizures occurring almost 3 hours after applying a permethrin spot-on (PSO) product with a formulation higher than  $\approx 45\%$  directly on their cat's coat.

This scenario is common in emergency rooms, as owners do not know that permethrin-based products intended to control ectoparasites in dogs should not be used in cats<sup>1-5</sup>. These highly concentrated formulations

may cause severe clinical signs or death, even by secondary exposure (e.g., licking, grooming, or having close contact with recently treated dogs)<sup>6</sup>.

The owners are concerned about their cat's welfare and the associated costs of treatment. You discuss with them two novel intralipid therapies useful for reducing hospitalisation times (soybean oil-based therapy and ClinOleic therapy).

### The evidence

Five case reports (Pelizzola et al., 2018; Ceccherini et al., 2015; Haworth et al., 2012; Brückner et al., 2012; and Kuo et al., 2013) and one randomised clinical trial (Peacock et al., 2015) were evaluated because of their relevance to the PICO question.

The Pelizzola et al. (2018) study evaluated three young cats treated with soybean oil-based IVLE therapy. The outcome measured in this study was the time to recovery after IVLE therapy administration and all the cases showed neurological improvement with an average time to recovery of 10 hours. The Ceccherini et al. (2015) study evaluated four cats between 2–14 years old. This case-report showed a mean time to recovery of 5 hours after soybean oil-based IVLE therapy. Haworth et al. (2012) provided evidence on three adult cats in which all showed neurological improvement after soybean oil-based IVLE therapy after an average time to recovery of 8.3 hours. The Brückner et al. (2012) study was the only one in which two patients were treated with the ClinOleic IVLE therapy. The average recovery time after the olive oil-based intralipid therapy was 39 hours. Kuo et al. (2013) evaluated the time to recovery of two cats with permethrin toxicosis treated with soybean oil-based IVLE therapy. In this study, both cats showed neurological improvement within an average period of 14 hours.

The randomised clinical trial by Peacock et al. (2015) evaluated the progression of clinical signs of cats with permethrin intoxication before and after treatment with soybean oil-based IVLE therapy compared to cats treated with saline solution control. The outcomes measured in this study were based on the differences around a clinical staging system designed by the authors, which ranged from Stage A for cats that had no abnormalities detected to Stage F for cats with grand mal seizures. There was a statistically significant difference in the distribution of relative frequencies of clinical stages over time between control cats and IVLE treated cats, where cats treated with soybean oil-based IVLE therapy showed lower clinical stages earlier. However, there were no significant differences between control and IVLE treated cats in the hospitalisation times, which can be explained by other factors, such as the availability of owners to collect their cats after recovery.

### Summary of the evidence

Pelizzola et al. (2018) <sup>6</sup>	
<b>Population:</b>	Young cats with permethrin toxicosis
<b>Sample size:</b>	Three cats
<b>Intervention details:</b>	Low-dose soybean oil-based IVLE infusion (Intralipid 20%, Fresenius Kabi). Initially a 1.5 ml/kg bolus of IVLE was given over 30 minutes, then a second bolus of 0.25 ml/kg/minute over 3 minutes, followed by a constant rate infusion (CRI) of 0.025 ml/kg/minute.
<b>Study design:</b>	Case report
<b>Outcome studied:</b>	Time of recovery after soybean oil-based IVLE therapy.
<b>Main findings: (relevant to PICO question):</b>	Case 1 showed neurological improvement 6 hours after low-dose soybean oil based IVLE administration, while cases 2 and 3 after 12 hours. The mean time was 10 hours.

