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SPECIAL ARTICLE

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2024 RECOVER Guidelines: Advanced Life Support. Evidence and knowledge gap analysis with treatment recommendations for small animal CPR

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Abstract

Objective: To systematically review the evidence and devise clinical recommendations on advanced life support (ALS) in dogs and cats and to identify critical knowledge gaps.

Design: Standardized, systematic evaluation of literature pertinent to ALS following Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Prioritized questions were each reviewed by Evidence Evaluators, and findings were reconciled by ALS Domain Chairs and Reassessment Campaign on Veterinary Resuscitation (RECOVER) Co-Chairs to arrive at treatment recommendations

Abbreviations: ALS, advanced life support; BiP, biphasic; BLS, basic life support; CCCPR, closed-chest CPR; CePP, cerebral perfusion pressure; CI, confidence interval; CoPP, coronary perfusion pressure; CPA, cardiopulmonary arrest; CRI, constant rate infusion; EDT, emergency department thoracotomy; EE, Evidence Evaluator; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HES, hydroxyethyl starch; IHCPA, in-hospital cardiopulmonary arrest; IO, intraosseous; IQR, interquartile range; MP, monophasic; OCCPR, open-chest CPR; OHCPA, out-of-hospital cardiopulmonary arrest; OR, odds ratio; PCA, postcardiac arrest; PEA, pulseless electrical activity; PICO, Population, Intervention, Comparator, and Outcome; PVT, pulseless ventricular tachycardia; ROSC, return of spontaneous circulation; VF, ventricular fibrillation.

commensurate to quality of evidence, risk:benefit relationship, and clinical feasibility. This process was implemented using an Evidence Profile Worksheet for each question that included an introduction, consensus on science, treatment recommendations, justification for these recommendations, and important knowledge gaps. A draft of these worksheets was distributed to veterinary professionals for comment for 4 weeks prior to finalization.

Setting: Transdisciplinary, international collaboration in university, specialty, and emergency practice.

Results: Seventeen questions pertaining to vascular access, vasopressors in shockable and nonshockable rhythms, anticholinergics, defibrillation, antiarrhythmics, and adjunct drug therapy as well as open-chest CPR were reviewed. Of the 33 treatment recommendations formulated, 6 recommendations addressed the management of patients with nonshockable arrest rhythms, 10 addressed shockable rhythms, and 6 provided guidance on open-chest CPR. We recommend against high-dose epinephrine even after prolonged CPR and suggest that atropine, when indicated, is used only once. In animals with a shockable rhythm in which initial defibrillation was unsuccessful, we recommend doubling the defibrillator dose once and suggest vasopressin (or epinephrine if vasopressin is not available), esmolol, lidocaine in dogs, and/or amiodarone in cats.

Conclusions: These updated RECOVER ALS guidelines clarify the approach to refractory shockable rhythms and prolonged CPR. Very low quality of evidence due to absence of clinical data in dogs and cats continues to compromise the certainty with which recommendations can be made.

KEYWORDS

canine, cardiopulmonary resuscitation, clinical trials, consensus guidelines, critical care, evidence-based medicine, feline

1 | INTRODUCTION

The Reassessment Campaign on Veterinary Resuscitation (RECOVER) initiative launched in 2011 with the goal of creating evidence-based guidelines for CPR in dogs and cats. These guidelines, including the 16 questions specific to ALS, were published in the 2012 RECOVER CPR Guidelines.[1] Advanced life support (ALS) is defined as the aspect of CPR performed after basic life support (BLS) has been initiated; ALS measures are delivered while BLS is ongoing. BLS includes chest compressions, endotracheal intubation, and ventilation, while ALS comprises drug therapies such as vasopressors, anticholinergics, and antiarrhythmics; correction of electrolyte disturbances, volume deficits, and severe anemia; and electrical defibrillation. Seventeen carefully formulated Population, Intervention, Comparator, and Outcome (PICO) questions to investigate the most critical aspects of ALS underwent systematic review, and treatment recommendations were formulated based upon that evidence evaluation.

The RECOVER 2024 ALS treatment recommendations were created using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, which is described in more detail in the RECOVER 2024 methodology paper.[2] The treatment recommendations were posted for an open comment review and all comments were carefully evaluated. The 2024 RECOVER CPR Guidelines consist of recommendations or suggestions for or against a specific procedure or intervention.[3]

2 | METHODS

A full explanation of the methods used to generate the ALS treatment recommendations is available in a companion paper.[2] What follows here is an overview. This ALS Domain Paper and the associated 2024 RECOVER CPR Guidelines[3] were generated using a modified version of the GRADE system for guidelines generation in health care.[4]

The RECOVER Co-Chairs assigned content experts to serve as chairs for the ALS Domain (GB, ER, JW). These Domain Chairs generated research questions in the PICO format including 4 clinically important outcomes for each PICO question. PICO questions were rated

as high priority, moderate priority, or lower priority. Thirty-two PICO questions were developed for evidence evaluation for ALS; 15 were rated as moderate or lower priority. Because of the number of PICO questions generated and the number of volunteers available to review and summarize evidence and generate treatment recommendations, only the 17 high-priority PICO questions were evaluated.

Domain Chairs prioritized the outcomes for each PICO question by clinical importance so that treatment recommendations could be generated based on the evidence pertaining to the highest priority outcomes for which clinically relevant evidence was available. Outcomes used for most PICO questions included favorable neurologic outcome, survival to hospital discharge, return of spontaneous circulation (ROSC), and surrogate markers of perfusion, in this order of priority. Additional or different outcomes were investigated for various PICO questions where Domain Chairs deemed this appropriate.

Specialist librarians (Information Specialists) worked with Domain Chairs to create search strings for entry into medical databases. Search strings were developed using an iterative process among Information Specialists and Domain Chairs to optimize the number and type of articles returned in the searches.[a] Peer review of search strategies occurred using modified Peer Review of Electronic Search Strategy Guidelines and informal meetings.[5] Once potentially relevant articles were identified, 2 Evidence Evaluators (EEs) (ie, specialist veterinarians, general veterinarians in emergency or specialty practice, or veterinary technician specialists in relevant fields such as emergency and critical care, anesthesia, and cardiology) reviewed abstracts independently to eliminate irrelevant material and leave only pertinent primary literature for review. Domain Chairs resolved any conflicts. Relevant publications were then reviewed for each PICO by the same EEs.

A purpose-developed, web-based evaluation system was used to guide EEs through a systematic review using a predetermined, standardized set of questions designed to identify key aspects of evidence quality (eg., risk of bias, consistency with population of interest, consistency of outcomes). This evaluation system used these data to generate Evidence Summary Tables for each outcome for every PICO question. EEs also wrote overview summaries of the evidence for their PICO question. Finally, the Domain Chairs generated Evidence Profile Worksheets consisting of a structured summary (introduction, consensus on science, treatment recommendations, justifications for the treatment recommendations, and knowledge gaps for future study) and additional notes made during evaluation of individual studies for each PICO question. These Evidence Profile Worksheets were reviewed and edited by the Co-Chairs. The Co-Chairs and Domain Chairs met to reach consensus on these documents. The treatment recommendations and links to the Evidence Profile Worksheets were then posted at the RECOVER Initiative website[b] for a 4-week open comment period beginning in August 2023; EEs and listservs for relevant specialty and other professional organizations were notified directly of this comment period. Following this period, comments were considered by the Co-Chairs and Domain Chairs, and relevant treatment recommendations honed to create a finalized set of treatment recommendations for ALS in dogs and cats, which appear in this paper. The structured summary for each ALS PICO question appears below, and the additional study evaluation notes appear in the full Evidence Profile Worksheets[a].

In accordance with the GRADE system, each treatment recommendation is written either as a *recommendation* where the RECOVER group found stronger evidence (or perceived risk/benefit relationship, where evidence was poor or not available) or as a *suggestion* where the RECOVER group found weaker evidence (or perception of risk/benefit relationship, where evidence was not available), for or against the intervention.

3 | ESTABLISHING VASCULAR ACCESS

Gaining access to a patient's circulatory system is the second step of initiating ALS in patients without preexisting vascular access. Intravenous access can be challenging, and intraosseous (IO) might be a suitable alternate route for drug administration during CPR. A second question pertaining to endotracheal drug administration in the 2012 RECOVER guidelines process (ALS-09) was not asked again, and the 2012 recommendations on this route of drug administration remain unchanged.[6]

3.1 | IO drug administration—ALS-14

In cats and dogs with cardiopulmonary arrest (CPA) (P), does IO administration of drugs (I) compared with intravenous drug administration (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

3.1.1 | Introduction

In dogs and cats undergoing CPR, intravenous access is considered ideal for administration of resuscitative medications and fluids/blood products. However, in some cases IV access may be difficult to obtain, and alternative methods, such as IO or endotracheal, have been proposed. In many patients, obtaining IO access may be easier than obtaining IV access. The goal of this PICO question was to determine if IO access is as efficacious as IV access for drug delivery during CPR.

3.1.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 2 clinical trials (very low quality of evidence, downgraded for very serious indirectness, serious imprecision, and serious inconsistency), 4 observational studies (very low quality of evidence, downgraded for serious indirectness), and 1 experimental study (low quality of evidence, downgraded for serious indirectness) informed the answer to the PICO question. In a prospective clinical trial of 1007 human patients with out-of-hospital cardiopulmonary arrest (OHCPA) randomized to either

IV access or IV access attempts for 2 minutes and then redirection to IO access (IV+IO), no differences were identified between the groups in survival with good neurologic outcome (IV+IO: 3.4% vs IV: 4%), survival to discharge (4.9% vs 8.4%), or ROSC (27% vs 27.6%).[7] However, patients in the IV+IO arm had a higher percentage of successful vascular access (76.6% vs 61.1%), higher percentage with epinephrine administered prehospital (71.3% vs 55.4%), shorter median time between call to emergency services and first epinephrine administration (23 [interquartile range, IQR: 18–28] vs 25 [IQR: 20–31] min), and shorter time to first dose of epinephrine after emergency medical services arrival at patient side (9 [IQR: 6–14] vs 11 [IQR: 7–18] min). In a second clinical trial of 3019 OHCPA patients with refractory ventricular fibrillation (VF) or pulseless ventricular tachycardia (PVT), patients were randomized to 6 arms (placebo, amiodarone, or lidocaine, administered IV or IO).[8] The authors reported improvements in survival with good neurologic function in patients treated with IV but not IO amiodarone, and improved survival to hospital discharge for both amiodarone and lidocaine when given IV, but not if given IO; however, the study was not designed to test the interaction between the 2 routes.

Two retrospective observational studies compared the effects of IV and IO access on outcomes after in-hospital cardiopulmonary arrest (IHCPA). Schwalbach at al evaluated 1039 patients with CPA and, using a multivariate analysis, showed no difference in rate of survival with favorable neurologic status (odds ratio [OR]: 0.74, 95% confidence interval [CI] 0.49–1.13, $P = 0.16$) or survival to discharge (OR: 0.71, 95% CI: 0.47–1.06, $P = 0.09$).[9] However, both the frequency of ROSC and time to ROSC were significantly worse in the IO group. A propensity-matched registry study of 603 prepubescent patients with IHCPA had insufficient numbers to statistically evaluate survival with good neurologic function but found no difference in frequency of ROSC or survival to discharge between patients receiving drugs IV versus IO.[10] Two additional retrospective studies evaluated outcomes in patients with OHCPA receiving drugs IV versus IO. In a study of 1576 people, Baert et al found no significant differences in favorable neurologic outcome or 30-day survival between the groups, but found lower frequency of ROSC in patients receiving drugs IO.[11] In a larger study of 6879 people with OHCPA, a propensity adjusted analysis showed lower frequencies of favorable neurologic outcome, survival to discharge, and sustained ROSC in patients receiving drugs IO than in the IV group.[12]

Finally, in a swine OHCPA VF model, VF was induced and left untreated for 10 minutes, after which BLS was started.[13] The IO group received epinephrine after 1 minute of BLS, and the IV group received epinephrine after 8 minutes. A third group received placebo. There was no difference in survival with good neurologic outcome between the IO and IV groups (6/10 vs 3/10, $P > 0.05$), but 24-hour survival was more common in the IO than the IV group (10/10 vs 4/10, $P = 0.001$). Frequency of ROSC was similar between the groups (10/10 vs 9/10, $P > 0.05$).

For the next most critical outcome of *survival to discharge*, 2 observational studies (very low quality of evidence, downgraded for serious indirectness) in addition to the 2 clinical trials (very low quality of evidence, downgraded for very serious indirectness, serious imprecision, and serious inconsistency), 4 observational studies (very low quality of evidence, downgraded for serious indirectness), and 1 experimental swine study described above (low quality of evidence, downgraded for serious indirectness) were identified. A registry-based study of 1549 pediatric OHCPA showed that although IO attempts were more commonly successful than IV attempts (difference in success of placement 21%, 95% CI: 17%–26%), logistic regression modeling using multiple imputation to address missing data showed that IO catheter patients were less likely to survive to discharge (adjusted OR: 0.46, 95% CI: 0.21–0.98).[14] However, the logistic regression model did not include variables associated with illness severity or type. The second was an OHCPA registry study including 1800 patients, which showed in a multivariable adjusted analysis that IO treated patients had similar frequency of survival to discharge to IV-treated patients (OR: 0.81, 95% CI: 0.55–1.21, $P = 0.31$), but lower frequency of ROSC (OR: 0.67, 95% CI: 0.50–0.88, $P = 0.004$).[15]

For the next important outcome of *ROSC*, in addition to the studies described for the 2 higher priority outcomes, 17 additional experimental studies in swine and 1 additional experimental study in lambs were identified that addressed the PICO question (very low quality of evidence, downgraded for serious indirectness and serious inconsistency). Of these, 2 studies in swine with prolonged, untreated VF (10 min) examined immediate tibial IO epinephrine versus delayed (8 min) epinephrine IV and showed that animals administered epinephrine via either route had a higher frequency of ROSC than animals not receiving epinephrine.[13,16] However, Mader et al showed an improved OR for ROSC in the immediate tibial IO group compared to the delayed IV group (OR: 3.3, 95% CI: 1.1–10.2), while Zuercher et al showed no difference between the tibial IO and delayed IV groups in ROSC frequency. Four studies compared early IV and tibial IO or humeral IO epinephrine administration in induced VF models (3 in swine and 1 in lambs).[17–20] All showed that the frequency of ROSC and time to ROSC were similar between the IV and IO groups. Four studies used hypovolemic swine models of VF. One showed no difference in frequency of ROSC between IV and humeral IO epinephrine administration,[21] 1 showed no difference between sternal IO, tibial IO, humeral IO, and IV epinephrine administration,[22] 1 showed that IV administration of epinephrine yielded higher ROSC frequency than humeral IO administration,[23] and 1 showed that tibial IO epinephrine administration was as effective as IV administration in euvolemic animals but IV administration yielded higher frequency of ROSC in hypovolemic animals than tibial IO administration.[24] Five swine studies, a mix of hypovolemic- and euvolemic-induced CPA, showed no difference in frequency of ROSC between IV and IO (tibial IO and/or humeral IO) administration of vasopressin.[25–29] Three additional studies comparing IV versus IO (humeral IO, sternal IO, tibial IO) administration of amiodarone in swine with prolonged shockable rhythms showed no difference in ROSC frequency.[30–32] Finally, 1 study of prolonged VF in swine showed that time to ROSC was shorter when vasopressin, epinephrine, and amiodarone were given via the sternal IO or IV route

than via the tibial IO route, but frequency of ROSC was similar in all 3 groups.[33]

Given the large amount of evidence for the 3 higher priority outcomes, the outcome *surrogate markers of perfusion* was not addressed for this PICO question.

