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To: San Diego County Base Hospital Physicians

FROM: Kristi L. Koenig, MD, FACEP, FIFEM, FAEMS, County EMS Medical Director
Gary M. Vilke, MD, FACEP, FAAEM, Chair, Base Hospital Physician's Committee

RE: Use of Expired Epinephrine During Times of Critical Shortages

In follow up to the [February 28](#) and [March 29, 2022](#), memos regarding the current critical epinephrine shortages, we provide guidance on the use of expired epinephrine. Paramedics may request a Base Hospital Physician Variation order for patients in cardiac arrest or who are hypotensive. Please review the following information regarding expired epinephrine with your base hospital physicians and MICNs:

- As you may be aware, there is a significant national shortage of epinephrine that will create periodic unavailability, at least through the end of 2022.
- Paramedic agencies may be unable to obtain epinephrine to fill inventory or replace expired doses.
- There are data to support that administering expired epinephrine is safe and effective, so long as the **vial remains clear on visual inspection**. Tested epinephrine had significant residual efficacy after the official medication expiration date and had no changes that might cause harm to a patient.^{1, 2}
- In a shortage crisis, an EMS provider may call a base hospital to request a Base Hospital Physician Variation to use expired epinephrine for a patient on a case-by-case basis. Please consider authorizing this variation if you determine it is the best option for the patient given the specific circumstances (e.g., time-sensitivity of need, transport time, lack of option for substitution with another treatment).

The San Diego County Base Hospital Physicians Committee (BSPC) has reviewed the use of expired epinephrine and supports this as a treatment option. BSPC believes the risk-to-benefit ratio warrants expired epinephrine use in cases where no reasonable alternate management is possible (e.g., substituting a different treatment or delaying medication administration until hospital arrival).

¹ Parish HG, Morton JR, Brown JC. A systematic review of epinephrine stability and sterility with storage in a syringe. Allergy Asthma Clin Immunol. 2019 Feb 21; 15:7. doi: 10.1186/s13223-019-0324-7. PMID: 30828350.

² Weir WB, Fred LY, Pike M, Rubakhin SS, Ludwig TJ, Shar AM, Zhu L, Frederick A, Uzoaru I, Wang L, Sweedler JV. Expired Epinephrine Maintains Chemical Concentration and Sterility. Prehosp Emerg Care. 2018 Jul-Aug;22(4):414-418. doi: 10.1080/10903127.2017.1402109. Epub 2018 Jan 26. PMID: 29373043.

RESEARCH

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A systematic review of epinephrine stability and sterility with storage in a syringe

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Abstract

Background: Epinephrine is a lifesaving medication in the treatment of anaphylaxis. Epinephrine auto-injectors are the preferred method of epinephrine administration, but are not universally available or affordable. Little is known about the effects on epinephrine when it is drawn up in advance and stored as prefilled syringes.

Objective: To study the stability and sterility of epinephrine when stored in syringes.

Methods: We searched Embase, Medline, and Web of Science in June 2016 for all studies of epinephrine stored in syringes in concentrations between 0.1 and 1 mg/mL that measured epinephrine stability and/or sterility over time, regardless of date published or language.

Results: Three studies were included, one testing two concentrations of epinephrine. Only one study tested epinephrine 1 mg/mL, the concentration clinically relevant for intramuscular use during anaphylaxis. Neither this study nor the one study testing 0.7 mg/mL epinephrine found significant degradation after 56 and 90 days, respectively. One of the two studies testing epinephrine at a concentration of 0.1 mg/mL found significant degradation by 14 days; the other found no degradation up to 168 days. Two studies tested for bacterial growth, with none detected after 28 and 90 days, respectively. One study tested for fungal growth, with none detected after 90 days.

Conclusions: Limited evidence suggests that syringes filled with 1 mg/mL epinephrine are stable and sterile for 90 days. More research is needed testing the duration of stability and sterility of prefilled syringes with the 1 mg/mL concentration most commonly used in anaphylaxis, testing more extensively in different storage conditions and across a wider range of marketed syringe brands.