<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Low sample size (three patients).</li> <li>• Different initial treatments for each case (alfaxalone, dexmedetomidine, and diazepam for case 1, diazepam and propofol for case 2, and propofol and midazolam for case 3).</li> </ul>
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<b>Ceccherini et al. (2015)<sup>7</sup></b>	
<b>Population:</b>	Adult cats with permethrin toxicosis
<b>Sample size:</b>	Four cats
<b>Intervention details:</b>	<p><b>Case 1:</b> IVLE bolus at 2 ml/kg in 3 minutes, followed by a CRI at 4 ml/kg/h for 5 hours.</p> <p><b>Case 2:</b> IVLE bolus was administered at a dosage of 1 ml/kg in 5 min, followed by CRI at 5 ml/kg/h for 3 hours. IVLE therapy was reduced at 2 ml/kg/h and administered for 6 hours.</p> <p><b>Case 3:</b> A bolus of IVLE at 2 ml/kg in 5 min followed by a CRI of 4 ml/kg/h for 3 hours.</p> <p><b>Case 4:</b> A bolus of IVLE at 2 ml/kg in 5 min followed by a CRI of 2 ml/kg/h for 4 hours.</p>
<b>Study design:</b>	Case report
<b>Outcome studied:</b>	Time of recovery after soybean-oil based IVLE therapy.
<b>Main findings: (relevant to PICO question):</b>	Case 1 showed neurological improvement 5 hours after IVLE administration, cases 2 and 3 after 6 hours, and case 4 after 4 hours. On average all cases showed neurological improvement within 5 hours from low-dose soybean oil-based IVLE administration.
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Low sample size (four patients).</li> <li>• Cases 2, 3, and 4 were referred after initial treatment in other hospital.</li> <li>• Authors used different doses and rate of bolus and CRI of IVLE therapy.</li> <li>• Different supportive treatments for each case (propofol plus dexmedetomidine for case 1, phenobarbital for case 2, diazepam, propofol, midazolam and dexmedetomidine for case 3, and dexmedetomidine for case 4).</li> </ul>

<b>Peacock et al. (2015)<sup>8</sup></b>	
<b>Population:</b>	Adult cats with permethrin toxicosis
<b>Sample size:</b>	Thirty-four cats
<b>Intervention details:</b>	All cats in the clinical trial were randomised to receive 15 mL/kg of either intravenous 0.9% saline (control) or 20% soybean oil-based IVLE therapy over 60 minutes. 14 cats received the control treatment and 20 cats received the soybean oil based IVLE treatment. For each cat, a clinical stage was recorded at set time points before and after the randomised treatment was administered. The distribution of clinical stage stratified overtime was compared across treatment groups.
<b>Study design:</b>	Randomised clinical trial
<b>Outcome studied:</b>	Time of recovery after soybean oil-based IVLE therapy.

	A clinical staging system was designed based on abnormalities found on physical examination of cats with permethrin toxicosis. The clinical staging system had 6 stages, ranging from Stage A for cats with no abnormalities to Stage F for cats with grand mal seizures. For each cat, a clinical stage was recorded at set time points before and after the randomised treatment (soybean oil-based IVLE therapy was administered). The distribution of clinical stage stratified overtime was compared across treatment groups.
<b>Main findings: (relevant to PICO question):</b>	There was a statistically significant difference in the distribution of clinical stages over time ( $P < 0.001$ ) and from presentation stage to Stage B ( $P = 0.006$ ), with IVLE treated cats ( $n = 20$ ) having lower clinical stages earlier than control cats ( $n = 14$ ). Clinical stages of permethrin toxicosis in IVLE treated cats improved earlier compared to control cats.
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Veterinarians were not blinded to the treatment. A failure to blind them may result in detection bias (the outcome assessments may be systematically influenced by practitioners).</li> <li>• External factors make it difficult to measure the difference in hospitalisation times between the control and IVLE treated cats, so we can only conclude a difference in the time in which a patient reached a point to be considered stable but not regarding their hospitalisation discharge.</li> <li>• Confounding effects due to the timing and different drug administration between groups for neuroexcitatory signs control (alfaxalone, butorphanol, midazolam, acepromazine, medetomidine, phenobarbitone and propofol).</li> </ul>

<b>Haworth et al. (2012)<sup>9</sup></b>	
<b>Population:</b>	Adult cats with permethrin toxicosis
<b>Sample size:</b>	Three cats
<b>Intervention details:</b>	<p><b>Case 1:</b> 20% IVLE therapy at a dose of 1.5 mL/kg over 30 minutes followed by a CRI of 0.25 mL/kg/min for 45 minutes (total of 48.5 mL).</p> <p><b>Case 2:</b> 20% IVLE therapy at a dose of 1.5 mL/kg over 90 minutes and an additional dose of 0.25 mL/kg/min over 30 minutes (total of 36 mL).</p> <p><b>Case 3:</b> 20% IVLE therapy at a dose of 0.25 mL/kg/min over an hour (total of 90 mL).</p>
<b>Study design:</b>	Case report
<b>Outcome studied:</b>	Time of discharge after 20% soybean oil-based IVLE therapy.
<b>Main findings: (relevant to PICO question):</b>	Cases 1 and 2 were discharged 9 hours after 20% IVLE therapy administration, while case 3, after 7 hours (mean time 8.3 hours).
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Low sample size (three patients).</li> <li>• Case 1 had a second exposure to permethrin, which may have influenced its recovery time. Also, this case received 20% IVLE therapy 72 hours after initial exposure.</li> </ul>