3.1.3 | Treatment recommendations

We recommend that CPR drugs be administered preferentially via an IV catheter rather than via an IO catheter (strong recommendation, very low quality of evidence).

If attempts at IV access are not successful within 2 minutes, we suggest that rescuers pursue IO catheter placement and to concurrently attempt to secure IV and IO access if adequate personnel are available (weak recommendation, very low quality of evidence).

3.1.4 | Justification of treatment recommendations

Although there are several clinical trials in people and a large number of experimental studies addressing this PICO question, the results are mixed, suggesting that IV access is likely superior to IO access for resuscitation drug administration during CPR. Given the evidence that early administration of resuscitation drugs is preferred, it is reasonable to pursue IO catheter placement if attempts at IV access are not immediately successful and to concurrently attempt to secure IV and IO access if adequate personnel are available. If both IV and IO access are available, the evidence suggests that preference be given to IV administration of resuscitation drugs.

3.1.5 | Knowledge gaps

There are very limited experimental data in dogs and no data in cats on the efficacy of IV versus IO administration of resuscitation drugs. Additionally, there is no evidence to inform choice of the optimal location for IO catheter placement in dogs or cats.

4 | REVERSAL AGENTS

Drug reversal agents are commonly employed in patients with sedative or anesthetic drug overdose, and there has been significant recent interest in the prehospital role of naloxone following accidental opioid overdose in people.[34] The role that reversal agents play during CPR is less well understood. An exploratory literature search identified no publications pertinent to nonopioid reversal during CPR. The recommendations from the RECOVER 2012 Guidelines for the respective reversals therefore remain unchanged. Given the new evidence expected, we repeated the PICO question specifically pertaining to the utility of naloxone during CPR in patients receiving an opioid in the peri-arrest period.

4.1 | Naloxone in CPR—ALS-13

In cats and dogs with CPA after recently administered opioid drugs (P), does not administering naloxone (I) compared to naloxone administration (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

4.1.1 | Introduction

Opioid medications are commonly used as analgesics in dogs and cats. In a large retrospective study of over 2,000,000 hospitalized human patients, those receiving a combination of opioids and sedatives had an adjusted OR of developing CPA of 3.47 (95% CI: 3.40–3.54, $P < 0.0001$), while those receiving opioids alone had an OR for CPA of 1.81 (95% CI: 1.77–1.85, $P < 0.0001$).[35] This PICO question evaluated the utility of administering naloxone to patients who had recently received an opioid prior to CPA.

4.1.2 | Consensus on science

No studies were identified that addressed the most critical outcome of *favorable neurologic outcome*.

For the next most critical outcomes of *survival to hospital discharge and ROSC*, 3 observational studies in people (very low quality of evidence, downgraded for serious risk of bias and serious indirectness) provided some evidence regarding the use of naloxone in patients experiencing CPA potentially related to opioid exposure. In a retrospective registry study of 2342 OHCPA patients, 180 (7.7%) were suspected to be related to opioid overdose and were administered naloxone.[36] Patients suspected of opioid overdose and administered naloxone had a higher rate of survival to hospital discharge (19% vs 12%, $P = 0.014$) than nonoverdose patients. However, there was no control population suspected of opioid overdose that did not receive naloxone for comparison. In a retrospective observational study of 726 patients with opioid overdose, 609 (85.4%) had pulses on presentation, and 94% of those responded to naloxone administration.[37] Naloxone was administered in the 16 patients in CPA in which CPR was attempted. Two developed ROSC, but none survived to discharge. In a third retrospective, observational study of 36 patients with OHCPA administered naloxone because of suspected prearrest opioid use, 15 (42% [95% CI: 26–58]) showed improvement in the ECG rhythm. The majority presented with pulseless electrical activity (PEA) or asystole. Three patients achieved ROSC, but only 1 patient survived to discharge.

No additional studies were identified that investigated *surrogate markers of perfusion*.

4.1.3 | Treatment recommendations

In cats and dogs with CPA after recently administered opioid drugs, we recommend that once BLS and other high-priority ALS interventions

have been initiated, naloxone should be administered (0.04 mg/kg IV or IO) (strong recommendation, very low quality of evidence).

We recommend immediate administration of naloxone (0.04 mg/kg IV or IO) in dogs and cats not in CPA that are bradycardic and/or unresponsive after administration of an opioid (strong recommendation, very low quality of evidence).

4.1.4 | Justification of treatment recommendations

Although there are no clinical trials or experimental studies that directly answer this PICO question, naloxone administration in patients who recently received opioids is a low-risk intervention and is effective at reversing life-threatening opioid overdose in people who are not yet in CPA. In addition, 1 retrospective observational study in humans showed that patients with OHCPA associated with opioid overdose administered naloxone have higher survival to discharge rates than patients arresting due to other causes, suggesting that attempting CPR in these patients is worthwhile.[35] In dogs and cats that are known or suspected to have received an opioid overdose that may have precipitated the arrest, administration of naloxone may theoretically have even more of a benefit.

For patients that have not arrested but have received an overdose of an opioid or are bradycardic or unresponsive after receiving an opioid, the committee recommends immediate administration of naloxone to attempt to prevent CPA based on the literature evaluated to answer this PICO question.

4.1.5 | Knowledge gaps

No clinical or experimental studies have specifically addressed the question of whether naloxone is beneficial in people, cats, or dogs with CPA in close proximity to opioid administration. In addition, there is no evidence about an optimal or maximum duration between opioid exposure and effective naloxone administration in dogs, cats, or people with CPA.

5 | DRUGS FOR NONSHOCKABLE RHYTHMS

The 2012 RECOVER Guidelines recommended the use of vasopressors (ie, epinephrine, vasopressin) and the anticholinergic drug atropine during CPR for nonshockable arrest rhythms (eg., asystole, PEA).[6]

Epinephrine has long been the mainstay of drug therapy in CPR.[38] It is used primarily for its α-mediated vasoconstrictive effects, likely predominantly α-adrenoreceptor effects, with this vasoconstriction improving coronary and cerebral perfusion pressures (CePPs) in experimental studies.[39] There are well-documented negative side effects of epinephrine administration, mostly mediated through β_1-adrenoceptor effects.[40] A series of PICO questions investigated the utility of epinephrine for nonshockable arrest rhythms, including questions about dosing and frequency of administration.

Anticholinergic (ie, vagolytic) drugs are used routinely in patients with bradycardia resulting from high vagal tone, especially in those undergoing sedation and anesthesia. Atropine has been included in veterinary CPR guidelines for nonshockable arrest rhythms, but while recent evidence has not suggested harm, it has not shown significant benefit in humans.[6,41] Herein, we formulated 2 PICO questions on the utility of atropine in dogs and cats with high vagal tone at the time of the arrest and the optimal dosing interval during CPR.

5.1 | Epinephrine for nonshockable rhythms—ALS-06

In cats and dogs with CPA and nonshockable arrest rhythms (P), does administration of no epinephrine (I) compared to administration of epinephrine (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

5.1.1 | Introduction

Low-dose epinephrine (0.01 mg/kg) is recommended during ALS for nonshockable rhythms in dogs and cats.[1] However, there is little evidence to support the use of epinephrine in dogs and cats undergoing CPR for nonshockable rhythms outside the research setting. In particular, there is little and conflicting evidence regarding the impact of epinephrine use on the most critical outcomes of favorable neurologic outcome and survival to hospital discharge. This PICO question investigated the utility of epinephrine for nonshockable arrest rhythms in dogs and cats.

5.1.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 1 clinical trial (PARAMEDIC2; low quality of evidence, downgraded for very serious indirectness) reported results over 3 papers.[42–44] This trial evaluated the use of low-dose epinephrine compared to placebo in 8014 adult human beings experiencing OHCPA that did not respond to initial CPR and defibrillation if appropriate; 79% of people initially had a nonshockable rhythm (unclear if this was from time of first responder arrival or if this was at the time of randomization/inclusion). The PARAMEDIC2 trial found no treatment benefit of epinephrine compared to placebo for functional neurologic outcome at hospital discharge or at 6 months. Six observational studies were identified (very low quality of evidence, downgraded for serious risk of bias, very serious indirectness, serious imprecision, and very serious inconsistency) that addressed the PICO question for the outcome of functional neurologic outcome.[45–50] The largest of these studies included 383,811 adults experiencing OHCPA, 93% of whom had a nonshockable rhythm at the time of inclusion.[50] This large observational study found no benefit to favorable neurologic outcome at 1 month, with the exception of the group in which CPR lasted for 15–19 minutes, in which epinephrine

improved functional neurologic outcome compared to nontreatment (OR: 1.33, 95% CI: 1.02–1.73). The next largest study included 110,239 adults experiencing OHCPA, 100% of whom had a nonshockable rhythm; this study found an association between epinephrine use and functional neurologic outcome at 1 month or hospital discharge, whichever was earlier.[47] Using propensity matching, the improvement in functional neurologic outcome with epinephrine was not appreciated in patients with PEA (7431 pairs; OR: 1.26, 95% CI: 0.86–1.85), but was noted in patients with asystole (8906 pairs; OR: 2.89, 95% CI: 1.42–6.05). However, the only relevant study identified that evaluated IHCPA was an observational study that included 6033 adults, 77% of whom had a nonshockable rhythm.[46] In this study of IHCPA, epinephrine administration was negatively associated with functional neurologic outcome (ie, receiving epinephrine was associated with a worse neurologic recovery than not receiving it) at discharge; authors noted concern for confounding by indication for these unexpected results, though most other studies on this subject are in a different patient set (OHCPA victims).

For the second most critical outcome of *survival to discharge*, we identified 2 clinical trials (low quality of evidence, downgraded for very serious indirectness, serious imprecision, and serious inconsistency) that addressed the PICO question. The clinical trial PARAMEDIC2 (see above) found that epinephrine improved *survival to discharge and to 12 months* compared to placebo.[42,44] In a smaller clinical trial of 601 adults with OHCPA (only 48% of whom had nonshockable rhythms), there was no difference in *survival to discharge* with epinephrine compared to placebo.[51] Eight observational studies (very low quality of evidence, downgraded for very serious indirectness, serious imprecision, and serious inconsistency) showed mixed results regarding epinephrine use and *survival to discharge* for adults suffering OHCPA, 68%–100% of whom had nonshockable rhythms. The 2 largest studies in adults (383,811 and 110,239 subjects) suffering OHCPA, 93%–100% of whom had nonshockable rhythms, both showed improvement in survival to discharge or 1 month with epinephrine compared to no epinephrine.[47,50] Four smaller observational studies, all in adult OHCPA patients with 68%–92% nonshockable rhythms, showed mixed results. The largest study including 41,383 people[48] demonstrated an association with higher 1-month survival with epinephrine, and the 3 other studies (total fewer than 7000 people) found either no such benefit (2 studies) or an association with worse survival (1 study) with epinephrine use compared to none.[49,52,53] The single study in adult IHCPA (6033 subjects) documented a negative association between the use of epinephrine and survival to discharge and 30 days, although, as mentioned earlier, this observational study suffered from very serious group disparities.[46] Finally, a single pediatric study in 3961 children, 92% of which had nonshockable rhythms, found no treatment benefit associated with epinephrine administration at 1 month.[45]

For the next important outcome of *ROSC*, both clinical trials and 7 out of 8 of the abovementioned observational studies found treatment benefit with epinephrine compared to placebo or none, respectively.

The outcome of *surrogate markers of perfusion* was not assessed because adequate evidence was identified to answer the PICO question for the higher priority outcomes.

5.1.3 | Treatment recommendations

We recommend the use of epinephrine for nonshockable rhythms during CPR in dogs and cats (strong recommendation, low quality of evidence).

5.1.4 | Justification of treatment recommendations

The largest clinical trial and 2 very large observational studies totaling nearly half a million adult human beings support the use of epinephrine in patients in CPA with nonshockable rhythms.

5.1.5 | Knowledge gaps

There were no studies identified in dogs and cats in the clinical setting to support or reject the use of epinephrine during CPR for nonshockable rhythms. Given the evidence available, the committee believes that a placebo-controlled trial of vasopressor administration in dogs and cats with nonshockable arrest rhythms is not justifiable. However, a trial comparing epinephrine to alternative vasopressors such as phenylephrine, norepinephrine, or vasopressin could be of value.

5.2 | Dosing interval of epinephrine—ALS-07

In cats and dogs with CPA (P), does administration of epinephrine at any other time interval (I) compared to administration of epinephrine every 3–5 minutes (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

5.2.1 | Introduction

Human and veterinary CPR guidelines recommend a dosing interval of every 3–5 minutes for low-dose epinephrine during CPR.[6,54–59] This recommendation is based largely on expert opinion and historically there have not been data to support one specific dosing interval over another.

5.2.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 1 observational study was identified that addresses the question (low quality of outcome, downgraded for serious indirectness, upgraded for large effect and for dose–response effect).[60]

For the next most critical outcome of *survival to discharge*, we identified 3 observational studies that addressed the question (very low quality of evidence, downgraded for serious indirectness and

serious inconsistency, upgraded for large effect and for dose–response effect).[60–62] All studies were in people and all 3 averaged the epinephrine dosing interval over the course of the CPR effort, then analyzed categorized epinephrine dosing intervals and outcome. One study was in adults with OHCPA, 1 was in adults with IHCPA, and 1 was in pediatric IHCPA patients.[60–62] The most striking aspect of these studies taken together is the strongly positive association of more frequent dosing with survival as demonstrated by Grunau et al in OHCPA patients that stands in contrast to the convincingly negative association between shorter dosing interval and survival as demonstrated in both the Warren and Hoymes studies in IHCPA. Warren et al showed in 20,909 adults with IHCPA that compared to the reference average epinephrine dosing interval of 4 to <5 minutes, survival to hospital discharge was significantly higher in patients with an average epinephrine dosing period of 6 to <10 minutes per dose, with an increasingly beneficial association on outcome the longer the interval was, up to a 9 to <10 minute interval.[62] Similarly, Hoyme et al showed in 1630 pediatric patients with IHCPA that compared to an average epinephrine dosing interval of 1–5 minutes, average intervals of >5 to <8 minutes and 8 to <10 minutes were associated with improved survival to discharge with a dose–response effect similar to that seen in Warren et al.[61] These findings are contrary to those reported in the study of Grunau et al, which showed that longer epinephrine dosing intervals were associated with lower hospital survival and lower survival with favorable neurologic status when compared to a <3-minute average dosing interval in adults with out-of-hospital cardiac arrest, despite similar baseline characteristics in proportion of shockable rhythms, bystander CPR, interval between emergency call and emergency personnel arrival, and total dose of epinephrine administered.[60]

For the next important outcomes of *ROSC* and *surrogate markers of perfusion*, we identified no studies that directly addressed the PICO question.

