

Healing of equine heel bulb lacerations: Evidence behind casting compared to bandaging alone

A Knowledge Summary by

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PICO question

In horses with heel bulb lacerations, does casting the distal limb compared to bandaging result in increased speed of healing and functional outcome?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

A single retrospective study was found to be relevant to the topic along with one case report and two case series, including one tutorial article

Strength of evidence

The majority of the current recommendations come from expert opinions, making the level of evidence low

Outcomes reported

There are currently insufficient data to compare the effect of foot/slipper casts versus bandaging alone on the rate of healing of equine heel bulb lacerations

Conclusion

Based on the information from these three publications, it is not possible to recommend the use of a foot cast over a bandage alone at this time

[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

You are called out to a 10-year-old Cob gelding which has sustained a heel bulb laceration after jumping into the neighbouring field over a fence covered in barbed wire. The laceration is located on the lateral heel bulb of the right hindlimb and is 5 cm long. It extends from the lateral hoof wall, across the coronet and reaches 2 cm proximal to the coronet in a lateroproximal to mediodistal direction. The horse is consistently lames at the trot in a straight line (3/5 AAEP) on that limb and the laceration appears very contaminated with soil.

The evidence

The literature comprises several non-peer reviewed publications, such as CPD material and tutorial articles. Only one retrospective case study, including a large number of horses treated with bandaging and/or casting, was found. Based on the publications currently available, there is sparse evidence that casting is superior to bandaging for healing of heel bulb lacerations in the horse and the quality of the evidence is considered low.

Summary of the evidence

Janicek et al. (2005)	
Population:	<ul style="list-style-type: none">• Horses• 75 Quarter Horses, six Thoroughbreds, five Tennessee Walking Horses, five Quarter Horses Appendix, three Paint Horses, three Appaloosas, two Arabians, two unknown<ul style="list-style-type: none">○ 11 stallions, 32 mares and 58 geldings• Age: mean 7 ± 4 years old (yo) (range, 1 to 23 years)• Medical records (1988–1994) of horses presented for lacerations of the heel bulb and distal portion of palmar and plantar aspects of the pastern
Sample size:	N=101
Intervention details:	<p>Work-up</p> <ul style="list-style-type: none">• Laceration cleansing and lavage with an antiseptic solution• Radiographs to identify foreign bodies and bone involvement• Wound examination to determine involvement of:<ul style="list-style-type: none">○ Navicular bursa (NB), distal interphalangeal joint (DIPJ), proximal interphalangeal joint (PIPJ), digital flexor tendon sheath (DFTS)○ Deep digital flexor tendon (DDFT)○ Collateral cartilages of third phalanx• N=1 horse euthanised at admission <p>Treatment</p> <ul style="list-style-type: none">• If synovial structure involvement identified, through-and-through needle lavage<ul style="list-style-type: none">○ 14–16 G needle placed remote to the wound○ Lavage with 1–2 L polyionic solution (pump used)○ Egress through wound itself○ Infusion of amikacin in synovial structure• Repeat the above (standing) every other day until cytologic and bacteriology results indicate resolution• Antimicrobials:<ul style="list-style-type: none">○ N=56 – Broad-spectrum antibiotic therapy for 2 weeks minimum<ul style="list-style-type: none">▪ N=36 – Trimethoprim-sulfadiazine, 15 mg/kg, orally (PO), q12h▪ N=20 – Enrofloxacin, 5 mg/kg, PO or intravenously (IV), q24h○ N=44 – No antibiotic treatment