Keywords: Epinephrine, Adrenaline, Syringe, Prefilled, Stability, Sterility, Storage, Time, Allergy, Anaphylaxis

Background

Epinephrine is the only first-line therapy for anaphylaxis. Guidelines recommend that individuals with life-threatening allergies carry one or more epinephrine auto-injectors (EAI) in case of contact with their allergen [1, 2]. However, in many parts of the world EAI are unavailable or not readily accessible [3], and rising costs of EAI, particularly in the United States, are creating a financial barrier for both private consumers and health care systems [4–7]. Patients may seek alternatives to

the EAI they need but cannot access or afford [4–7]. In some countries, insurance plans cover epinephrine in vials provided with syringes for self-preparation, but not auto-injector devices [8]. In pre-hospital and hospital settings, the high costs of EAI has resulted in increased use of epinephrine in vials and ampules, drawn up into a syringe either in advance or at the time of use [9–11].

Parents and caregivers have difficulty drawing up epinephrine from a vial into a syringe accurately or reliably [12], as may patients themselves. Preparing and storing epinephrine in syringes in advance may decrease errors as well as ensure timely administration, compared with drawing up epinephrine at the time of need. This systematic review was performed to identify and evaluate all published studies on the stability and sterility of

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epinephrine when drawn up and stored in prefilled syringes.

Methods

The databases Embase.com, Medline in Ovid, and Web of Science were searched in June 2016 for relevant studies. This literature search was conducted following PRISMA guidelines [13]. No limits were applied to the searches except for the time constraints of the databases themselves. Medline contains literature from 1946 to the present, Embase.com from 1974 on, and Web of Science from 1985 on. In Medline and Embase, appropriate Medical Subject Headings (MeSH) or Emtree headings were used, respectively, in addition to keywords and text words. Medline and Embase were searched by our experienced librarian (J.R.M.) for the keywords *epinephrine* or *adrenalin* in combination with *syringe*, *“pre-filled”*, or *prefilled*. Web of Science was searched for the keyword *syringe** in combination with *epinephrin** or *adrenalin** in the title. All studies captured in the search were imported into an electronic reference manager for management and review. Duplicates were removed using the “Find Close Duplicates” function in the reference manager, which was checked manually to ensure that no studies were incorrectly removed. Duplicates that were not identified electronically due to slight formatting differences between databases were manually removed during first review and accounted for in the total number of duplicates. Potentially relevant articles in other languages were translated into English using Google Translate. All potentially relevant English language studies were searched forward in Web of Science in order to find newer sources in which the original ones were cited. The references of all potentially relevant English language studies were reviewed to search for additional relevant studies.

Inclusion criteria

Included studies assessed epinephrine in clinically relevant concentrations between 0.1 and 1 mg/mL that had been drawn up into prefilled syringes. In the United States and Canada, epinephrine as an anaphylaxis drug is commercially available in EAs in two concentrations, 1 mg/mL and 0.5 mg/mL [14, 15]. When epinephrine is administered intramuscularly during anaphylaxis using a needle and syringe, as is often done in the hospital setting, it is typically drawn up from a vial or ampule with a 1 mg/mL concentration. Epinephrine at a concentration of 0.1 mg/mL was also considered clinically relevant due to its use as a cardiac resuscitation drug. Included studies reported epinephrine concentration at each time point as any of: (a) the percent of the labeled dose, based on manufacturer’s standards, (b) the relative percent of

the initial dose measured at the start of the study, or (c) the relative percent of a control dose. Included studies described storage of epinephrine in accordance with commercial manufacturer guidelines, which recommend 1 mg/mL epinephrine ampules, vials, and auto-injectors be stored at controlled room temperature (defined as 20 °C to 25 °C, with a mean kinetic temperature not more than 25 °C and excursions permitted between 15 and 30 °C) and protected from light [14–21]. Included studies contained epinephrine as the only active ingredient in the syringe (other than drug stabilizers, such as sodium bisulfite or sodium metabisulfite; simple buffers, such as hydrochloric acid; and salts such as sodium chloride); therefore, studies that tested a mixed solution of epinephrine and another active ingredient (e.g. lidocaine with epinephrine) were excluded. Studies were excluded if the epinephrine tested exceeded the expiration date prior to or during the course of the study.