5.2.3 | Treatment recommendations

We suggest administering epinephrine at a standard dosing interval of 3–5 minutes (weak recommendation, very low quality of evidence).

5.2.4 | Justification of treatment recommendations

There is conflicting evidence in the human literature, showing dramatically different effects in out-of-hospital (benefit of more frequent dosing) compared to in-hospital (benefit of less frequent dosing) CPA. The precise reason(s) for this difference are unclear and thus how to apply this information to canine and feline CPA patients at a veterinary hospital is unknown. Based on the inconsistency in the findings, we do not recommend changing the treatment recommendation made for the 2012 RECOVER CPR Guidelines.

5.2.5 | Knowledge gaps

The appropriate dosing interval for epinephrine in dogs and cats in CPA is unknown.

It is unknown whether this interval may vary depending on lag time to start of high-quality CPR with ALS interventions.

The appropriate dosing interval of epinephrine in dogs and cats is a high-priority knowledge gap in the veterinary literature.

5.3 | High- versus low-dose epinephrine—ALS-08

In cats and dogs with CPA (P), does the use of high-dose epinephrine (0.1 mg/kg IV) (I) compared to standard-dose epinephrine (0.01 mg/kg IV) (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)

5.3.1 | Introduction

Limited evidence is available to determine the ideal dose of epinephrine during CPR in dogs and cats. Experimental and limited clinical evidence have suggested that high-dose epinephrine (ie, ~0.1 mg/kg) may improve chances of ROSC but may worsen survival or neurologic outcome when compared to low- (standard-) dose epinephrine (ie, ~0.01 mg/kg).[63] Examination of literature surrounding this PICO question aimed to determine whether there is a benefit to routine use of high-dose epinephrine as opposed to low dose in dogs and cats undergoing CPR.

5.3.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, we identified 4 clinical trials (low quality of evidence, downgraded for very serious indirectness) and 2 experimental studies (very low quality of evidence, downgraded for very serious indirectness) that addressed the PICO question.[64–69] All 4 clinical trials investigated OHCPA in human adults; the largest included 3327 people and all 4 combined contained ~5500 subjects. None of the 4 trials showed improvement in neurologic outcome at discharge when comparing high-dose epinephrine to standard, low-dose epinephrine. One trial containing only 816 people suggested a trend toward worse functional neurologic outcome with high-dose epinephrine.[64] Both experimental studies that addressed functional neurologic outcome were in swine, and neither found a difference in functional neurologic outcome at 24 hours when comparing high-dose to standard-dose epinephrine; both studies used 0.2 mg/kg as "high dose" and 0.02 mg/kg as "low dose."

For the next most critical outcome of *survival to discharge*, we identified 6 clinical trials (low quality of evidence, downgraded for very serious indirectness) and 3 experimental studies (very low quality of evidence, downgraded for very serious indirectness) that addressed

the PICO question.[56,64–71] The 2 clinical trials that were not listed under functional neurologic outcome were small and together contributed only ~600 additional people, 68 of whom were pediatrics with IHCPA. Five of 6 trials found no benefit to high-dose epinephrine compared to low-dose epinephrine on survival to discharge. One trial in children with IHCPA showed worse neurologic status at 24 hours post-CPR with high-dose compared to low-dose epinephrine, and no children in the high-dose group survived to discharge compared to 4 children in the low-dose epinephrine group.[70] Three experimental studies, 2 in swine and 1 in dogs, found no improvement in 24-hour survival (swine) or 2-hour survival (dogs) when high-dose epinephrine was compared to low-dose epinephrine.[56,68,69]

We identified 6 clinical trials (very low quality of evidence, downgraded for very serious indirectness and serious inconsistency) and 6 experimental studies (low quality of evidence, downgraded for serious indirectness) that addressed the next important outcome of *ROSC*.[55,56,64–73] Two of the clinical trials,[64,67] 1 of which was the largest trial including 3327 adults with OHCPA, found that high-dose epinephrine improved ROSC compared to low-dose epinephrine, while the other 4 trials failed to identify a difference. Of the 6 experimental studies, including 3 studies in dogs and 1 in cats, none found an improvement in ROSC with use of high-dose compared to low-dose epinephrine. Despite this, 2 of the canine studies found that ROSC was achieved more quickly with high-dose than with low-dose epinephrine.[55,56]

No evidence was found to investigate the outcome of *surrogate markers of perfusion*.

5.3.3 | Treatment recommendations

We recommend against the routine use of high-dose epinephrine during CPR in dogs and cats (strong recommendation, low quality of evidence).

5.3.4 | Justification of treatment recommendations

There is no evidence that routine use of high-dose epinephrine improves functional neurologic outcome or survival in dogs, cats, or other species, and some limited information in people suggests worse neurologic outcome and short-term (24 h) survival with high doses. There is inconsistent evidence for improvement in ROSC with use of high-dose epinephrine in people, and no evidence for improvement in ROSC in experimental models in dogs, cats, or swine.

5.3.5 | Knowledge gaps

There are no observational studies or clinical trials in the target species to investigate the possible utility of high-dose epinephrine in dogs and cats.

5.4 | Atropine in patients with high vagal tone—ALS-09

In cats and dogs with CPA associated with high vagal tone (P), does not using atropine (I) compared with using atropine (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

5.4.1 | Introduction

Atropine, a parasympatholytic, is recommended to prevent CPA in patients with bradycardia secondary to high vagal tone. The RECOVER 2012 CPR Guidelines also suggest that it can be considered during CPR in dogs and cats with nonshockable arrest rhythms, particularly in animals with high vagal tone as a suspected trigger for arrest.[6] However, atropine has been removed from human CPR guidelines, and the evidence is primarily supportive of atropine as part of treatment of severe bradycardia, rather than as part of CPR. This question investigates whether atropine is beneficial in dogs and cats with high vagal tone preceding CPA.

5.4.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, there are 2 retrospective observational studies of people with nonshockable arrest rhythms (very low quality of evidence, downgraded for serious risk of bias and very serious indirectness), neither of which showed an outcome benefit of atropine.[41,74]

For the next most critical outcome of *survival to discharge*, a total of 4 retrospective observational studies of people with nonshockable arrest rhythms (very low quality of evidence, downgraded for serious risk of bias and very serious indirectness) were identified. The 2 previously mentioned studies showed no association between atropine administration and this outcome.[41,74] One of the additional studies found an association between atropine administration and reduced likelihood of survival to discharge using a multivariate analysis for IHCPA (OR: 0.21, 95% CI: 0.06–0.81).[75] The remaining study showed a survival to discharge benefit associated with administration of either epinephrine and/or atropine, but did not examine the effects of the 2 drugs independently.[76]

For the next important outcome of *ROSC*, 4 experimental animal studies in dogs were identified (low quality of evidence, downgraded for serious risk of bias and serious inconsistency). The most direct evidence involved an asphyxial PEA arrest model in 75 dogs that received chest compressions, epinephrine every 3 minutes, and a single injection of 1 of 4 doses of atropine or placebo.[77] Dogs receiving standard-dose atropine (0.04 mg/kg IV) had comparable ROSC rates to dogs receiving placebo. ROSC rates were lower for dogs receiving higher doses of atropine (ie., 0.1, 0.2, and 0.4 mg/kg IV). In another experimental study of 40 dogs with induced asphyxial CPA leading to PEA

and treated with chest compressions and ventilation, animals receiving an α-adrenergic agonist had significantly higher ROSC rates than those given saline placebo, but dogs treated with atropine or calcium chloride had similar ROSC rates to placebo controls.[78] However, a study of dogs with PEA induced by asphyxiation showed that animals receiving epinephrine and atropine (0.025 mg/kg IV) had higher rates of ROSC than those receiving epinephrine and 5% dextrose in water (10/11 vs 8/12, $P < 0.01$).[79] Finally, in a study of dogs with bradycardic CPA induced with digoxin and propranolol, administration of atropine prior to the arrest prevented CPA.[80]

Three retrospective observational studies in people with nonshockable arrest rhythms (very low quality of evidence, downgraded for serious risk of bias and very serious indirectness) examined the association of atropine with ROSC.[41,74,75] Of these, only 1 showed an association with increased ROSC in patients with asystole (OR: 1.6, 95% CI: 1.4–1.7, $P < 0.0001$).[74]

The outcome of *surrogate markers of perfusion* was not assessed because adequate evidence was identified to answer the PICO question for the higher priority outcomes.

5.4.3 | Treatment recommendations

We suggest that atropine (0.04 mg/kg IV or IO) may be administered once during CPR for dogs and cats with nonshockable arrest rhythms (weak recommendation, low quality of evidence).

We recommend that if atropine is used, it is given as early as possible in the CPR effort (strong recommendation, very low quality of evidence).

We recommend against administering repeated doses of atropine during CPR for dogs and cats with nonshockable arrest rhythms (strong recommendation, very low quality of evidence).

We recommend the use of atropine (0.04 mg/kg IV or IO) in dogs and cats with bradycardia causing hemodynamic compromise to attempt to prevent progression to CPA (strong recommendation, expert opinion).

5.4.4 | Justification of treatment recommendations

The evidence surrounding the potential benefit of atropine during CPR for patients with nonshockable arrest rhythms is conflicting and extremely limited. Although the majority of studies showed no difference in outcomes in these patients with administration of atropine, 1 observational study in humans demonstrated an association between atropine administration and reduced likelihood of survival to discharge,[74] and 1 experimental dog study showed a potential benefit.[79] Given the very limited evidence of harm associated with standard-dose atropine, the committee suggests that the use of atropine in dogs and cats with nonshockable arrest rhythms may be considered, especially if the arrest was preceded by bradycardia due to high parasympathetic tone.

There is convincing evidence that higher doses of atropine are associated with worse outcomes in dogs compared to placebo control.[77] Because multiple doses are likely to lead to accumulation, effectively equivalent to administering a higher dose we recommend against giving more than a single dose of atropine during CPR. Given that the physiologic rationale for the use of atropine is that high vagal tone may have contributed to the arrest, we recommend that atropine be given as early in the CPR attempt as possible.

5.4.5 | Knowledge gaps

The incidence of vagally mediated arrests in dogs and cats is unknown but is assumed to be relatively high in hospitalized patients. There are no studies evaluating the utility of atropine in dogs and cats with high vagal tone and/or bradycardia at the time of the arrest. The majority of the studies included either experimentally induced arrest in healthy dogs or people with OHCPA with long response times and generally dismal outcomes.

5.5 | Atropine dosing interval during CPR—ALS-19

In cats and dogs with any cause of CPA (P), does any other atropine dosing interval (I) compared with atropine every 3–5 minutes (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

5.5.1 | Introduction

Veterinary guidelines state that one may consider atropine administration at a dosing interval of every 3–5 minutes during CPR in patients with nonshockable arrest rhythms.[6] There have been little data in veterinary medicine to support a specific dosing interval. The recommendation for atropine administration during CPR was removed from human CPR guidelines in 2010.[81]

5.5.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 1 clinical trial was identified (very low quality of evidence, downgraded for serious risk of bias, very serious indirectness, and serious imprecision). A study of 7448 adults by the SOS-KANTO Study Group showed that epinephrine and atropine administration together resulted in similar 30-day neurological outcome as epinephrine alone.[74]

For the next most critical outcomes of *survival to hospital discharge and ROSC*, we identified 1 clinical trial (very low quality of evidence, downgraded for serious risk of bias, serious indirectness, and serious imprecision), 12 observational studies (downgraded for serious indirectness, serious imprecision, and serious inconsistency), and 1 experimental study (very low quality of evidence, downgraded for very serious indirectness and imprecision).[41,74,77,82–92] The clinical trial (adults with OHCPA) and observational studies (5 in adults with

OHCPA, 1 in adults with IHCPA, 1 in children with OHCPA, and 5 in adults who either did not specify arrest location or included both IHCPA and OHCPA) were all in people. The experimental study utilized mongrel dogs. Most studies evaluated the association of atropine administration with survival and did not specifically examine repeated atropine administration and its association with outcome.

Chang et al found in a study of 361 adults with OHCPA in Taiwan that a lower atropine dose was positively associated with survival to discharge.[84] Similarly, a study of 159 adults who underwent CPR at a hospital in Pakistan found that a higher total atropine dose was associated with decreased survival to discharge (OR: 0.68, 95% CI: 0.47–0.99, $P = 0.05$).[86] Agreeing with these findings, Dumot et al found in a study of 445 adults receiving ALS that atropine use was associated ($P < 0.01$) with poor survival to discharge and administration of any atropine during resuscitation cut the survival rate in half.[87] Additional atropine doses resulted in survival to hospital discharge rates of less than 5%. In this study, the number of atropine ampules administered to survivors was a quarter of that administered to nonsurvivors (0.4 vs 1.7 ampules). A study of 7448 adults by the SOS-KANTO Study Group showed that epinephrine and atropine administration together resulted in higher ROSC than epinephrine alone for adults with asystole, but a similar 30-day neurological outcome was noted.[74] However, in adults with PEA, the epinephrine with atropine group had a significantly lower survival rate than those who received epinephrine alone ($P = 0.02$). In a study of adults with both IHCPA and OHCPA by Stiell et al, no association was noted between atropine administration and ROSC or survival to discharge.[92] However, administration of atropine during the fourth quartile of CPR was associated with improved ROSC. Behnke et al showed in an experimental study in 75 mongrel dogs with an asphyxial model of PEA that the standard dose of atropine did not improve ROSC or survival compared with placebo and that higher doses of atropine tended to decrease ROSC.[77]

No evidence was found to investigate the outcome of *surrogate markers of perfusion*.

5.5.3 | Treatment recommendations

We suggest against administering multiple doses of atropine (weak recommendation, very low quality of evidence).

5.5.4 | Justification of treatment recommendations

There is little evidence for administration of atropine in people with CPA, which led to its removal from the American Heart Association's Advanced Cardiac Life Support guidelines in 2010.[81] There is even less information on dosing frequency or total dosage of atropine administration in people, though some data suggest a higher dose of atropine is associated with decreased survival in people and dogs. In addition, although the pharmacokinetics of intravenous atropine in dogs and cats have not been well studied, there is evidence that at a dose of 0.03 mg/kg IV, heart rate remains increased in dogs for 30 minutes after administration.[93] In people, the half-life of IV atropine is approximately 4 hours.[94] This suggests that repeated doses of atropine in dogs and cats could result in excessive plasma concentrations, which could lead to detrimental effects on myocardial oxygen consumption in the postcardiac arrest (PCA) period. The applicability to dogs and cats with CPA, however, is unknown. Based on the findings in clinical studies in humans, we suggest against repeated atropine administration during CPR in dogs and cats.