	<ul style="list-style-type: none"> • Multiple protocols for wound treatment: <ul style="list-style-type: none"> ○ < 8 hours duration or minimal contamination <ul style="list-style-type: none"> ▪ primary closure ▪ foot cast* or bandage ○ > 8 hours duration <ul style="list-style-type: none"> ▪ second intention healing ▪ foot cast or bandage ○ Severe and contaminated with debris <ul style="list-style-type: none"> ▪ Foot bandage for 7–10 days ▪ Casting after foot bandage <p>*Foot cast = double layer 3–4 inches stockinette + 3 rolls of 3 inches/7.5 cm fiberglass cast tape up to middle of proximal phalanx</p> <p>Follow-up information acquired by telephone interview with the owner or the trainer or both</p>
<p>Study design:</p>	<p>Retrospective case series</p>
<p>Outcome studied:</p>	<ul style="list-style-type: none"> • Successful outcome: sound horse able to be used at a level of performance that equaled or exceeded the level achieved before surgery <ul style="list-style-type: none"> ○ foot cast versus foot bandage ○ synovial involvement versus no synovial involvement
<p>Main findings: (relevant to PICO question):</p>	<ul style="list-style-type: none"> • Wound treatment: <ul style="list-style-type: none"> ○ N= 30 – primary closure (polydioxanone or polypropylene sizes 1 or 2) ○ N=70 – second intention healing • Immobilisation: N= 52 foot cast (duration: 2.8 ± 1 weeks) and N= 76 foot bandage (duration: 3.2 ± 2.2 weeks) <ul style="list-style-type: none"> ○ N= 24 – cast only <ul style="list-style-type: none"> ▪ duration: 3.1 ± 0.9 weeks ○ N= 28 – cast followed by bandage <ul style="list-style-type: none"> ▪ duration cast + bandage: 5.1 ± 2.1 weeks ○ N=48 – bandage only <ul style="list-style-type: none"> ▪ duration: 4.1 ± 1.3 weeks • Duration of cast immobilisation alone significantly shorter than bandaging alone. • Significant difference in outcome for primary wound closure versus second intention healing (latter failed more often). • Follow-up available for 61/100 horses <ul style="list-style-type: none"> ○ Mean time to follow-up after discharge: 37 ± 26 months <ul style="list-style-type: none"> ▪ 51/61 (84%) judged to have a successful outcome by owner/trainer ▪ 10/61 (16%) had unsuccessful outcome: remained persistently lame or unable to be used as intended ○ 15/61 were managed with a cast alone

	<ul style="list-style-type: none"> ▪ 2/15 (13.3%) had cast complications (pressure necrosis of skin) • 11/61 (18%) hoof wall defect developed after injury
Limitations:	<ul style="list-style-type: none"> • No control group and no random allocation of wound treatment (cast vs bandage) • Choice of foot dressing was at attending clinician's discretion • Very little detail on complications for bandaging group and bandaging + casting together • Unclear how many horses: <ul style="list-style-type: none"> ○ with second intention healing or primary wound closure were treated with a foot cast alone or bandage alone and if this is a confounding factor ○ with synovial involvement were treated with a foot cast versus a bandage alone and which one would lead to faster healing in such cases • Limited outcome information and very subjective as assessed by trainer/owner

Booth & Knottenbelt (1999)	
Population:	Horses (one Arab, one Irish draft and two unknown)
Sample size:	N=4
Intervention details:	<ul style="list-style-type: none"> • Location of wounds: <ul style="list-style-type: none"> ○ Coronet (N=1) ○ Heel bulb laceration (N=2) ○ Laterodistal aspect one forelimb (N=1) • Surgical debridement in all cases • Wounds sutured (N=2) • Bandage daily for 5 days (N=1 horse, prior to cast application) • Foot cast applied in all cases <ul style="list-style-type: none"> ○ 4 weeks duration (N=3) ○ 8 weeks duration (N=1)
Study design:	Tutorial article with small case series as examples
Outcome studied:	<ul style="list-style-type: none"> • Mainly wound healing: <ul style="list-style-type: none"> ○ soundness ○ hoof wall defect
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> • All wounds healed • N=1: cast sore (cast on for 4 weeks) <ul style="list-style-type: none"> ○ of no apparent clinical significance • N=1: hoof wall defect (noticed at 4 years follow-up)
Limitations:	<ul style="list-style-type: none"> • Very small case series with limited details for each • No bandage group to compare