One investigator (H.G.P.) reviewed all study titles and abstracts to identify potentially relevant studies. These resulting studies were reviewed by two investigators (H.G.P. and J.C.B.), who each read the full text independently to determine eligibility. The rationale for excluding each potentially relevant study was discussed to confirm consistent reasoning. Any discrepancies in inclusion were resolved through discussion. Data including measured epinephrine concentrations at each time point, results of statistical tests, notes on other degradation tests or solution appearance, results of sterility testing, sample sizes for each test, timing of each test, and characteristics of the epinephrine source, syringe and needle, syringe preparation conditions, and storage conditions were collected from each included study independently by two investigators (H.G.P. and J.C.B.). Any discrepancies in data collection were resolved through discussion and re-examination of the study. When relevant study details were missing from an included study, attempts were made to contact the corresponding author of the study to obtain these details. The concentration of epinephrine remaining at each time point was recorded for all studies as either the percentage of labeled dose of the test sample or the mean percentage relative to an initial dose, based on which information was available.

Results

Literature searches resulted in 209 studies from Medline, 396 studies from Embase, and 17 studies from Web of Science. Of these, 156 studies were duplicates between the databases, yielding 466 unique studies. There were 454 studies excluded on first review based on titles, abstracts, or articles that clearly indicated non-relevance, leaving six potentially relevant studies published in

English [11, 22–26] and six published in other languages. The six English language studies were then searched forward in Web of Science, yielding nine new studies. All nine were excluded on first review. The references of the six English language studies were then reviewed, yielding no additional relevant studies. The six potentially

relevant English articles underwent further review, and three of these studies were determined to be eligible for inclusion (Fig. 1) [11, 22, 24]. Of the three studies excluded at this stage, one was excluded because the epinephrine was stored in a continuously infusing syringe pump system rather than a simple syringe, which was