5.5.5 | Knowledge gaps

The appropriate dosing interval for atropine in dogs and cats in CPA is unknown. The necessity of atropine administration during CPA in dogs and cats is also unknown. It is unknown whether atropine administration and dosing during CPA should be based on the underlying disease process (eg., arrests precipitated by increased vagal tone) or arrest rhythm.

6 | TREATMENT OF SHOCKABLE RHYTHMS

Electrical defibrillation is a highly effective treatment for shockable arrest rhythms if administered as early as possible, with success of first shock termination of VF or PVT ranging from 61% to 98% in people.[95] Therefore, prompt identification and treatment of shockable rhythms are essential in optimizing outcome in cats and dogs undergoing resuscitation. Aspects investigated in this series of PICO questions include timing of shocks, energy setting, type of defibrillator, and adjunctive pharmacological treatments.

6.1 | Monophasic versus biphasic defibrillation—ALS-11

In cats and dogs with CPA due to a shockable rhythm (P), does the use of a monophasic (MP) defibrillator (I) compared to a biphasic (BiP) defibrillator (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

6.1.1 | Introduction

In patients with VF or PVT, successful defibrillation is necessary to achieve ROSC. The most common defibrillation waveforms in use are BiP and MP. In MP defibrillation, a high-energy unidirectional current is used, whereas BiP defibrillation allows for lower energy, bidirectional currents. Current veterinary and human guidelines recommend BiP defibrillation when available over MP defibrillation because higher energy defibrillation has been associated with greater myocardial and other tissue injury.[6,54,96]

6.1.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 2 clinical trials (very low quality of evidence, downgraded for very serious indirectness and serious inconsistency) and 1 observational study (very low quality of evidence, downgraded for serious risk of bias and serious indirectness) were identified. A multicenter, randomized, controlled trial of adults with OHCPA demonstrated a higher percentage of patients with good cerebral performance category at the time of discharge (87% vs 53%, $P = 0.03$) with BiP therapy.[97] Another clinical trial in adults with nontraumatic OHCPA with VF randomly allocated participants to receive either MP or BiP defibrillation.[98] No difference in neurologic outcome was noted between groups. An observational study of all adults with OHCPA in Japan between 2005 and 2014 found improved neurologic outcome with BiP defibrillation compared to MP defibrillation.[99]

Four clinical trials (the 2 mentioned above and 2 additional trials) in adults with OHCPA evaluated the next most critical outcome of *survival to discharge* between BiP and MP defibrillation (very low quality of evidence, downgraded for very serious indirectness and serious inconsistency). The 2 previously mentioned studies showed no improvement in survival to discharge.[97,98] Similarly, the 2 additional clinical trials showed no benefit of BiP over MP for this outcome.[100,101] However, improved survival was noted with BiP compared to MP defibrillation (BiP 45% vs 31%, $P = 0.0002$) in the subset of patients in whom CPA was witnessed and when defibrillation was administered within 4–10 minutes in 1 study.[100] In addition, 1 observational study demonstrated improved survival to 1 month with BiP compared to MP defibrillation.[99] Finally, 1 experimental swine study showed no difference in survival between BiP and MP defibrillation in a prolonged VF model left untreated for the first 10 minutes.[102]

Five clinical trials in people (very low quality of evidence, downgraded for very serious indirectness and serious inconsistency) evaluated the next important outcome of *ROSC*. Three of the 5 OHCPA studies showed no improvement in frequency of ROSC with BiP defibrillation compared to MP.[98,100,103] Of the remaining 2 trials, 1 examined OHCPA and 1 IHCPA, and both demonstrated significantly greater frequency of ROSC in patients treated with BiP versus those treated with MP defibrillation.[97,101] In the first study, a BiP defibrillator was compared to 2 defibrillators with varying MP waveforms, and ROSC frequency was higher with the BiP (76%) than the MP (54%, $P = 0.024$).[101] In the other trial, 76% of patients were successfully defibrillated with BiP versus 54% with MP ($P = 0.01$).[97] In addition, the previously described observational study showed a higher frequency of ROSC with BiP than MP defibrillation.[99] Nine experimental studies (4 in pigs and 5 in dogs) compared BiP and MP defibrillation in various arrest models (very low quality of evidence, downgraded for serious risk of bias, serious indirectness, serious imprecision, and serious inconsistency). Overall, 5 studies showed no benefit of BiP over MP defibrillation in terms of the frequency of ROSC.[102,104–106] Of the 4 remaining studies that showed a benefit of BiP over MP defibrillation, 3 were canine studies.[107–110]

Six experimental studies in dogs and pigs evaluated *surrogate markers of perfusion* (very low quality of evidence, downgraded for serious risk of bias, serious indirectness, and serious imprecision). Most studies identified less myocardial dysfunction, lower energy requirements, shorter periods of CPR, and lower values for markers of cardiac injury with BiP therapy.[102,104,105,111,112] One study in 10 toy breed dogs found more severe ECG abnormalities, more persistently elevated cardiac biomarkers, and severely depressed left ventricular cardiac performance in the MP group compared to the BiP group.[108] However, all dogs included in the study survived.

6.1.3 | Treatment recommendations

We recommend using a BiP defibrillator over an MP defibrillator in dogs and cats with shockable rhythms (strong recommendation, very low quality of evidence).

6.1.4 | Justification of treatment recommendations

Multiple studies show improved neurologic outcome, survival to discharge, and ROSC with BiP defibrillation compared to MP defibrillation. Many experimental studies in pigs and dogs show improved hemodynamics and decreased myocardial injury with BiP defibrillation.

6.1.5 | Knowledge gaps

While studies in people and experimental studies in pigs and dogs support the use of BiP defibrillators over MP defibrillators, no clinical studies in dogs and no studies in cats have been performed. The effects of MP versus BiP defibrillation waveform on outcome during CPR in dogs and cats with shockable rhythms are considered a low-priority knowledge gap.

6.2 | Fixed versus escalating energy defibrillation—ALS-12

In cats and dogs with CPA due to a shockable rhythm (P), does the use of standard dose fixed energy shocks (I) compared with escalating energy shocks (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

6.2.1 | Introduction

High defibrillation energy has been associated with increased myocardial injury during the postresuscitation period.[96] However, unsuccessfully defibrillated patients with VF or PVT invariably fail to achieve ROSC. Two energy strategies have been suggested for repeated BiP defibrillation: a fixed energy strategy (commonly repeated doses of

150 J in adult humans) and an escalating energy strategy (commonly 200–300–360 J in adult humans).[113] Current veterinary guidelines state that an escalating defibrillation energy protocol, compared to a fixed energy protocol, may be considered when using both BiP and MP defibrillators.[6] The American Heart Association guidelines for human ALS suggest that either fixed or escalating defibrillation energy protocols may be considered.[54]

6.2.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 1 clinical trial in people was identified (low quality of evidence, downgraded for very serious indirectness).[114] The clinical trial found no difference in neurologic outcome or survival in adults with OHCPA treated with an escalating versus fixed energy protocol; however, the study was not adequately powered to do so. While the results showed no difference in conversion rates of a single initial BiP shock at 150 versus 200 J, the authors did show that with repeated shocks, escalating doses (200–300–360 J) resulted in a higher conversion frequency (36.6% vs 24.7%, $P = 0.035$) and higher VF termination frequency than a fixed, lower dose (150–150–150 J) regimen (82.5% vs 71.2%, $P = 0.027$).[114] One observational study in humans (very low quality of evidence, downgraded for serious risk of bias and serious indirectness) did not contain a control group, but found that low-energy fixed BiP shocks could result in similar neurologic outcomes, survival to discharge, and ROSC as those historically reported with escalating MP therapy.[115]

For the next critical outcome of *survival to discharge*, in addition to the trial by Stiell et al described above, a second clinical trial in adults with IHCPA directly compared low-energy, fixed shocks (150 J) and high-energy, escalating shocks (200–300–360 J) (low quality of evidence, downgraded for very serious indirectness).[113] If ROSC was not achieved after the third shock in the fixed shock group, they were converted to high-energy, escalating shocks. No difference in survival (24 h, 7 days, or 30 days), ROSC, or first shock termination was noted between groups. However, a rhythm conversion rate of 39% was noted after failed lower shocks, when the dose was then escalated to 360 J on the fourth shock. Therefore, the authors recommended starting at the low initial shock dose and then switching to high energy (360 J) if the patient was not successfully defibrillated after the first shock. In addition to the White study described above, 1 additional observational study (very low quality of evidence, downgraded for serious risk of bias and for serious indirectness) in adults with OHCPA with presumed cardiac etiology showed no difference in survival between those treated with a fixed protocol of 360 J versus those treated with an escalating protocol of 200–360 J.[116]

For the next important outcome of *ROSC*, in addition to the clinical and observational trials described above, 1 experimental swine study compared fixed dose BiP defibrillation (150 J) with escalating dose defibrillation (200–300–360 J).[117] This study found higher successful defibrillation and ROSC in the escalation therapy group compared to the fixed therapy group (15/18 pigs vs 5/17 pigs, $P < 0.002$). Nine pigs in the fixed energy group were successfully defibrillated when converted to the escalating therapy group after 3 fixed shocks.

No evidence was identified to investigate *surrogate markers of perfusion*.

6.2.3 | Treatment recommendations

We recommend that for dogs and cats with shockable arrest rhythms, if an initial standard-BiP-dose (2 J/kg) electrical defibrillation is unsuccessful, the second and subsequent BiP shocks be delivered at a dose of 2× the initial dose (4 J/kg) (strong recommendation, low quality of evidence).

6.2.4 | Justification of treatment recommendations

The 2 human clinical trials reviewed for the PICO question provide compelling evidence that in adult humans, there is no difference in the efficacy of the first electrical defibrillation between standard BiP dosing (150 J) and high-energy BiP dosing (200 J). Therefore, we recommend that the standard dosing regimen for MP and BiP defibrillation continue to be used for the initial shock in dogs and cats with shockable arrest rhythms. However, if the initial shock is unsuccessful, the evidence from the clinical trials and the 1 experimental swine study reviewed for this PICO question suggest that at a minimum, doubling the initial dose for subsequent shocks improves the efficacy of subsequent electrical defibrillations. Additional dose escalation may be beneficial, but the dose at which risk outweighs benefit is unknown; thus, the committee chose not to recommend increasing the defibrillator energy to more than twice the initial dose.

6.2.5 | Knowledge gaps

The optimal defibrillation energy dosing and escalation protocols for dogs and cats have not been studied. Previous studies have only examined a small subset of defibrillation dosing strategies targeted at adult humans.

6.3 | Epinephrine for shockable rhythms—ALS-16

In cats and dogs with CPA and shockable arrest rhythms (P), does administration of epinephrine (I) compared to no administration of epinephrine (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

6.3.1 | Introduction

The 2012 RECOVER CPR Guidelines recommend the use of epinephrine for the shockable CPA rhythms of VF and PVT only in

cases of prolonged shockable rhythms (>10 min).[6] While epinephrine administration is associated with ROSC in experimental studies in dogs, previously there was no evidence of improvement in functional neurologic outcome or survival to discharge with its use.[55–59] Also, there was concern that epinephrine may worsen these outcomes in dogs and cats with shockable rhythms since the drug could increase myocardial oxygen demand in the hypoxic state of CPA. This PICO question aimed to evaluate the evidence regarding the use of epinephrine in dogs and cats with shockable arrest rhythms.

6.3.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, we identified 8 studies, 2 clinical trials, and 6 observational studies in people that addressed the PICO question.[51,60,118–123] We identified 2 clinical trials (very low quality of evidence, downgraded for very serious indirectness and serious imprecision) that addressed the PICO question.[51,118] Both studies investigated the use of epinephrine in refractory shockable OHCPA in people and found no effect on functional neurologic outcome with use of epinephrine. Using the planned evidence evaluation process, we identified 4 observational human studies: 3 in patients with OHCPA and 1 in those with IHCPA (very low quality of evidence, downgraded for serious risk of bias, very serious indirectness, and serious inconsistency).[46,119–121] The 3 studies including OHCPA patients found no effect of epinephrine on functional neurologic outcome in shockable rhythms, and the single study on patients with IHCPA found that epinephrine administration was associated with worse outcome in shockable rhythms; the IHCPA study also found an association between administration of epinephrine and length of the CPR effort, which was identified as a serious confounder and thus renders that study's results less valuable. During evidence summary preparation, we found 2 additional observational studies in people by PubMed search that addressed the PICO question.[122,123] These studies are both large-scale investigations of the early use of epinephrine in shockable rhythms in IHCPA, and both found that early administration of epinephrine to people with shockable rhythms in IHCPA was associated with worse functional neurologic outcome. Both studies found worse functional neurologic outcome using propensity matching to control for confounders such as time to defibrillation and underlying conditions. Considering these 2 studies, the group of 6 observational studies suffer very serious inconsistency.

For the next critical outcome of *survival to discharge*, we found that the same 8 studies addressing favorable neurologic outcome were the studies that addressed this outcome.[51,60,118–123] We identified 2 clinical trials (low quality of evidence, downgraded for very serious indirectness) that addressed the PICO.[51,118] Both studies investigated the use of epinephrine in refractory shockable OHCPA in people and found that epinephrine had no effect on survival. As mentioned above, we initially only identified 4 observational human studies: 3 in OHCPA and 1 in patients with IHCPA (very low quality of evidence, downgraded for serious risk of bias, very serious indirectness, and very serious inconsistency, and upgraded for large effect in the largest of the studies).[46,119–121] The 3 studies of OHCPA found no effect of epinephrine on survival, and the single study on patients with IHCPA found that epinephrine administration was associated with worse survival in shockable rhythms; the IHCPA study also demonstrated an association between administration of epinephrine and length of the CPR effort, which was identified as a serious confounder and thus renders that study's results less valuable. While preparing the evidence summaries, we located 2 additional observational studies in people by PubMed search that were relevant to this PICO.[122,123] Both studies used propensity matching to control for confounders such as time to defibrillation and underlying conditions and are both larger scale studies of the early use of epinephrine in shockable rhythms in IHCPA. They found that early administration of epinephrine to people with shockable rhythms in IHCPA was associated with worse survival.