	<ul style="list-style-type: none"> • Unclear why one cast was left in place for 8 weeks <ul style="list-style-type: none"> ○ heel bulb laceration case • Unclear how many cast were placed under general (versus regional anaesthesia) and if difference in cast complications • Affected limb not always identified <ul style="list-style-type: none"> ○ unclear if difference in healing between fore and hind limbs • Very limited long-term follow-up (available for one case only)
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Ketzner et al. (2009)	
Population:	<p>Horses</p> <ul style="list-style-type: none"> • 27 Quarter Horses, six Paints, five mixed breeds, three Warmbloods, two Arabians, two Thoroughbreds, one Appaloosa, one Saddlebred, one Belgian, one unknown breed • Three stallions, 26 mares and 20 geldings • Age: mean 7.2 ± 5.5 years old (yo) (range, 1 to 25 years) <p>Medical records (1995–2007) of horses with wounds of the pastern and foot region, presented to three university equine hospitals.</p>
Sample size:	N=49 horses with 50 wounds (cases)
Intervention details:	<p>Work-up</p> <ul style="list-style-type: none"> • Under general anaesthesia or after perineural analgesia • Skin around laceration scrubbed with Povidone-iodine (PI) or Chlorhexidine • Wound bed cleaned with 1.0% PI • Sterile palpation of wound bed to determine: <ul style="list-style-type: none"> ○ Synovial structure involvement <ul style="list-style-type: none"> ▪ If suspected, structure distended using sterile Ringer’s lactate solution (RL) in site distant from wound ○ Bone involvement ○ Instability <p>Treatment</p> <ul style="list-style-type: none"> • If synovial structure involvement identified, synovial lavage performed <ul style="list-style-type: none"> ○ With 1 L of sterile LRS ○ Injection of 500 mg of amikacin in synovial structure • Antimicrobials systemically for 42/50 wounds (84%) <ul style="list-style-type: none"> ○ 19/42 (45.2%) penicillin and gentamicin ○ 19/42 (45.2%) oral trimethoprim-sulfadiazine ○ 4/50 (8%) [sic] other antimicrobials • 6/50 (12%) received no antimicrobials • 2/50 (9.5%) had no antimicrobials information in record • If severely contaminated wounds or involvement of synovial structure, antimicrobials locally prior to casting

	<ul style="list-style-type: none"> ○ For synovial infections: all had intra-articular (IA) amikacin (two of which also had timentin IA), one also had 5 intravenous injections with gentamicin in the regional limb ● Wound closure for acute or minimally contaminated wounds <ul style="list-style-type: none"> ○ primary closure, tension relieving patterns ○ Size 2 United States Pharmacopeia (USP), polypropylene ● Phalangeal cast: Double layer stockinette + 3–4 layers of 3 inches/7.5 cm fiberglass cast tape from sole to mid-pastern + polymethylmetacrylate under the sole <ul style="list-style-type: none"> ○ If cast placed standing, pastern region layed first in weight-bearing position and then foot including heel wedge, once pastern hardened ○ If cast placed under general anaesthesia, foot done first, with toe extended, followed by pastern region. <p>Follow-up information acquired by telephone interview with the owner or during re-evaluation</p>
Study design:	Retrospective case series
Outcome studied:	<ul style="list-style-type: none"> ● Soundness: sound if no lameness and back to previous level ● Wound appearance <ul style="list-style-type: none"> ○ Excellent (no scaring), very good (minimal scaring), excessive scaring ● Complications
Main findings: (relevant to PICO question):	<p>Injuries</p> <ul style="list-style-type: none"> ● 26/50 (52%) forelimb wounds and 23/50 (46%) hindlimb wounds ● 20/49 (40.8%) horses presented < 24 hours after injury and 29/49 (59.2%) presented > 24 hours after injury ● No overt lameness in 14/43 (32.6%), lameness in 29/43 (67.4%) <ul style="list-style-type: none"> ○ Lameness not recorded in seven horses (14%) ● 8/50 wounds (16%) had synovial involvement <p>Casting</p> <ul style="list-style-type: none"> ● Overall, average duration of treatment prior to casting 3.7 ± 6.6 days (range 0–29 days) ● If synovial involvement, average of 6 ± 5.8 days (range 0–14 days) ● Total cast duration of 17.2 ± 5.9 days (range 9–36 days) <p>Wound repair</p> <ul style="list-style-type: none"> ● 33/42 (78.6%) repaired under general anaesthesia versus 9/42 (21.4%) under standing sedation <ul style="list-style-type: none"> ○ Not recorded in eight horses ● 28/44 (63.6%) wounds were sutured versus 16/44 (36.4%) left unsutured <ul style="list-style-type: none"> ○ Not recorded in six horses