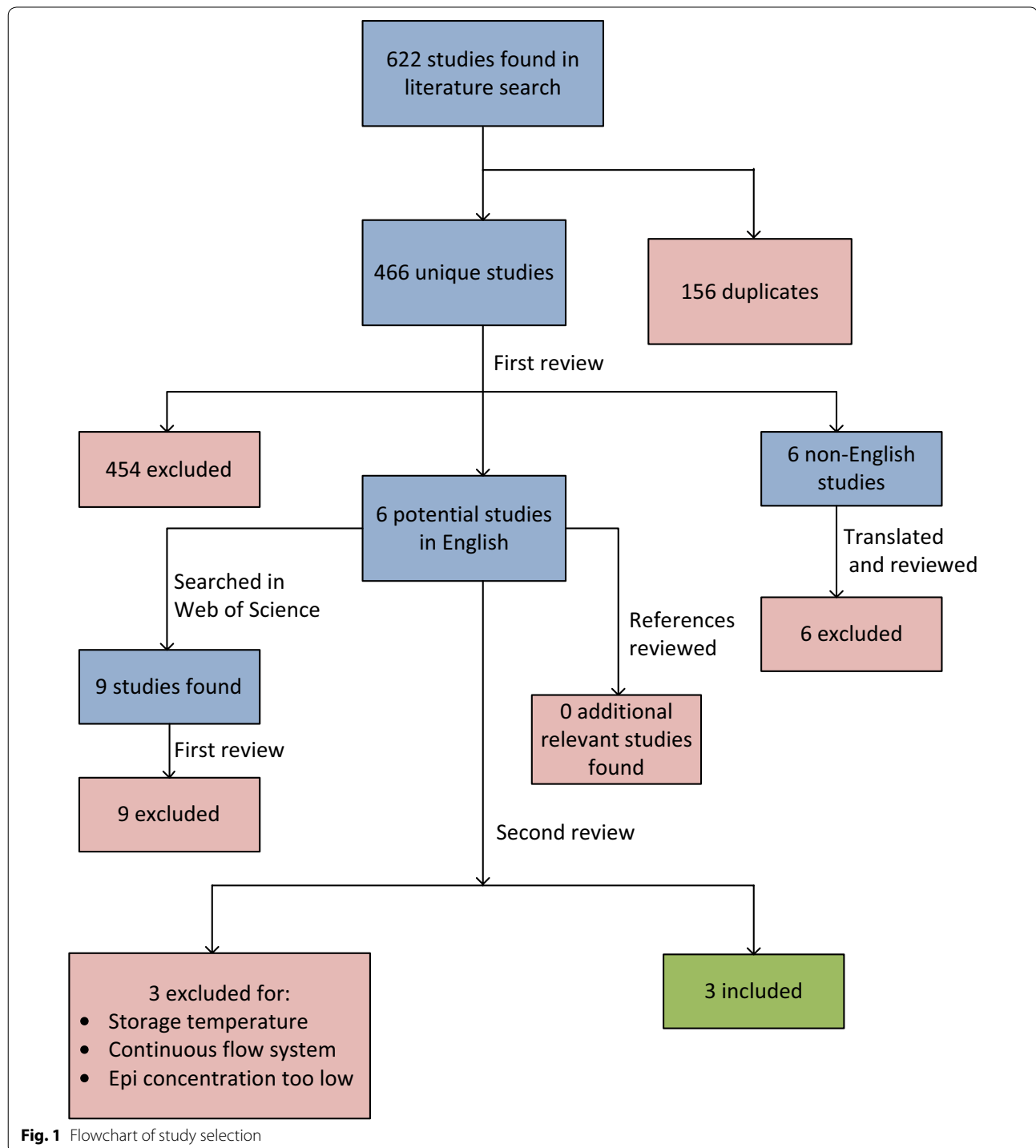


Fig. 1 Flowchart of study selection

excluded due to the mobile nature of that system [23]. Another study was excluded because the syringes were stored in incubators at 38 °C, which is well above the recommended storage range for epinephrine [25]. The third excluded study diluted the 1 mg/mL epinephrine to a 1 in 100 solution before storage in sterile plastic syringes, making the concentration of epinephrine stored too low for inclusion [26]. The six studies published in a different language (three in French [27–29], one in Dutch [30], one in Spanish [31], and one in Danish [32]) were translated from their respective languages into English using Google Translate and reviewed by two authors. None of these six studies were determined to be eligible for inclusion.

Ultimately, three studies were included in this review (Fig. 1) [11, 22, 24]. There were no differences to resolve regarding study eligibility or data abstraction. The characteristics of the included studies are shown in Table 1.

The three included studies tested the epinephrine samples for degradation after different storage times, as shown in Table 2. In all three studies, there were multiple study arms being compared. In two cases, one arm of the study met inclusion criteria but the other did not. When this occurred, the study was included and the excluded arm was presented in Table 2 in italics, for comparison purposes.

Only one study evaluated 1 mg/mL epinephrine, as would typically be used to treat anaphylaxis [24]. No significant epinephrine degradation was found in prefilled syringes at any time point up to the 3 months of storage studied.

One included study compared the stability of epinephrine stored in prefilled syringes between two different concentrations of epinephrine [22]. This study found that 0.7 mg/mL epinephrine remained stable for the 8-week duration of the study, whereas 0.1 mg/mL epinephrine showed clinically significant degradation by 14 days. The syringes were stored with 18G needles attached, which exposed the epinephrine in the needle to air during storage. Another included study evaluated 0.1 mg/mL epinephrine and found no clinically significant degradation at any point over the 24-week duration of the study [11]. In the latter study, the syringes were stored without needles, tightly sealed with a plastic cap, and protected inside a heat-sealed light-proof plastic pocket.

Two of the three included studies performed tests to determine the sterility of the prefilled syringe samples during the study period (Table 3) [11, 24]. Kerddonfak tested for gram-negative bacteria, gram-positive bacteria, and fungal cultures after 1, 2, and 3 months of storage and detected no growth in any sample, regardless of

whether the samples were prepared under a sterile laminar flow hood or in open air. In a few syringes, some brown particles were found at the needle cap after storage. These particles were cultured and found to be neither bacterial nor fungal, and were hypothesized to be from a reaction between epinephrine and the air at the needle cap. Zenoni performed particulate testing, limulus amebocyte lysate (LAL) testing for the presence of endotoxin, and visual inspection of the solutions at time zero and after 4 weeks (timing and methods verified by personal communication) and all tests were negative.