For the next important outcome of *ROSC*, we identified 2 clinical trials, 3 observational studies, and 5 experimental studies that addressed the PICO question for the outcome of ROSC. We identified 2 clinical trials (moderate quality of evidence, downgraded for very serious indirectness, upgraded for large effect) that addressed the PICO question.[51,121] Both studies investigated the use of epinephrine in refractory shockable OHCPA in people and found that epinephrine significantly increased the odds of ROSC. Using the planned evidence evaluation process, we identified 3 observational human studies—2 in OHCPA and 1 in patients with IHCPA (very low quality of evidence, downgraded for very serious indirectness and serious imprecision, upgraded for large effect particularly in the largest study)—that addressed the PICO question.[46,119,120] Both studies of OHCPA found that epinephrine administration in refractory shockable rhythms improved ROSC, while the study on patients with IHCPA found that epinephrine administration was associated with lower odds of ROSC in shockable rhythms; the IHCPA study also found an association between administration of epinephrine and length of the CPR effort, which was identified as a serious confounder and thus renders that study's results less valuable. During evidence summary preparation, we found 2 additional observational studies in people by PubMed search that addressed the PICO question.[122,123] These studies are both larger-scale studies including propensity-matched analysis of the early use of epinephrine in shockable rhythms in IHCPA, and both found that early administration of epinephrine to people with shockable rhythms in IHCPA was associated with lower odds of ROSC. Taken together, the observational studies for the outcome of ROSC for this PICO suffer very serious inconsistency across studies. Finally, we identified 5 experimental studies—all in dogs—that addressed the PICO question (moderate quality of evidence, downgraded for serious imprecision and upgraded for large effect). All 5 studies showed that epinephrine improved ROSC in shockable rhythms across fibrillatory periods as short as 3 minutes and as long as 12 minutes.

The final important outcome of *surrogate markers of perfusion* was not summarized because a treatment recommendation could be made using evidence from the above 3 critical outcomes.

6.3.3 | Treatment recommendations

We recommend against the use of epinephrine in shockable rhythms in dogs and cats before the first defibrillation attempt (strong recommendation, very low quality of evidence).

We suggest the use of vasopressin (0.8 U/kg), or epinephrine (0.01 mg/kg) if vasopressin is not available, in shockable rhythms in dogs and cats in which the shockable rhythm persists beyond the first shock (weak recommendation, expert opinion).

6.3.4 | Justification of treatment recommendations

For the 3 most critical outcomes of favorable neurologic outcome, survival to discharge, and ROSC, large observational IHCPA studies in people suggest that early use of epinephrine during CPR with a shockable rhythm may be harmful. While the experimental canine evidence for the important outcome of ROSC was moderate in quality and suggested benefit, the committee ultimately decided that an acutely or critically ill hospitalized dog experiencing CPA with a shockable rhythm was more similar physiologically to an acutely or critically ill hospitalized person experiencing CPA with a shockable rhythm than it was to a healthy dog experiencing artificially induced fibrillatory CPA in a laboratory setting. While epinephrine can improve coronary perfusion pressure (CoPP) in all forms of CPA, which may lead to improved ROSC under certain conditions, the fact that early administration of epinephrine in a shockable rhythm was associated with worse functional neurologic outcome, survival to discharge, and ROSC in an in-hospital clinical setting was considered to outweigh a theoretical or experimentally suggested benefit of the treatment. Therefore, the committee concluded that epinephrine should not be administered during the first cycle of BLS in dogs and cats with shockable arrest rhythms.

The committee suggests that vasopressin be used as the first-line vasopressor in dogs and cats with a shockable rhythm that persists beyond the first shock based on the known benefit of improved CoPP under the effect of vasoconstriction during CPA and the lack of clear evidence that vasopressin is harmful in dogs and cats undergoing CPR. However, vasopressin is less widely available in veterinary practice than epinephrine, prompting the committee to also suggest the use of epinephrine if vasopressin is not available. This should be considered with the understanding that dogs and cats initially in nonshockable arrest rhythms commonly convert to shockable rhythms after administration of 1 or several doses of epinephrine[124]; this, and any further administration of epinephrine, has the potential for harm by exacerbating these shockable rhythms through epinephrine's β_1-effects.

6.3.5 | Knowledge gaps

It is unknown whether epinephrine administration is beneficial in dogs and cats with naturally occurring CPA and a shockable rhythm. It is unknown whether use of vasopressin (or other vasoconstrictor) improves critical outcomes in dogs and cats in CPA with a shockable rhythm at any stage (early or late). It is unknown whether the utility of epinephrine in patients with initial shockable rhythms is different than in patients with initially nonshockable rhythms that convert to shockable rhythms after administration of epinephrine.

6.4 | Lidocaine for shockable rhythms—ALS-01

In cats and dogs with a shockable rhythm that are being defibrillated (P), does the use of lidocaine (I) compared to not using lidocaine (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

6.4.1 | Introduction

Current veterinary and human CPR guidelines suggest that lidocaine may improve outcomes in patients with refractory shockable rhythms that do not respond to initial defibrillation.[6,54] Further evidence in dogs suggests that lidocaine may increase the defibrillation threshold when an MP defibrillator is used, while a more recent study in pigs suggested that this increase in defibrillation threshold does not occur with BiP defibrillation.[125,126] This PICO question investigated the effects of lidocaine as an adjunctive therapy for refractory shockable rhythms on outcome.

6.4.2 | Consensus on science

Two clinical trials and 1 observational study were found that addressed the most critical outcome of *favorable neurologic outcome* (low quality of evidence, downgraded for serious indirectness and serious imprecision). In a large, randomized controlled clinical trial, 3026 adult human patients with refractory shockable rhythms (defined as shockable rhythms that persisted after 1 or more defibrillation attempts) were randomized to receive placebo, amiodarone, or lidocaine.[127,128] The investigators found no difference in functional neurologic outcome between the groups. A subgroup analysis of the same data evaluating patients who initially had nonshockable rhythms and converted to shockable rhythms also showed no difference in favorable neurologic outcomes between the groups.[129] One retrospective study of 889 children less than 18 years of age with refractory shockable rhythms similarly showed no improvement in functional neurologic outcomes in the group receiving lidocaine compared to a placebo.[130]

Five clinical trials and 4 observational studies addressing the next most critical outcome of *survival to discharge* were identified (moderate quality of evidence, downgraded for serious indirectness).[8,127,129–135] Of these, 1 clinical trial, a re-analysis of a large clinical trial of 3026 adult human patients with refractory shockable rhythms, showed

improved survival to discharge in the patients who received intravenous lidocaine after 1 unsuccessful shock compared to controls (adjusted risk ratio 1.21, 95% CI: 1.02–1.45), but not in patients receiving IO lidocaine.[8] In addition, a large, retrospective registry study of over 27,000 adult human patients showed an increased survival to discharge in patients who did not convert to a perfusing rhythm after a single shock and were administered lidocaine (OR: 1.88, 95% CI: 1.40–2.53, $P = 0.0001$).[134]

Five clinical trials and 6 observational studies addressing the next important outcome of *ROSC* were identified (moderate quality of evidence, downgraded for serious indirectness).[8,127–136] Of these, 1 clinical trial and 2 observational studies showed improvements in ROSC in patients receiving lidocaine compared to those who did not.[8,134,136] These included the only veterinary observational study investigating this question.[136]

No studies were identified that addressed *surrogate markers of perfusion* for this PICO question.

6.4.3 | Treatment recommendations

We suggest that IV or IO lidocaine be administered to dogs (2 mg/kg) with refractory PVT or VF after the initial shock has been unsuccessful (weak recommendation, moderate quality of evidence).

We suggest that IV or IO lidocaine not be administered in cats with refractory PVT or VF after the initial shock has been unsuccessful (weak recommendation, moderate quality of evidence).

6.4.4 | Justification of treatment recommendations

Two human studies showed a small improvement in survival in patients administered intravenous lidocaine.[8,134] One human study reported improved rates of ROSC with the addition of lidocaine along with electrical defibrillation, although this did not translate to an improved survival to discharge.[135] The available veterinary evidence is limited, although a retrospective study[136] reported a small subgroup of dogs receiving lidocaine that were more likely to survive to hospital discharge. Lidocaine was not identified as harmful in any study, and it is readily available, so its use is reasonable in patients where the primary treatment (defibrillation) has been attempted several times and has been unsuccessful.

The use of intravenous lidocaine in cats is controversial due to their reported sensitivity to its central nervous and cardiovascular effects.[137] One study showed substantial cardiovascular toxicity of intravenous lidocaine infusions in cats during inhalant anesthetic procedures and recommended against their use as an adjunctive therapy for this purpose.[138] The sensitivity of cats to lidocaine has been postulated to be the result of the species' reduced hepatic glucuronidation capacity.[139] Given these potential detrimental effects and the limited evidence of efficacy, we have recommended against the use of this drug in cats during CPR.

6.4.5 | Knowledge gaps

There are no studies in dogs or cats investigating the efficacy or safety of lidocaine for the treatment of refractory shockable arrest rhythms. In addition, it is unknown in any species how many electrical defibrillations should be attempted before administering an antiarrhythmic.

6.5 | Amiodarone use in shockable rhythms—ALS-02

In cats and dogs with a shockable rhythm that are being defibrillated (P), does the use of amiodarone (I) compared to not using amiodarone (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

6.5.1 | Introduction

The gold standard for treatment of PVT and VF is BLS and defibrillation. However, the role of adjunctive therapies for shock-resistant PVT or VF is unclear. Current veterinary guidelines state that in dogs with shock-resistant PVT or VF, amiodarone may be considered.[6] In human medicine, the role of antiarrhythmics (eg., amiodarone, lidocaine, bretylium, nifekalant) during CPR remains unclear. This PICO question investigated whether amiodarone is efficacious as adjunctive therapy in dogs and cats with shockable arrest rhythms.

6.5.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 3 clinical trials in adult humans (moderate quality of evidence, downgraded for serious indirectness) and 2 observational studies, 1 in children and 1 in adults, were identified (very low quality of evidence, downgraded for serious indirectness and serious imprecision).[8,127,129,132,140] The clinical trials were double-blinded and evaluated adults with nontraumatic OHCPA and shock-refractory VF or PVT (defined as persistent or recurrent shockable rhythms after 1 or more shocks anytime during resuscitation). Patients were randomized to receive amiodarone, lidocaine, or placebo following vasopressor administration. Neither amiodarone nor lidocaine resulted in a more favorable neurologic outcome compared to placebo.[8,127,129] The observational studies found no difference between lidocaine and amiodarone for favorable neurologic outcome with refractory PVT or VF; however, no control group was used in these studies.[132,140] One study showed increased defibrillation success after 3 shocks in patients receiving amiodarone compared to patients receiving lidocaine.[140]

For the second most critical outcome of *survival to discharge*, the same 3 clinical trials in adults were identified. In addition, 8 observational studies in people (very low quality of evidence, downgraded

for serious indirectness) and 4 experimental studies in pigs (low quality of evidence, downgraded for serious indirectness and serious imprecision) were identified.[130,132–134,140–147] One of the clinical trials showed that for witnessed arrests, patients administered lidocaine or amiodarone had significantly higher survival to discharge when compared to placebo.[127] Additionally, lidocaine and amiodarone recipients required fewer shocks, but there was no difference in survival to discharge.[129] Furthermore, 1 study showed that amiodarone or lidocaine administered IV, but not IO, was associated with significantly improved survival to discharge compared to placebo.[8] Many of the observational studies lacked a control population, complicating their interpretation. Many of these studies compared antiarrhythmics to one another (ie, lidocaine vs amiodarone, nifekalant vs amiodarone); the majority found no difference in survival to discharge between different antiarrhythmics. Interestingly, in a study of adults with nontraumatic cardiac arrest, Huang et al found that survival to ICU admission, survival to discharge, and 1-year survival were highest when patients with refractory shockable rhythms were given both lidocaine and amiodarone.[134] Survival to discharge was less likely in those only administered amiodarone, lower still in those only administered lidocaine, and lowest in those receiving neither. Ji et al demonstrated higher ROSC and 24-hour survival, decreased number of shocks, lower defibrillation energy, epinephrine dose, and duration of CPR in pigs with refractory shockable rhythms administered amiodarone or nifekalant when compared to saline.[144] Similarly, Zoerner et al found greater 3-hour survival in pigs administered amiodarone in a hemorrhagic shock VF model.[147] However, Karlis et al found higher survival with nifekalant compared to amiodarone and saline and no difference in 48-hour survival between the control and amiodarone groups.[146] Similarly, Glover et al found no difference in survival between amiodarone and placebo.[145]

For the next most important outcome of *ROSC*, we evaluated 1 clinical trial (low quality of evidence, downgraded for serious indirectness), 2 observational studies (very low quality of evidence, downgraded for serious indirectness), and 7 experimental studies (very low quality of evidence, downgraded for serious indirectness, serious imprecision, and serious inconsistency), 3 in dogs and 4 in swine. The clinical trial and the 2 observational studies showed no difference in frequency of ROSC with the use of amiodarone in patients with refractory shockable rhythms.[129,130,141] The experimental studies had heterogenous study designs, but overall 1 of 4 swine studies and 2 of 3 canine studies showed improvement in the frequency of ROSC in animals receiving amiodarone.[144,148,149] The remainder of the studies showed no difference in ROSC between the amiodarone and control groups.[146,147,150,151]

For the outcome of *surrogate markers of perfusion*, 9 experimental studies were identified (very low quality of evidence, downgraded for serious indirectness, serious imprecision, and serious inconsistency). It is important to note that multiple experimental studies demonstrated lower CoPP in dogs and pigs administered amiodarone in the absence of concurrent vasopressor therapy.[144,149,150] The vasodilatory effects of amiodarone may be reduced when epinephrine is administered concurrently with amiodarone.[148] It should also be noted that IV amiodarone does not appear to increase the defibrillation threshold, unlike oral amiodarone.[152,153] Of the 9 studies, 4 were in dogs. Two showed improvement in surrogate markers of perfusion in dogs with refractory shockable rhythms with the addition of amiodarone, 1 showed no difference, and 1 showed worsened surrogate markers of perfusion.[148–150,154]

6.5.3 | Treatment recommendations

If lidocaine is unavailable, we suggest that amiodarone be administered intravenously (5 mg/kg) during CPR for PVT or VF refractory to the first shock in dogs (weak recommendation, very low quality of evidence).

We suggest that amiodarone be administered intravenously (5 mg/kg) during CPR for PVT or VF refractory to the first shock in cats (weak recommendation, very low quality of evidence).

We recommend against the use of amiodarone formulations containing polysorbate-80 in dogs due to the adverse hemodynamic side effects of these formulations that have been documented (strong recommendation, moderate quality of evidence).