	<ul style="list-style-type: none"> <li>• Authors used different doses and rates of bolus and CRI of 20% IVLE therapy.</li> </ul>
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Brückner et al. (2012) <sup>10</sup>	
<b>Population:</b>	Young cats with permethrin toxicosis
<b>Sample size:</b>	Two cats
<b>Intervention details:</b>	Bolus of 2 ml/kg of a 20% soybean oil-based and 80% olive oil emulsion (ClinOleic 20%, Baxter, UK) followed by a CRI of 4 ml/kg/h for 4 hours. In case 1, it was repeated at the same dosage the following day.
<b>Study design:</b>	Case report
<b>Outcome studied:</b>	Time of recovery after ClinOleic therapy.
<b>Main findings: (relevant to PICO question):</b>	Case 1 showed clinical improvement 48 hours after ClinOleic IV administration. Case 2 showed clinical improvement 30 hours after ClinOleic IV administration.
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Low sample size (two patients).</li> <li>• Differences between time of administration of ClinOleic IV after initial exposure (24 hours for case 1 and 9 hours for case 2).</li> </ul>

Kuo et al. (2013) <sup>11</sup>	
<b>Population:</b>	Adult cats with permethrin toxicosis
<b>Sample size:</b>	Two cats
<b>Intervention details:</b>	<p><b>Case 1:</b> A bolus of soybean oil-based IVLE (2.5 mL/kg) was administered over 5 minutes, followed by an IVLE infusion of 1 mL/min (0.33 mL/kg/min) for 30 minutes. IVLE therapy was reduced at 1 mL/min for other 30 minutes. An additional dose of IVLE was administered at day 2, with a total volume of 226 mL (61 mL/kg) given over 17 hours.</p> <p><b>Case 2:</b> A bolus of soybean oil-based IVLE (2.2 mL/kg) was administered, followed by an IVLE infusion of 1 mL/min (0.27 mL/kg/min) for a total of 75 minutes. The same IVLE therapy was repeated 9 hours after presentation.</p>
<b>Study design:</b>	Case report
<b>Outcome studied:</b>	Time of recovery after soybean oil-based IVLE therapy.
<b>Main findings: (relevant to PICO question):</b>	Case 1 showed neurological improvement 12 hours after IVLE administration, while case 2, 17 hours after IVLE administration (mean time 14 hours).
<b>Limitations:</b>	<ul style="list-style-type: none"> <li>• Low sample size (two patients).</li> <li>• Both cases required additional IVLE doses and authors used different doses and rates of bolus and CRI of IVLE therapy.</li> </ul>

## Appraisal, application and reflection

Most of the information available evaluated the use of soybean oil-based intravenous lipid emulsion (IVLE) therapy to manage permethrin toxicosis in cats. The outcome of interest for this Knowledge Summary was the recovery time and time for discharge among cats with permethrin toxicosis treated with soybean oil-based IVLE therapy or ClinOleic IVLE therapy. Studies that provided information on any other outcomes were excluded because they were not relevant to answer the PICO question.

Any IVLE therapy, as described by (Gwaltney-Brant et al., 2018), should be used 'in addition to, not instead of, standard symptomatic and supportive care because it is still an experimental procedure.'

All the case reports evaluated in this study suggest that cats with permethrin intoxication had an improvement in clinical signs after the administration of soybean oil-based or olive oil-based IVLE (ClinOleic) therapies, however, differences in recovery time were found.