	<p>Follow-up</p> <ul style="list-style-type: none"> • between 2–93 months following hospital discharge (mean 33.3 ± 25.1 months) <ul style="list-style-type: none"> ○ lost 3 horses to follow-up • Overall, 41/46 (89.1%) horses sound, 4/46 (8.7%) still lame, 1/46 (2.2%) euthanised as non-response to treatment • Of synovial involvement cases, 6/7 (85.7%) sound, 1/7 (14.2%) with residual lameness <ul style="list-style-type: none"> ○ lost one horse with septic coffin joint to follow-up <p>Cosmetic appearance of wounds</p> <ul style="list-style-type: none"> • 8/38 (21.1%): excellent • 26/38 (68.4%): good • 4/38 (10.5%): excessive scarring involving the coronary band and hoof • For four horses, owners had no recollection if there was scarring or not • Three horses lost to follow-up • One horse was euthanised
<p>Limitations:</p>	<ul style="list-style-type: none"> • Specific location of wounds non-identified (unknown how many involved the coronary band, heel bulb, pastern, etc.) • No group treated with bandaging only for comparison/control • Type of synovial lavage non-specified (arthroscopic versus through-and-through needle lavage) • Incoherent information on systemic antibiotics • No details on regional antimicrobials for contaminated wounds • Doses for intra-articular medication and intravenous regional limb perfusions are not specified • Little detail regarding complications, namely none on cast sores

Milner (2008)	
Population:	13-year-old Cob gelding
Sample size:	N=1
Intervention details:	<ul style="list-style-type: none"> • Crescent shape full-thickness laceration of medial heel bulb in left forelimb <ul style="list-style-type: none"> ○ No synovial involvement identified ○ Exposure of proximomedial edge of medial ungular cartilage • Wound lavage and foot bandage changed daily until day 4 • On day 4, hydrosurgical (Versajet™) and sharp debridement under general anaesthesia <ul style="list-style-type: none"> ○ 1.25 mm cerclage wires (x2) used to retain the

	<ul style="list-style-type: none"> medial hoof wall in place <ul style="list-style-type: none"> ○ Foot cast (to mid-proximal pastern) for the following 14 days ● After cast removal, shoe with central support and polyurethane infiller in the sole for 4 weeks <ul style="list-style-type: none"> ○ Removal of wires at 4 weeks ● Re-shod with central support shoe at 8 weeks
Study design:	Case report
Outcome studied:	No specific outcome studied: <ul style="list-style-type: none"> ● presence or not of a hoof wall defect ● soundness ● laceration healing
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> ● Good apposition of wound edges and medial hoof wall at cast removal ● At 2 months after presentation: <ul style="list-style-type: none"> ○ Sound ○ Good healing and apposition of the heel bulb laceration
Limitations:	<ul style="list-style-type: none"> ● Case report (N=1) ● Very little detail on how the cast was made and applied ● No long-term follow-up

Appraisal, application and reflection

There are very few studies evaluating the efficacy of using distal limb casts when treating heel bulb lacerations compared with bandages alone in horses. Based on the publication from Janicek et al. (2005), casting as opposed to bandaging may reduce the treatment duration of heel bulb lacerations. However, the length of treatment and the success of wound healing are both directly related to the way these wounds are approached, namely if they are treated by primary or secondary closure (Janicek et al., 2005). Since the number of horses in each group (bandaging versus casting) treated with primary closure versus delayed primary or second intention healing was not specified, the conclusion that distal limb casting results in faster healing of heel bulb laceration remains questionable. Janicek et al. (2005) recommended all heel bulb wounds which are minimally contaminated with debris and of short duration following injury (< 8 hours) be managed by primary closure and physical support of the site with either a bandage or a cast. In cases of wounds severely contaminated or traumatised, the authors recommended a foot bandage for 7–10 days prior to cast immobilisation. While these recommendations are very logical and allow more frequent monitoring of the wound healing and care, the study results are inconclusive when it comes to favour bandaging or casting to speed up wound healing. On the other hand, Burba et al. (2013), an expert opinion article aimed at veterinary surgeons, stated that heel bulb lacerations were best treated by primary closure when possible and with the use of a foot cast. As this is an opinion piece rather than an original study, no compelling evidence in favour of using foot casts over bandaging was found for these cases.