6.5.4 | Justification of treatment recommendations

Clinical trials and observational studies in people and experimental studies in pigs and dogs found conflicting results for the efficacy of amiodarone for the treatment of refractory PVT and VF. Many of the observational studies lacked a placebo group (instead comparing lidocaine to amiodarone therapy), complicating their interpretation. There is very little evidence suggesting that amiodarone is superior to lidocaine in these studies. The evidence of profound adverse hemodynamic effects in dogs of amiodarone formulations containing polysorbate-80 indicates that these formulations should not be used during CPR in dogs.[155] The alternative aqueous formulations of amiodarone are reportedly safer,[156] but they are prediluted to a low concentration, requiring infusion of large volumes (approximately 3.3 mL/kg) to achieve the recommended dose, which may be impractical during CPR. There is 1 case report of successful treatment of VT in a cat using the aqueous formulation of amiodarone.[157] For these reasons, the committee suggests that amiodarone can be used for dogs and cats with PVT or VF refractory to an initial attempt at defibrillation, but if lidocaine is available, it is the more practical and safer drug in dogs.

6.5.5 | Knowledge gaps

There are no controlled studies evaluating amiodarone administration in dogs and cats with spontaneous CPA, and amiodarone has not been evaluated in cats. The optimal timing and dosage for amiodarone administration during CPR are unknown. Additionally, whether amiodarone should be administered concurrently with lidocaine to improve outcomes is unknown. Compared to human medicine, shockable rhythms in veterinary medicine appear less common.[124] Therefore,

the role of amiodarone for management of refractory PVT or VF is considered a low-priority knowledge gap in the veterinary literature.

6.6 | Beta blockers for shockable rhythms—ALS-03

In cats and dogs with a shockable rhythm (P), does the use of beta blockers (I) compared to not using beta blockers (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

6.6.1 | Introduction

Refractory VF and refractory PVT (previously defined as a shockable rhythm resistant to 3 shocks) are believed to be at least partially due to high catecholamine tone resulting from severe stress. This may be compounded by the administration of exogenous catecholamines (such as epinephrine) during CPR. The peripheral vasoconstriction resulting from the α-adrenoceptor effects of these catecholamines is believed to be beneficial during CPR, but the β_1-effects may perpetuate refractory shockable rhythms. The use of beta-blockers has been proposed as a potential adjunctive therapy to mitigate these β_1-effects and improve defibrillation success. Current veterinary guidelines do not make any recommendations on the use of beta-blockers during CPR.[6]

6.6.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, there are 5 experimental studies in pigs and rats showing improvement in neurologic outcome scores with the use of beta-blockers (very low quality of evidence, downgraded for serious indirectness and serious imprecision).[158–162] However, both studies in rats involved treatment with beta-blockers prior to induction of VF. Two small retrospective human observational studies failed to show statistically significant improvements in survival with good neurologic outcome in patients with refractory VF treated with esmolol compared to those not receiving esmolol, but both were considered underpowered to detect a difference (very low quality of evidence, downgraded for serious risk of bias, serious indirectness, and serious imprecision).[163,164] However, 1 of these studies[164] showed significantly higher rates of ROSC in the patients treated with esmolol. There are no clinical trials evaluating the use of beta-blockers as adjunctive therapy in patients with refractory shockable rhythms.

For the next most critical outcome of *survival to discharge*, 4 observational studies in people (very low quality of evidence, downgraded for serious risk of bias, serious indirectness, serious imprecision, and serious inconsistency) and 9 experimental studies in swine and rats (very low quality of evidence, downgraded for serious risk of bias, serious indirectness, serious imprecision, and serious inconsistency) were identified. Of these, the highest quality evidence came from a large retrospective study of 8266 people older than 65 years of age, which found no difference in 30-day survival between those who had been prescribed a beta-blocker in the 90 days prior to CPA and those who had not been prescribed a beta-blocker.[165] Of the other 3 studies, 1 showed no difference in 30-day, 3-month, or 6-month survival between 16 patients with refractory VF receiving esmolol and 25 who did not receive esmolol.[164] Another showed that of 28 human patients admitted to a hospital after OHCPA, a significantly higher proportion (5/11) of the survivors to discharge had been on beta-blocker therapy than of nonsurvivors (1/17).[166] The final study showed that among patients with OHCPA and refractory VF, 4 out of 6 patients treated with esmolol had sustained ROSC, while 8 out of 19 not treated with esmolol had sustained ROSC, but due to the small number of patients included, no statistical analysis was conducted.[163]

In addition, 9 experimental studies in pigs and rats with refractory VF were identified that evaluated outcomes comparable to survival to discharge (very low quality of evidence, downgraded for serious risk of bias and serious indirectness). Of these, 7 found that animals treated with a beta-blocker had improved survival compared to controls.[158,159,161,167–170] The other 2 found no difference in survival between animals treated with beta-blockers and controls.[160,162]

Three observational human studies relevant to the next important outcome of *ROSC* were identified (very low quality of evidence, downgraded for serious risk of bias, serious indirectness, serious imprecision, and serious inconsistency). One showed that in 41 OHCPA patients with refractory VF, 13 out of 16 patients receiving esmolol achieved ROSC compared to 6 out of 25 patients not receiving esmolol ($P < 0.001$), while 9 out of 16 patients receiving esmolol achieved sustained ROSC compared to 4 out of 25 not receiving esmolol ($P = 0.007$).[164] A second study of 8266 patients with OHCPA showed no difference in ROSC between patients on beta-blockers compared to those not on beta-blockers.[165] Finally, the Driver study described in the section above did not provide a statistical analysis to compare ROSC rates due to the low number of patients in the study.[163]

There were 14 experimental studies in swine and rats and 1 in dogs that examined the effect of beta-blockers on ROSC rates in animals with refractory VF (very low quality of evidence, downgraded for serious indirectness and serious inconsistency). Study designs are very heterogeneous with some involving pretreatment and many using concurrent interventions, but overall 9 of the studies showed improvements in the rates of ROSC in animals receiving beta-blockers compared to control animals.[158,161,167,169–174] In 1 of those studies, CPR was administered in dogs 1 minute after induction of VF.[174] Dogs pretreated with propranolol followed by a propranolol constant rate infusion (CRI) had improved rates of ROSC (10/10) compared to control dogs (7/10), and CPR duration was shorter in the dogs treated with propranolol (159 ± 27 vs 205 ± 57 s, $P < 0.05$). The other 5 studies showed no difference in ROSC rates in animals treated with beta-blockers compared to control animals.[159,160,162,168,175,176] No studies showed harm in the use of beta-blockers in patients with refractory VF.

Twelve experimental animal studies in pigs and rats that addressed *surrogate markers of perfusion* were identified (low quality of evidence, downgraded for serious indirectness). Although the study designs were heterogenous, 10 out of 12 studies showed a benefit

in surrogate markers of perfusion or postresuscitation tissue injury biomarkers in animals treated with beta-blockers combined with electrical defibrillation and BLS.[158–162,168,169,171,172,175] One study in 16 pigs demonstrated improved ROSC rates and 4-hour survival in animals treated with esmolol at the beginning of CPR compared to controls, but no difference in CoPP and a lower maximum systolic arterial pressure after ROSC.[167] Finally, a study in 20 piglets with 10 minutes of untreated VF followed by resuscitation with extracorporeal membrane oxygenation showed no difference in ROSC, cardiac output, central venous pressure, arterial pressures, pulmonary artery occlusion pressure, or other cardiac function parameters between piglets treated with beta-blockers and a placebo group.[176]

6.6.3 | Treatment recommendations

We suggest administering esmolol (0.5 mg/kg IV or IO over 3–5 min followed by a CRI at 50 μ/kg/min) in dogs and cats with shockable rhythms that do not convert after the first defibrillation (weak recommendation, very low quality of evidence).

6.6.4 | Justification of treatment recommendations

There are no clinical trials and few, very-low-quality observational studies in people assessing the efficacy of beta-blockers in the treatment of patients with shockable arrest rhythms. There is 1 experimental study in dogs and 14 experimental studies in pigs and rats that utilized heterogeneous study designs, but taken as a whole, they show either improvement or no difference in outcomes in animals treated with beta-blockers with experimentally induced VF. Notably in the 1 canine study, dogs pretreated with propranolol had higher rates of ROSC and shorter duration of CPR. None of the studies evaluated showed a detrimental effect of beta-blocker administration in patients with VF.

Most dogs and cats with naturally occurring shockable arrest rhythms develop them after initial nonshockable rhythms, which are commonly treated with epinephrine.[124] This suggests that β_1-stimulation may be partially responsible for the progression to a shockable rhythm, increasing the likelihood that a β_1-antagonist may be beneficial in these patients. Given the physiologic rationale for the use of beta-blockade in animals with refractory shockable arrest rhythms and the lack of evidence of harm across any of the studies evaluated, the panel concluded that the use of a beta-blocker in patients with shockable rhythms that do not respond to initial electrical defibrillation is reasonable. The panel also concluded that β_1-specific beta-blockers should be recommended rather than more generic beta-blockers (such as propranolol) because of concerns for potentially detrimental bronchoconstriction from β_2-antagonism. There were no studies evaluating esmolol dosing in dogs and cats during CPR. Generally recommended esmolol dosing in dogs and cats for treatment of tachycardias is based upon human dosing, so the committee felt that dosing based on the human clinical literature was reasonable.[164,177]

6.6.5 | Knowledge gaps

The optimal timing of beta-blocker administration, duration of beta-blocker therapy, and the specific optimal β_1-blocker for use during CPR in dogs and cats are unknown. The potential efficacy of beta-blockers on outcome during CPR in dogs and cats is considered a moderate priority knowledge gap.

7 | OTHER PHARMACOLOGIC INTERVENTIONS DURING CPR

While vasopressors and anticholinergics are the primary pharmacologic ALS interventions of current veterinary CPR guidelines, additional pharmacologic therapies have been used as adjunctive interventions. The following PICO questions investigated the utility of fluid therapy, buffer therapy, calcium for the management of hyperkalemia, and glucocorticoids.

7.1 | Fluid therapy during CPR—ALS-10

In euvolemic cats and dogs with CPA (P), does the use of an intravenous fluid bolus (I) compared to not using an intravenous fluid bolus (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

7.1.1 | Introduction

Fluid boluses have historically been administered during CPR with the goal of increasing cardiac filling to increase cardiac output. However, during CPR in euvolemic patients who do not have cardiac filling deficits, CoPP and CePP may be decreased by fluid boluses as intravascular volume expansion may increase central venous and right atrial pressure more than aortic systolic and diastolic pressure. The 2012 RECOVER CPR Guidelines recommended against routine administration of IV fluid boluses during CPR unless patients had known or strongly suspected hypovolemia.[6] This PICO question examines the effect of fluid boluses during CPR in euvolemic dogs and cats on clinically relevant outcomes.

7.1.2 | Consensus on science

For the 2 most critical outcomes of *favorable neurologic outcome* and *survival to discharge*, no evidence was available to inform an answer to the PICO question.

For the next important outcome of *ROSC*, there is 1 experimental study that provides some indirect evidence of a beneficial effect of volume loading in euvolemic dogs undergoing CPR (very low quality of evidence, downgraded for serious risk of bias and very serious indirectness). Sanders et al examined 31 mongrel dogs with prolonged induced VF in which CPR was performed for 30 minutes prior to the first shock.[178] Dogs receiving fluid boluses and sodium bicarbonate prior to arrest and during the CPR attempt had higher ROSC rates than those that did not receive fluids or sodium bicarbonate (8/11 vs 0/10). Two additional groups were evaluated with a similar protocol, but 1 group received only fluids and the other only bicarbonate. The incidence of ROSC was similar between these groups (2/12 vs 5/14), but ROSC incidence was significantly higher in the group of dogs receiving both bicarbonate and fluids.

For the next important outcome of *surrogate markers of perfusion*, 4 experimental studies in dogs and 1 experimental study in cats (very low quality of evidence, downgraded for serious risk of bias and very serious indirectness due to confounding interventions) overall showed no improvement or a detrimental effect of fluid boluses on CoPP and/or CePP.[178–182] Although the studies generally demonstrated a consistent increase in aortic pressure and blood flow, the concurrent increase in CVP in the animals yielded either no net improvement or a decrease in CoPP and/or CePP.

Gentile et al compared aortic systolic and diastolic pressures, right atrial systolic and diastolic pressures, and CoPP in 19 healthy anesthetized dogs undergoing CPR for induced VF that either received epinephrine and defibrillation alone ($n = 6$), epinephrine plus a 500-mL bolus (16–23 mL/kg) of 0.9% saline intravenously ($n = 5$), or epinephrine plus a 500-mL bolus of 0.9% saline into the aorta ($n = 8$).[182] Systolic aortic pressure, diastolic aortic pressure, systolic right atrial pressure, and diastolic right atrial pressure all increased significantly with fluid boluses, but maximal CoPP did not significantly differ between groups. In an experimental study of 18 euvolemic dogs with induced VF, rapid infusion of 11 mL/kg of either lactated Ringer's solution ($n = 9$) or whole blood ($n = 9$) after 10 minutes into CPR resulted in a 34% increase in cardiac output, while myocardial and cerebral blood flow decreased by 26% and 35%, respectively. This was attributed to a significant increase in diastolic right atrial pressure that much surpassed a small increase in diastolic aortic pressure.[181] Ditchey and Lenfield studied 12 dogs using a model of induced VF.[180] Measurements of carotid blood flow showed increases with fluid boluses (1 L of 0.9% NaCl or 10% hydroxyethyl starch [HES]), but cerebral and coronary blood flow decreased with fluid boluses, presumably due to increased venous pressure. In a study of 31 mongrel dogs, Sanders et al showed no differences in CoPP in a prolonged VF model (CPR was performed for 30 min before the first shock) between dogs receiving an infusion of fluids prearrest to achieve a right atrial pressure of 6–8 mm Hg and infusions of sodium bicarbonate during the arrest and dogs not receiving fluids or sodium bicarbonate.[178] Finally, Fischer and Hossman studied 14 cats using an induced VF model.[179] All cats had standard CPR with chest compressions, epinephrine, and electrical defibrillation. Six cats were additionally volume loaded with 2 mL/kg HES over 10 minutes. Cats that received HES had significantly less evidence of cerebral ischemia on necropsy, though they had decreased CoPP and CePP during CPR. All cats achieved ROSC.[179]

7.1.3 | Treatment recommendations

We recommend against the use of intravenous fluid boluses in euvolemic dogs and cats during CPR (strong recommendation, very low quality of evidence).

We recommend the use of intravenous fluid boluses in dogs (20 mL/kg isotonic crystalloid or equivalent) and cats (10–15 mL/kg isotonic crystalloid or equivalent) with known or suspected hypovolemia during CPR (strong recommendation, expert opinion).

7.1.4 | Justification of treatment recommendations

All evidence available to inform this treatment recommendation is experimental, is in VF models, and is largely confounded by concurrent treatments including sodium bicarbonate administration. However, there is consistent evidence that fluid boluses administered during CPR to dogs and cats that are euvolemic prior to induced CPA lead to increases in diastolic right atrial pressure that exceed increases in diastolic aortic pressure, leading to decreased CoPP and CePP, suggesting that fluid boluses are in general detrimental in this population. One study showed significant increases in the incidence of ROSC in dogs treated prior to induction of VF with fluid boluses and sodium bicarbonate compared to dogs receiving either fluid boluses alone, sodium bicarbonate alone, or neither.[178] This is confounded by the fact that this treatment started prior to induction of VF and by the fact that these were anesthetized, experimental dogs that underwent prolonged CPR for 30 minutes prior to the first attempt at electrical defibrillation.