In the first case study evaluated (Pelizzola et al., 2018) it was shown that three patients had neurological improvement after being treated with soybean oil-based IVLE therapy. The average time to recovery with this therapy was 10 hours. One of the most important limitations is that each patient had different treatment protocols and the study design did not quantify the intrinsic effect of IVLE therapy or in combination with other medications (injectable anaesthetics, anticonvulsants). Also, it is worth mentioning that, as reported by Pelizzola et al. (2018), there were differences between each permethrin product concentration among the cases evaluated. However, as described by Boland et al. (2010) there is no reported correlation between the amount of permethrin exposure and the severity of clinical signs induced, so this may not lead to significant differences in the time to recovery.

In the second case study evaluated (Ceccherini et al., 2015), it was found that four patients had neurological improvement within an average of 5 hours after low-dose soybean oil-based IVLE administration. An important aspect to consider is that three patients were treated in another clinic before arriving at the hospital, so information about any previous treatment was not available. Another limitation of this study is that different dosages and CRI were used for each patient, which in combination with a low sample number, can make it difficult to establish a dosing protocol for this treatment.

In the third case study evaluated (Haworth et al., 2012) three patients showed a clinical improvement after soybean oil-based IVLE therapy administration with a mean time to recovery of 8.3 hours. One of the key limitations of this study is that one case received the IVLE therapy 72 hours after the exposure and had a second permethrin exposure once discharged from the hospital, which influenced the overall recovery time. The remaining cases received IVLE therapy 16 hours after exposure.

The fourth case study evaluated (Brückner et al., 2012) was the only one that evaluated the time to recovery after ClinOleic IVLE therapy administration. The most important limitation of this study is the sample size (two patients). Both cats showed clinical improvement within 30 and 48 hours, with an average time to recovery of 39 hours. However, it is important to notice that there were differences in administration of ClinOleic IVLE therapy after initial exposure (24 hours for case 1 and 9 hours for case 2), which can influence the time to recovery between both cases. None of the patients showed any adverse reaction and both patients showed neurological improvement after the ClinOleic IVLE therapy but with a higher average time to recovery compared to those patients treated with soybean oil-based IVLE therapy.

The fifth case study evaluated (Kuo et al., 2013) found that soybean oil-based IVLE therapy was an effective adjuvant treatment to decrease the recovery time in patients with permethrin toxicosis, with an average time to recovery of 14 hours. The most important limitation was the sample size (two cases) and that both cases required additional IVLE doses, which makes it difficult to establish a dosage protocol. As stated by the authors, this IVLE therapy was well tolerated in both cases and no adverse effects were detected.

Finally, the sixth study evaluated (Peacock et al., 2015) was a randomised clinical trial and the strongest evidence available. A statistically significant difference in recovery time ( $P = <0.006$ ) was found among patients

treated with soybean oil-based IVLE therapy compared to control patients. The mean time to recovery was 5.5 hours (95% CI 1.6–9.5 hours) in soybean oil-based IVLE treated patients and 16.2 hours (95% CI 9.1–23.3 hours) in control patients. This interim statistical analysis result gave rise to prematurely stop the trial and administer the soybean oil-based IVLE therapy to the control patients.

This study also used other medications in combination with IVLE therapy, but no statistically significant differences were found among control and treated patients. Another limitation of this study is that it was not blinded, which can lead to detection bias. However, the clinical staging system designed by the authors showed almost perfect agreement in a Cochran-Mantel-Haenszel test for intra-viewer variability (consistent results by the same viewer), and interviewer variability (consistent results by different viewers), which increases the reproducibility, and reduces the variability and risk of bias in the outcome measurement. It is also worth noting that external factors, such as owners availability to pick up each patient, make it difficult to measure the difference in hospitalisation times between the control and IVLE treated cats, so we can only conclude a difference in the time in which a patient reached a point to be considered stable but not regarding their hospitalisation discharge.

All the studies appraised used different dosage protocols of intravenous boluses or continuous rate infusion of lipids. Currently, there is no consensus among guidelines or protocols for IVLE therapy dosage in feline patients with permethrin intoxication but on average, the dosage protocols used for both IVLE therapies ranged from an initial bolus of 1–2.5 ml/kg and a CRI of 4–5 ml/kg/h.