The potential involvement and treatment of synovial sepsis appears to be an important factor influencing outcome in cases of heel bulb laceration. Janicek et al. (2005) reported that lacerations involving a synovial structure had a significantly poorer outcome than those without. Synovial involvement also influences the approach to the wound. In the study by Janicek et al. (2005), all wounds communicating with synovial structures were left to heal by second intention following surgical management of sepsis. The authors recommended that all lacerations involving synovial structures are considered contaminated and

recommended delayed primary closure after repeated synovial lavages and natural sealing of the communication between the synovial structure and the wound itself. In the small case series from Booth and Knottenbelt (1999), 50 % of the lacerations were sutured, although the reason for this is not stated in the paper. In a similar publication from Ketzner et al. (2009), 63.6% of wounds were sutured and the authors found no significant difference in outcome between cases involving or not involving a synovial structure. In a more recent publication on wounds of the lower limb Eggleston (2018), recommends that a wound communicating with a synovial structure be managed with replaceable bandages until it can be confirmed that synovial communication is sealed and the infection resolved. Celeste and Szöke (2005) also recommended bandaging until infectious complications are resolved, after which casting the distal limb in successive periods of 2–3 weeks should be performed. Whilst these recommendations are logical, they constitute expert opinion and we have failed to find corroborating evidence in the literature gathered for this knowledge summary. Prospective studies comparing horses with heel bulb lacerations sutured (or not) in the same fashion, with and without synovial involvement, and divided into two separate groups (bandage versus 'slipper cast') are lacking. If such studies were performed, a standardised treatment plan prior to casting or bandaging would need to be implemented to allow direct comparison of the efficacy of the supportive dressing.

The incidence of cast sores with all types of cast is reported to be anywhere between 45% to 81% (Eggleston, 2018). However, if the cast is applied properly and is monitored regularly, the potential for serious complications is significantly reduced and are uncommon (Booth & Knottenbelt, 1999; and Eggleston, 2018). Janicek et al. (2005) reported that 2/15 horses managed with a cast alone developed pressure necrosis of the skin, which was of limited clinical significance. To further reduce this risk, a 'slipper cast' can be used for casting the foot. It reduces the risk of deep skin erosions if the cast material does not end in the mid-pastern region (Celeste and Szöke, 2005).

Closure of heel bulb lacerations can be challenging due to skin tension and the production of excessive granulation tissue (EGT) is a concern if these wounds are left to heal by second intention (Eggleston, 2018). Booth and Knottenbelt (1999) stated that when properly applied, distal limb casts improve the functional and cosmetic outcome of distal limb injuries. Indeed, since a cast is by definition sturdier than a bandage, is it thought to provide better immobilisation of the distal limb. This led to the clinical impression that casting prevents movement of the foot and wound dehiscence (Janicek et al., 2005; Milner, 2008; and Booth & Knottenbelt, 1999) as well as decreasing the production of EGT (Smith, 1993). We have failed to find evidence to support this assertion in the available literature and believe this should be considered as expert opinion as well. In the case series from Ketzner et al. (2009), 68.4% of wounds treated with casting healed with minimal scarring compared to 21.1% which healed without scarring. While this study includes wounds located to the pastern and hoof area, the number involving heel bulbs is not specified and all horses were treated with a casting, none with bandaging. An *in vitro* study comparing the immobilisation provided by both types of external coaptation would provide more information.