7.1.5 | Knowledge gaps

Although there is compelling experimental evidence suggesting that fluid boluses decrease CoPP and CePP in induced VF models of CPA, there are no clinical trials evaluating the effects of fluid boluses in clinical patients during CPR. However, given the experimental evidence, it is difficult to suggest that there is adequate clinical equipoise to warrant a clinical trial.

7.2 | Calcium for treatment of hyperkalemia—ALS-15

In cats and dogs with CPA associated with hyperkalemia (P), does the use of no calcium during CPR (I) compared with calcium administration (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

7.2.1 | Introduction

Hyperkalemia, when severe, may be associated with CPA due to effects on the resting membrane potential of myocardial and nodal cells of the heart. Administration of calcium gluconate raises the threshold potential in these cells, normalizing the difference between the resting and threshold potentials, and thus decreases the cardiac toxicity of hyperkalemia. Hyperkalemia can develop in patients in CPA, likely due to cell death and the extracellular shift in potassium caused by acidosis. This PICO question investigates the utility of calcium salts in the treatment of patients in CPA with hyperkalemia.

7.2.2 | Consensus on science

No studies were identified in the initial literature search to directly inform the answer to this PICO question for any of the outcomes.

Several studies were identified that investigated the use of calcium in patients in CPA. The use of calcium chloride for patients in CPA with nonshockable arrest rhythms has been investigated. One case series was identified describing 4 pediatric patients with cardiac arrest during surgical procedures who all responded to intraventricular calcium chloride administration and recovered with good neurologic function.[183] Plasma potassium concentrations were not measured in any of these patients.

One prospective observational study of OHCPA in adults showed that the use of calcium chloride was associated with ROSC in 27 out of 480 patients, all of which had refractory PEA.[184] No patients with refractory VF or asystole achieved ROSC after administration of calcium chloride. One other observational cohort study of 529 adult human IHCPA patients and 1 clinical trial of 73 patients with OHCPA with refractory asystole showed no effect of calcium chloride administration on ROSC or survival.[92,185] Finally, an observational study of OHCPA in adults showed significantly worse survival to hospital admission rates for patients with both asystole and PEA administered calcium compared to those not receiving calcium.[186] In 1 experimental study in dogs, the use of calcium chloride in experimentally induced PEA led to worse survival than epinephrine and led to similar survival rates to placebo.[187]

After completion of the GRADE process, an additional observational study in people was identified (very low quality of evidence, downgraded for serious indirectness and serious imprecision).[188] This was a retrospective analysis of 109 patients in CPA who had documented serum potassium concentrations of >6.5 mEq/L. The authors found that administration of sodium bicarbonate and calcium in these patients was associated with an increased frequency of ROSC for >20 minutes, and for patients with serum potassium concentrations >6.5 and <9.4 mEq/L, it was associated with an increased frequency of survival for >24 hours. The number of patients with serum potassium concentrations >9.4 mEq/L was very small (7 patients) and none survived for >24 hours, preventing statistical analysis of the effect of sodium bicarbonate and calcium on this outcome.

7.2.3 | Treatment recommendations

We recommend against the routine administration of calcium in dogs and cats in CPA regardless of the arrest rhythm (strong recommendation, very low quality of evidence).

In patients in CPA, we recommend administration of a single dose of 10% calcium gluconate (50 mg/kg IV or IO over 2–5 min) or 10% calcium chloride (15 mg/kg IV or IO over 2–5 min) if hyperkalemia was known or suspected to have contributed to the arrest (strong recommendation, very low quality of evidence).

In patients with CPA, we recommend administration of a single dose of 10% calcium gluconate (50 mg/kg IV or IO over 2–5 min) or 10% calcium chloride (15 mg/kg IV or IO over 2–5 min) when arterial hyperkalemia (>6.5 mmol/L) is documented prior to or during CPA (strong recommendation, very low quality of evidence).

In patients with CPA, we suggest administration of a single dose of 10% calcium gluconate (50 mg/kg IV or IO over 2–5 min) or 10% calcium chloride (15 mg/kg IV or IO over 2–5 min) when severe venous hyperkalemia (eg., >7.5 mmol/L) is documented prior to or during CPA (weak recommendation, expert opinion).

We suggest administration of sodium bicarbonate (1 mEq/kg IV or IO) in patients with hyperkalemia (eg., >7.5 mmol/L) and pH < 7.2 documented prior to or during CPA (weak recommendation, very low quality of evidence).

7.2.4 | Justification of treatment recommendations

The clinical and experimental evidence identified to answer this PICO question did not directly address the use of calcium administration in patients in CPA with hyperkalemia but did suggest that the use of calcium during CPR is unlikely to be beneficial regardless of the arrest rhythm. Given the known cardioprotective benefit of slow IV boluses of calcium salts in patients with hyperkalemia and the results of the Wang study[188] identified after completion of the GRADE process, the committee felt that a recommendation to administer calcium to patients with documented hyperkalemia during CPR was warranted. Given the lack of evidence, the committee could not recommend a specific concentration of potassium at which treatment could be recommended and also acknowledges that the limited evidence upon which these recommendations are made is based on arterial potassium concentrations, which in poorly perfused patients can be markedly lower than venous potassium concentrations. Ultimately, the clinician will need to consider all aspects of the clinical case when making decisions about administration of calcium and sodium bicarbonate in cases of documented hyperkalemia.

7.2.5 | Knowledge gaps

The benefit of calcium in dogs and cats with naturally occurring CPA associated with hyperkalemia has not been directly evaluated, and the

specific plasma potassium concentration at which intervention is warranted is also unknown. The optimal dose of calcium has not been determined.

7.3 | Glucocorticoids in CPR—ALS-04

In cats and dogs in CPA (P), does glucocorticoid use during CPR (I) versus not using glucocorticoids (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

7.3.1 | Introduction

Glucocorticoid deficiency has been documented during and after CPA, prompting the question of the utility of glucocorticoid supplementation during CPR.[189] The 2012 RECOVER CPR Guidelines recommend against the routine use of glucocorticoids during CPR because of the weak evidence of benefit and the known potential for harm.[6] Human guidelines state that glucocorticoids have an unclear benefit for OHCPA. For IHCPA in people, there is no recommendation for or against their use.[54] Recommendations are currently based on a handful of studies in human medicine.

7.3.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 2 clinical trials (very low quality of evidence, downgraded for serious indirectness, serious imprecision, and serious inconsistency) and 1 experimental study (very low quality of evidence, downgraded for very serious risk of bias) were identified.[190–192] Mentzelopoulos et al[190] randomized 100 adults to either receive vasopressin and epinephrine every cycle for 5 cycles along with a single dose of methylprednisolone or receive epinephrine alone. If ROSC was achieved, the patients in the experimental group also received "stress dose" hydrocortisone in the PCA period. There were no survivors with good neurological outcome in either group. In a subsequent clinical trial, Mentzelopoulos et al[191] randomized 268 adults using the same study design as above and found better Cerebral Performance Category scores in the survivors in the experimental group compared to the placebo group. The 1 experimental study showed that dogs treated with therapeutic hypothermia and thiopental or therapeutic hypothermia, thiopental, phenytoin, and methylprednisolone in the PCA period had lower neurologic deficit scores ie, worse neurologic function) than dogs treated with only therapeutic hypothermia or maintained normothermic.[192]

For the next most critical outcome of *survival to discharge*, the same 2 clinical trials (very low quality of evidence, downgraded for serious indirectness, serious imprecision, and serious inconsistency) and 2 observational studies were identified (very low quality of evidence, downgraded for very serious indirectness and serious imprecision).[193,194]

The 2 clinical trials evaluating adults with IHCPA described previously also evaluated survival to discharge. The earlier Mentzelopoulos study reported improved survival to discharge in the group receiving methylprednisolone (9/48 in the experimental group, and 2/52 in the control group, $P = 0.02$).[190] The later study also demonstrated increased survival to discharge in the experimental group (29/130) compared to the control group (18/138). The observational studies were in adults and included both those with IHCPA and OHCPA. Niimura et al[194] found in a study of 2233 adults with either OHCPA or IHCPA that hydrocortisone administration ($n = 61$) was associated with a higher survival to discharge compared to no hydrocortisone administration ($n = 2172$). When propensity score matching was utilized to adjust for imbalances between the study populations, there was no significant difference in survival to discharge between the groups ($P = 0.08$). White et al[193] performed a record review of 25 adults who had CPA with PEA and received dexamethasone during CPR. In this group, the authors found high rates of survival to discharge (16%). However, no control group was examined. This group also included a large percentage (36%) of patients who suffered CPA secondary to septic or hemorrhagic shock, compromising translation of these findings to other patient populations.

For the next most critical outcome of *ROSC*, the same 2 clinical trials (very low quality of evidence, downgraded for serious indirectness, serious imprecision and serious inconsistency) and 2 observational studies were identified (very low quality of evidence, downgraded for very serious indirectness and serious imprecision).[190,191,194] In addition, 3 experimental studies were identified that addressed the question (very low quality of evidence, downgraded for serious indirectness, serious inconsistency, and serious imprecision).[195–197] The 2 clinical trials evaluating adults with IHCPA described previously also evaluated ROSC. The earlier Mentzelopoulos study reported improved ROSC frequency in the group receiving methylprednisolone (39/48 [81%] in the experimental group, and 27/52 [52%] in the control group, $P = 0.003$).[190] The later trial also demonstrated increased frequency of ROSC in the experimental group (109/130 [83.9%] vs 91/138 [65.9%]; OR: 2.98, 95% CI: 1.39–6.40, $P = 0.005$). Niimura et al[194] found in a study of 2233 adults with cardiac arrest that hydrocortisone administration ($n = 61$) was associated with an increased frequency of ROSC when compared to no hydrocortisone administration ($n = 2172$) (26% vs 4%, $P < 0.001$). However, multiple important disparities in baseline characteristics existed in this study, including higher vasopressor and lidocaine dosages and a higher rate of mild therapeutic hypothermia in the hydrocortisone group.[194] The 3 experimental studies were in pigs and rats and had inconsistent results. Smithline[196] found significantly higher frequency of ROSC in rats treated with mechanical ventilation, chest compressions, standard ALS therapy, and high-dose hydrocortisone (92%) compared to rats administered low-dose hydrocortisone (50%) or placebo (50%). However, 2 studies in swine showed no improvement in ROSC frequency when hydrocortisone or methylprednisolone was added to standard BLS and ALS therapy.[195,197]

For the important outcome of *surrogate markers of perfusion*, the same 2 clinical trials described previously (very low quality of

evidence, downgraded for serious indirectness, serious imprecision, and serious inconsistency) and 2 of the previously described experimental animal studies (very low quality of evidence, downgraded for serious indirectness, serious inconsistency, and serious imprecision) addressed the question.[190,191,195,197] The 2 clinical trials showed improved arterial blood pressure during CPR and shortly after ROSC in the patients receiving glucocorticoids, as did 1 of the 2 experimental studies in swine.

7.3.3 | Treatment recommendations

We suggest against the routine administration of glucocorticoids during CPR (weak recommendation, very low quality of evidence).

In dogs and cats with vasopressor resistant-hypotension at the time of CPA or with known or suspected hypoadrenocorticism, we suggest intravenous administration of glucocorticoids during CPR (weak recommendation, expert opinion).

7.3.4 | Justification of treatment recommendations

The literature on the use of glucocorticoids during CPR is confounded by the use of multiple interventions (eg., vasopressin, thiopental, phenytoin, cyclosporine, therapeutic hypothermia, and others) in addition to glucocorticoids in the experimental group, making development of a clinical guideline on the use of glucocorticoids during CPR challenging. In addition, there is little consistency across studies in the type and dose of glucocorticoid used during CPR. Given the lack of evidence of a benefit that can be attributed to glucocorticoids and the potential harm of the use of glucocorticoids, especially in patients with poor perfusion, the committee decided that the weak evidence of benefit was outweighed by the potential detrimental effects of glucocorticoids. However, in cases in which absolute or relative hypoadrenocorticism is suspected to be a precipitating cause of the arrest, it is reasonable to administer glucocorticoids.

7.3.5 | Knowledge gaps

The specific effects of glucocorticoid administration in dogs and cats during CPR on clinically important outcomes are unknown. A single intervention clinical trial investigating this question would be a valuable addition to the literature. The dosage and optimal glucocorticoid drug to use during CPR are also unknown. The effects of glucocorticoids on outcome during CPR are considered a moderate-priority knowledge gap in the veterinary literature.

8 | OPEN-CHEST CPR

Open-chest CPR (OCCPR) is an invasive technique to provide direct cardiac massage. It is important to understand which patients might benefit from this intervention, as it can potentially increase morbidity.

8.1 | OCCPR—ALS-05

In dogs with CPA (P), does closed-chest CPR (CCCPR) (I) compared to OCCPR (C) improve favorable neurologic outcome, survival to discharge, ROSC, or surrogate markers of perfusion (O)?

8.1.1 | Introduction

The 2012 RECOVER CPR Guidelines advise prompt OCCPR in specific clinical scenarios, including tension pneumothorax and pericardial effusion.[1] In human medicine, emergency department thoracotomy (EDT) may be used for cardiac arrest secondary to penetrating trauma.[198] However, the utility and timing of OCCPR outside these specific situations are unknown, particularly considering the cost of OCCPR and the intensity of subsequent management.

8.1.2 | Consensus on science

For the most critical outcome of *favorable neurologic outcome*, 1 observational study inadults (very low quality of evidence, downgraded for serious risk of bias and serious indirectness) and 3 experimental studies in dogs were identified (very low quality of evidence, downgraded for serious imprecision and serious inconsistency).[199–202] A study by Kern et al[200] examined 29 mongrel dogs with induced VF that received standard CPR for 15 minutes and subsequent defibrillation. Unsuccessfully defibrillated dogs were then randomized to receive 2 minutes of either OCCPR or CCCPR. The study showed no difference in neurological scores between the 2 groups.[200] In another study in dogs with VF and immediate defibrillation or 30 subsequent minutes of CCCPR or OCCPR, the authors found that OCCPR resulted in improved neurological scores when compared to CCCPR.[201] Of 12 dogs with CPA induced via potassium chloride that were then randomized to either OCCPR or CCCPR, all dogs with OCCPR were resuscitated and behaved normally at 72 hours.[202] Only 3 out of 7 of CCPCR dogs survived and 2 of these had incapacitating neurological deficits.