Overall, the clinical effectiveness of ClinOleic IVLE therapy in reducing time to recovery after permethrin intoxication in cats is still unclear and further research on this relevance, as well as robust clinical trials comparing both intralipid therapies should be conducted. The studies gathered for this review suggest that soybean oil-based IVLE therapy is the preferable treatment and the most studied for permethrin toxicity among feline patients. It is important to recognise that supportive treatment<sup>11,12</sup>, dermal decontamination<sup>7,11,12</sup>, muscle relaxers<sup>12,13</sup> anaesthetics<sup>12</sup>, and anticonvulsants<sup>12,13</sup> are examples of recognised first-choice treatments and any intralipid therapy must be used as part of an adjuvant protocol. Considering that IVLE therapy is still an experimental procedure, it is important to assess for any adverse reaction that could arise (i.e., hyperlipidaemia, pancreatitis, haemolysis, phlebitis, vomiting)<sup>14–16</sup>. It is recommended to follow the dosage protocols reviewed in this Knowledge Summary to reduce complications and adverse effects. Previous authors<sup>14,17</sup> have recommended checking for visual evidence of gross lipaemia (i.e., milky plasma or serum) through a peripheral blood sample before administering additional IVLE therapy doses or every 2 hours, and discontinue IVLE therapy if no improvement is noted after three doses (bolus and CRI).

## Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on OVID Platform: 1973 – 2020 Pubmed Database: 1973/01/01 – 2020/12/31 Web of Science Core Collection: 1973/01/01 – 2020/12/31 Scopus Advanced Document Search: 1973/01/01 – 2020/12/31
Search terms:	CAB Abstracts: (((cat* or feline* or felid* or adult cat) and (Intralipid or intralipid therapy or IVLE or intralipid infusion or intravenous lipid emulsion)) or (Refined olive oil or ClinOleic or Refined soybean oil or mixture of refined olive oil)) and (Recovery* or recuperation* or improvement* or treatment)) and (permethrin or permethrin intoxication).  Pubmed: (((cats* or feline* or felid* or “adult cat”) and (“Intralipid” or “intralipid therapy” or “IVLE” or “intralipid infusion” or “intravenous



	<p>lipid emulsion")) or ("Refined olive oil" or "ClinOleic" or "Refined soybean oil" or "mixture of refined olive oil")) and (Recovery* or recuperation* or improvement* or treatment) and (permethrin* or intoxication*))</p> <p>Web of Science: (((((((cats* or feline* or felid* or "adult cat") and ("intralipid" or "intralipid therapy" or "IVLE" or "intralipid infusion" or "intravenous lipid emulsion")) or ("Refined olive oil" or "ClinOleic" or "Refined soybean oil" or "mixture of refined olive oil")) and (Recovery* or recuperation* or improvement* or treatment) and (permethrin* or intoxication*))))))</p> <p>Scopus: ALL ( cat* OR feline* OR felid* OR "adult cat" ) AND ( "Intralipid" OR "intralipid therapy" OR "IVLE" OR "intralipid infusion" OR "intravenous lipid emulsion" ) AND ( "Refined olive oil" OR "ClinOleic" OR "Refined soybean oil" OR "mixture of refined olive oil" ) AND ( recovery* OR recuperation* OR improvement* OR treatment ) AND ( permethrin* OR intoxication* )</p>
Dates searches performed:	10 Dec 2021

Exclusion / Inclusion Criteria	
Exclusion:	Articles in languages different to English; non-peer reviewed literature such as technical reports and web-based guidelines; the paper fail to provide succinct evidence on the outcome of interest (time to recovery); single-subject case studies.
Inclusion:	Articles published between years 1973–2020; the patients in the study must be cats diagnosed with permethrin intoxication; patients treated with soybean oil-based IVLE therapy or ClinOleic IVLE therapy.

Search Outcome						
Database	Number of results	Excluded – Irrelevant to PICO question	Excluded – Non-peer reviewed literature	Excluded – Sample size < 2	Excluded – Irrelevant to outcome of interest	Total relevant papers
CAB Abstracts	10	2	1	2	0	5
PubMed	13	5	0	2	2	4
Web of Science	15	6	0	1	0	2
Scopus	15	11	0	0	4	0
Total relevant papers when duplicates removed						6

## CONFLICT OF INTEREST

The author declares no conflicts of interest.

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