Casting is also potentially beneficial in cases of heel bulb laceration involving the coronet. When the coronary band is involved in the laceration, reconstructive surgery is paramount to decrease the risk of permanent deformation of the hoof wall and other complications such as hoof cracks and horn spurs (Celeste and Szöke, 2005). Of the 61 horses available at follow-up in the Janicek et al. (2005) study, 18% developed a hoof wall defect, but the number of horses treated with a foot cast compared to bandaging alone or a combination of the two is not stated. In the study from Ketzner et al. (2009), 10.5% of all wounds healed with excessive scarring at the coronary band and hoof. As previously mentioned, all horses in that cases series were treated with casting and the number of wounds involving the coronary band/hoof remains unclear. It is therefore not possible to determine if this excessive scarring of the coronet and hoof is the result of a cast complication or of to original injury. The duration of the casting period is also controversial and the ideal timeframe for this immobilisation method is currently unknown. While some authors (Janicek et al., 2005; and O'Neill & O'Meara, 2010) recommend that casts remain in place for 2–4 weeks in order to allow healthy granulation tissue to cover the wound, the publications identified in this submission each used casting for different periods of time, making it difficult to compare the benefit of shorter versus longer periods in casts.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts 1973 to Week 48 2018 PubMed NCBI 1910 to December 2018
Search terms:	<p>CAB:</p> <ol style="list-style-type: none"> 1 (equine or equines or horse or horses or equus or equid or equids or mare or mares or broodmare or broodmares or pony or ponies or filly or fillies or colt or colts or yearling or yearlings or stallion or stallions or thoroughbred or thoroughbreds or standardbred or standardbreds or racehorse or racehorses or "race horse" or "race horses").mp. or exp horses/ or exp equus/ or exp equidae/ or exp mares/ or exp colts/ or exp foals/ or exp stallions/ or exp thoroughbred/ or exp racehorses/ (162478) 2 ((heel or heels) and (bulb or bulbs)).mp (84) 3 (immobilisation or immobilise or immobilised or immobilises or immobilization or immobilize or immobilized or immobilizes or (stabilisation or stabilise or stabilised or stabilises or stabilization or stabilize or stabilized or stabilizes) or (coronet or coronets or "Robert Jones" or RJB or "coronary bands" or "coronary band") or (bandages or bandaging or bandaged or bandage or binding or bind or bound or binds or dresses or dressing or dressed or dressings or cast or casts or casting or phalangeal cast or fix or fixed or fixing or fixes or wrap or wraps or wrapped or wrapping)).mp. or exp bandages/ (419534) 4 1 and 2 and 3 (13) <p>PubMed:</p> <ol style="list-style-type: none"> 1 (horse OR horses OR equine OR equines OR equus OR equidae OR equid OR mare OR mares OR broodmare OR broodmares OR brood mare OR brood mares OR pony OR ponies OR yearling OR yearlings OR filly OR fillies OR colt OR colts OR stallion OR stallions OR thoroughbred OR thoroughbreds OR standardbred OR standardbreds OR racehorse OR racehorses OR "race horse" OR "race horses") 2 ((heel or heels) and (bulb or bulbs)) 3 (immobilisation OR immobilise OR immobilised OR immobilises OR immobilization OR immobilize OR immobilized OR immobilizes OR stabilisation OR stabilise OR stabilised OR stabilises OR stabilization OR stabilize OR stabilized OR stabilizes OR coronet OR coronets OR "Robert Jones" OR RJB OR "coronary bands" OR "coronary band" OR bandages OR bandaging OR bandaged OR bandage OR binding OR bind OR bound OR binds OR dresses OR dressing OR dressed OR dressings OR cast OR casts OR casting OR cast OR fix OR fixed OR fixing OR fixes OR wrap OR wraps OR wrapped OR wrapping)

	4 (#1 AND #2 AND #3) Hand search: Paper identified outside of original search.
Dates searches performed:	7/12/2018 and 11/12/2018

Exclusion / Inclusion Criteria	
Exclusion:	<ul style="list-style-type: none"> • Articles not relevant to PICO question <ul style="list-style-type: none"> ○ Treatment other than casting or bandaging ○ Species other than equine • Conference papers/proceedings not published
Inclusion:	<ul style="list-style-type: none"> • Relevant to PICO question <ul style="list-style-type: none"> ○ Foot bandage or hoof cast/slipper cast ○ Correct wound type (heel bulb/coronet laceration)

Search Outcome						
Database	Number of results	Excluded – duplicates	Excluded – not published	Excluded – not relevant to PICO question	Excluded – wrong species treated	Total relevant papers
CAB Abstracts on the OVID interface	13	0	3	6	1	3
PubMed accessed via the NCBI website	5	4	0	1	0	0
Hand search	1	0	0	0	0	1
Total relevant papers						4

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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