Anthi et al[199] examined 29 human adults with cardiac arrest within 24 hours following cardiac surgery.[199] In this population, CCCPR was performed for 3–5 minutes, then followed by OCCPR if needed. Thirteen people achieved ROSC with CCCPR and 14 achieved ROSC with OCCPR; all were discharged neurologically intact. However, no control population was used to compare OCCPR to CCCPR directly.

For the next most critical outcomes of *survival to discharge* and *ROSC*, 5 observational studies in addition to the Anthi study described above were identified in people (4 in adults and 1in children) with traumatic CPA (very low quality of evidence, downgraded for serious risk of bias and serious indirectness).[198,199,203–206] Four experimental studies were also identified for these outcomes, all in previously healthy dogs (very low quality of evidence, downgraded for serious imprecision and serious inconsistency).[200–202,207] The observational studies in people demonstrated little to no benefit with OCCPR when compared to

CCCPR, while the experimental studies in dogs largely demonstrated improved survival with OCCPR.

The Kern et al study of 29 mongrel dogs with induced VF showed improved ROSC frequency, 24-hour survival (12/14 vs 4/14), and 7-day survival (11/14 vs 4/14) with OCCPR.[200] Similarly, the Bircher et al study found that in dogs with VF CPA, OCCPR resulted in improved frequency of ROSC and survival at 24 hours compared to CCCPR.[201] As described above, Benson et al found in 12 dogs with cardiac arrest induced via potassium chloride that all dogs with OCCPR were resuscitated and survived to 72 hours, while only 3 out of 7 of CCCPR dogs achieved ROSC.[202] DeBehnke et al found in a myocardial infarct model in 26 dogs with subsequent VF that there was no difference in ROSC or survival between dogs receiving OCCPR and those receiving CCCPR.[207]

Schulz-Drost et al examined adults who underwent EDT for trauma, a subset of whom underwent EDT for cardiac arrest.[198] For these, the survival rate was 4.8% for blunt trauma but was 20.7% for penetrating trauma. Prieto et al analyzed patients 16 years or younger who underwent EDT within 30 minutes of arrival to a hospital.[204] Of the 53 patients with no signs of life who received EDT, none survived. In a retrospective study of patients with blunt trauma undergoing CPR in the emergency department, Endo et al found higher survival to discharge for CCCPR (3.6% vs 1.8%) and 24-hour survival (9.6% vs 5.6%) when compared to OCCPR.[205] With propensity matching, significantly lower odds of survival to discharge and survival at 24 hours were found with OCCPR. However, it was difficult to determine why OCCPR was initiated in patients and made it challenging to compare the 2 groups. In a later study, Endo et al found that OCCPR was associated with survival to discharge in trauma patients with signs of life upon hospital arrival when compared to CCCPR (15.2% vs 11.7%).[206] This association persisted during logistic regression analysis and propensity score matching.

While it was not the most critical outcome examined, there have been numerous experimental studies in dogs evaluating *surrogate markers of perfusion* with OCCPR, many of which suggest a benefit over CCCPR (low quality of evidence, downgraded for serious imprecision). Many studies in dogs with induced VF found higher arterial pressures, carotid blood flow, cardiac output, cerebral perfusion, and/or CoPP in OCCPR compared to CCCPR.[200,201,207–212] Kern et al demonstrated that OCCPR after 40 minutes of VF in dogs resulted in better arterial pressures and coronary perfusion than CCCPR after 20 minutes of VF.[213] Weiser et al found that average cardiac output was significantly higher in OCCPR (55%) when compared to CCCPR (22%).[214] The difference in cardiac output between OCCPR and CCCPR was particularly pronounced in dogs greater than 10 kg. In a study by Rieder et al of 10 dogs in which CPA was induced via potassium chloride administration while undergoing a laparotomy, OCCPR resulted in significantly higher cardiac index, mean arterial pressure, and carotid blood flow when compared to CCCPR.[215] A transdiaphragmatic approach in which 1 hand reached through the diaphragm to compress the heart against the sternum and the other hand compressed the sternum externally resulted in optimal hemodynamics compared to other techniques. Two additional experimental studies in dogs demonstrated reduced brain injury via histopathological examination when resuscitated by OCCPR compared to CCCPR.[202,216]

8.1.3 | Treatment recommendations

We recommend OCCPR in dogs and cats with abdominal organs or substantial accumulations of fluid or air in the pleural or pericardial spaces (strong recommendation, expert opinion).

We recommend direct cardiac massage in dogs and cats undergoing abdominal or thoracic surgery (strong recommendation, low quality of evidence).

We suggest OCCPR in dogs and cats with penetrating thoracic trauma or rib fractures at or near the chest compression point (weak recommendation, very low quality of evidence).

In medium- and large-breed round-chested and wide-chested dogs in which OCCPR is feasible and clients are amenable to the procedure, we recommend that CCCPR be started immediately and OCCPR be started as soon as possible (strong recommendation, low quality of evidence).

We suggest attempting OCCPR in cats and small dogs (<15 kg) only if they have pleural or pericardial disease, if they have penetrating thoracic trauma, if they are undergoing abdominal or thoracic surgery, or if CCCPR appears to be inadequate (weak recommendation, expert opinion).

We recommend discussing the pros and cons of OCCPR in any dog at risk of CPA when obtaining a "CPR code" at the time of hospitalization if OCCPR is offered by the practice and is indicated (strong recommendation, expert opinion).

8.1.4 | Justification of treatment recommendations

Many but not all experimental studies in dogs demonstrated improved neurologic outcome, survival, ROSC, and hemodynamics with OCCPR when compared to CCCPR. These findings were especially profound for large dogs and dogs already undergoing laparotomy. The recommendation is complicated, however, by observational studies in people who have largely failed to demonstrate a benefit with OCCPR when compared to CCCPR. Given the positive results in the experimental studies in dogs, the committee recommends OCCPR as soon as possible in medium- to large-breed round-chested or wide-chested dogs in which OCCPR is feasible. Factors that could reduce feasibility of OCCPR in medium and large round-chested and wide-chested dogs include owner consent, local practice limitations that would limit the required post-ROSC care, and rescuer OCCPR procedure competence. In addition, considering the likely increased efficacy of CCCPR in keel-chested medium- and large-breed dogs, the committee thinks it is reasonable to default to CCCPR in these patients. Although outcomes are better with OCCPR in a subset of animals, the committee recognizes that even in practices with the skill set and facilities required for the procedure, it is likely that OCCCPR will continue to be a rarely performed procedure due to the invasiveness, client preference, and

required more intense PCA care. Given the likely futility of CCCPR in dogs and cats with pleural or pericardial fluid, air, or abdominal organ displacement and the lack of feasibility of closed-chest compressions in dogs and cats that arrest during laparotomy or thoracotomy, a strong recommendation for OCCPR is made in these circumstances.

8.1.5 | Knowledge gaps

The optimal timing for intervention with OCCPR for dogs and cats with CPA is unknown. It is unknown at what weight OCCPR should be considered as a primary intervention in dogs with CPA. The diseases for which OCCPR should be considered in dogs and cats are poorly described. The appropriate time to intervene with OCCPR in dogs and cats with CPA is considered a high-priority knowledge gap in the veterinary literature.

9 | DISCUSSION

Most of the PICO questions informing this update of ALS treatment recommendations for dogs and cats were initially evaluated in 2012. Re-evaluation was done intentionally to develop an initial foundation of evidence evaluated using the GRADE process in an attempt to provide more standardized, reproducible, and scientifically justifiable treatment recommendations.[2] Consequently, the treatment recommendations are in many cases similar to the 2012 RECOVER CPR Guidelines, but some important new or modified interventions have been introduced. For many PICO questions, significant knowledge gaps remain due to a paucity of available evidence in pertinent species. As such, the writing group relied heavily on expert opinion in both the 2012 and the current RECOVER CPR treatment recommendations. We made treatment recommendations despite lack of evidence in many cases because of the need for clear, consistent standards for critical ALS interventions. Specifically, 8 out of a total of 33 ALS treatment recommendations were made based on expert opinion alone, and 17 were based on very low quality of evidence. Moving forward, we anticipate ongoing rolling updates to questions for which additional evidence becomes available as well as new questions not examined in this current process. We expect that some treatment recommendations will change as more evidence becomes available.

The RECOVER 2024 evidence evaluation process led to several important updates in ALS treatment recommendations, some of which are summarized in Box 1. While these updates are important to optimize favorable outcomes for patients undergoing CPR, it should be noted that ALS interventions are adjunctive and cannot replace, so should never detract from, high-quality BLS. However, the addition of high-quality ALS interventions has the potential to further improve outcomes in patients with CPA.[217]

High-dose epinephrine (0.1 mg/kg) should no longer be considered at any time during CPR in dogs and cats. Although high-dose epinephrine has been associated with increased frequency of ROSC in people, it has also been associated with decreased frequency of survival to discharge and with worse neurologic outcomes.[64,66–70] Therefore, the terms "high-dose" and "low-dose" epinephrine have been retired; we recommend standard dosing of epinephrine at 0.01 mg/kg IV or IO every 3–5 minutes in nonshockable CPA rhythms and suggest the same dose in animals with shock-resistant VF and PVT.

BOX 1: Major updates

- Atropine should not be repeated during CPR and, if given, should be administered as early as possible for patients with nonshockable arrest rhythms.
- IV access is preferred over IO access for CPR drug administration.
- For shockable rhythms, the initial defibrillation should be done at standard dose. The second and all subsequent shocks should be delivered at double the standard dose.
- High-dose epinephrine (0.1 mg/kg) should not be administered during CPR. Epinephrine should be dosed at 0.01 mg/kg IV or IO every 3–5 minutes for patients with nonshockable rhythms.
- For patients with shockable rhythms who do not convert after the first defibrillation and a subsequent full 2-minute cycle of chest compressions, in addition to continued defibrillation every cycle, the following adjunctive therapies may be used:
  - vasopressin (or epinephrine if vasopressin is unavailable)
  - esmolol
  - antiarrhythmic
    - lidocaine in dogs
    - amiodarone in cats

High doses of atropine have been associated with worse outcomes during CPR in dogs.[77] Because of these worse outcomes and the likelihood that the elimination half-life of atropine in dogs and cats is longer than the average CPR attempt, we suggest a single dose of atropine (0.04 mg/kg, ideally IV) may be administered early in the CPR attempt. Atropine may be useful particularly for suspected vagally mediated CPA.

Another substantial revision of the ALS guidelines is targeted at patients with refractory shockable rhythms. Although similar data are not available for dogs and cats, 61%–98% of people with shockable arrest rhythms convert after the first electrical defibrillation attempt.[95] The writing group chose to define a refractory shockable rhythm as one that fails to convert after the first defibrillation attempt. With this definition, we provide a clearly actionable directive and remove the uncertainty with the previous recommendation of escalating ALS measures for shockable rhythms after prolonged, shock-resistant VF/PVT without defining what "prolonged" equates to.[6,218] Three treatments were evaluated for refractory shockable rhythms: vasopressor therapy (vasopressin, or epinephrine if

vasopressin is unavailable), antiarrhythmics (lidocaine in dogs, amiodarone in cats), and esmolol. The evidence for the use of these drugs for refractory shockable rhythms is scant, particularly in dogs and cats, but there were no studies showing a detrimental effect of these interventions after the initial shock, while some evidence supported the utility of each. It is unknown which patient populations may benefit from specific interventions or the order in which to attempt these interventions. Since most dogs and cats with shockable rhythms develop them after initial nonshockable rhythms (and presumably epinephrine administration),[124] esmolol may have some utility for those that received epinephrine prior to the onset of a refractory shockable rhythm. Esmolol will attenuate the beta effects of epinephrine, which could contribute to perpetuation of shockable arrest rhythms.[124] Research investigating the utility of these interventions in our patient populations is necessary to guide future recommendations.

The dose escalation strategy for defibrillation of dogs and cats with refractory shockable arrest rhythms was also modified. The 2012 RECOVER CPR Guidelines recommended increasing the defibrillation dose by 50% after each shock to a maximum of 10 J/kg. The new guidelines are based on several clinical trials and a swine experimental study that demonstrated that most subjects responded to an initial standard defibrillation dose, but a small additional number responded to a higher dose, double the standard dosing.[113,114,117] Therefore, we recommend an initial dose of 2 J/kg for external BiP (or 4 J/kg for MP) defibrillation; if unsuccessful, the dose should be doubled to 4 J/kg (8 J/kg for MP defibrillation) and maintained at that dose for subsequent defibrillation attempts. While we did not search for evidence for optimal defibrillation technique, it is also important to note that factors other than the defibrillator dose contribute to the transthoracic and ultimately transcardiac current flow. Therefore, in dogs and cats with shock-resistant VF/PVT, we also recommend assessing the quality of the defibrillation technique (ie., paddle position, paddle force, conductive gel) in order to maximize the chance of termination of the shockable rhythm.[219]

Given the demonstrated outcome benefits of OCCPR compared to CCCPR, the 2024 RECOVER CPR Guidelines continue to recommend that OCCPR be performed as soon as the necessary equipment is available in any patient in which the clinician feels the approach is warranted, the clinician has the expertise and resources necessary, and client consent has been obtained.[201,202,220] Given the complexity and associated morbidity of the procedure, we recommend obtaining a resuscitation code status at the time of admission to the hospital, when a more detailed discussion of risks and benefits is possible.

Further updates to the Guidelines will require additional veterinary clinical studies to better inform ALS interventions in dogs and cats. High-priority knowledge gaps include the optimal timing of OCCPR and pharmaceutical interventions for refractory shockable rhythms. Studies that evaluate these ALS interventions will aid in the generation of evidence-based guidelines in the future.

AUTHOR CONTRIBUTIONS

Jacob Wolf: Formal analysis; writing—original draft; writing—review and editing. **Gareth J. Buckley**: Conceptualization; Formal analysis; Supervision; writing—review and editing. **Elizabeth A. Rozanski**: Conceptualization; Formal analysis; Supervision; writing—original draft; writing—review and editing. **Daniel J. Fletcher**: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; writing—original draft; writing—review and editing. **Manuel Boller**: Conceptualization; formal analysis; funding acquisition; investigation; methodology; writing—original draft; writing—review and editing. **Molly Crews**: Data curation; investigation; writing—review and editing. **Jamie M. Burkitt-Creedon**: Formal analysis; Investigation; Methodology; Project administration; writing—original draft; writing—review and editing. **Kelly A. Weigand**: Data curation; Investigation; writing—review and editing. **Molly Crews**: Data curation; Investigation; writing—review and editing. **Erik D. Fausak**: Data curation; Investigation; Methodology; Project administration; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

Dr. Burkitt-Creedon is the editor of the Journal but only participated in the review process as an author. The authors declare no other conflicts of interest.

REPRINTS

Reprints will not be available.

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ENDNOTES

[a] Search Strategies and other primary documents, Open Science Framework: http://osf.io/DB2AM.
[b] www.recoverinitiative.org (accessed on March 19, 2024).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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