Discussion

The incidence of allergies and anaphylaxis continues to increase worldwide, especially among children [33]. Epinephrine is a critical life-saving therapy for anaphylaxis and must be readily available to those at risk in order to reduce morbidity and mortality [1]. EAI is the preferred administration method for epinephrine due to their relative ease of use and proven stability [1, 34]. EAI contains epinephrine in a sealed container that protects the drug from exposure to oxygen and light, allowing the epinephrine to remain pharmacologically stable for at least 1 year after the device is produced. Some studies have indicated that epinephrine stored in EAI may remain stable and clinically usable for much longer than 1 year, although results vary by device and between studies [35–37]. Auto-injector devices reduce errors by eliminating some of the variables of administering the drug, such as determining the correct dose [12, 38]. The EAI user does not have to see the needle prior to use, or be experienced in how to self-administer a medication using a needle and syringe, potentially reducing barriers to use [39].

The prospect of administering epinephrine safely without an EAI raises concerns among doctors and patient advocates, who believe it is more complicated to administer the correct dose safely using a syringe and needle [5]. However, patients and providers have had to consider this alternative in many parts of the world where EAI are unavailable or cost-prohibitive. As of 2007, auto-injectors containing 0.3 mg of epinephrine were officially available in only 39 countries worldwide (20% of the 195 countries) [3]. EAI with doses appropriate for infants were not available in any country at that time, although a 0.1 mg EAI with a shorter needle was recently marketed in the United States [40]. Even in areas where auto-injectors are distributed, they may not be accessible to all patients at risk of anaphylaxis. EAI are potentially cost-prohibitive, particularly in the United States, where escalating EAI costs, rising insurance deductibles for many patients, and varying coverage of EAI makes for a complicated system for consumers to

Table 1 Characteristics of included studies

Study	Epinephrine source concentration (mg/mL)	Epinephrine source container	Epinephrine source manufacturer and location	Storage syringe and needle type	Syringe manufacturer and location	Preparation/transfer conditions	Storage conditions	Varying conditions studied
Donnelly [22]	1	Ampule	Parke-Davis Limited; Scarborough, Ontario, Canada	10 mL sealed glass vial, or 10 mL plastic syringe with 18G needle attached and capped	Glass vials: Miles Incorporated; Spokane, Washington, United States Plastic syringes: Becton, Dickinson and Company (BD); Franklin Lakes, New Jersey, United States	Epinephrine diluted with sterile water to 0.1 mg/mL or 0.7 mg/mL before transfer to syringe or vial	Stored protected from light and at room temperature	Storage container: sealed glass vial vs plastic syringe with needle attached
Kerddonfak [24]	1	Ampule	Government Pharmaceutical Organization; Bangkok, Thailand	Disposable plastic 1 mL syringe with 23G needle attached and recapped	Nipro; Osaka, Japan	1 mL of epinephrine transferred into syringe under either laminar flow hood or open air, then air bubbles removed from syringe	Stored in pencil box to protect from light, storage at ambient room temperature (26±3 °C, measured at 8–9 a.m.)	Transfer conditions: laminar flow vs open air
Zenoni [11]	1	Ampule	Monico; Venice, Italy	1 mL Luer-lock polycarbonate latex-free syringe with no needle attached, sealed with a plastic cap	BD; Republic of Singapore	Epinephrine diluted with pyrogen-free water to 0.1 mg/mL and transferred into syringe in contamination controlled environment	Stored in heat-sealed light-proof plastic pocket, at room temperature (20–24 °C) or 2–8 °C	Storage temperature: 20–24 °C vs 2–8 °C

vs versus

Table 2 Stability of epinephrine in prefilled syringes

Study	Concentration of epinephrine (mg/mL)	Variable conditions	# of samples in study arm	Time period of storage (24 h days)	Mean percent of initial (or labeled ^a) dose remaining (%)	Significance test used	Significant degradation of epinephrine concentration? (yes/no)	Notes
Donnelly [22]	0.1	Stored in plastic syringe	4 ^b	7	96.0 ± 1.01	Clinical significance: < 90% of mean initial dose remaining	No	No other signs of degradation noted; all solutions remained clear and colorless; needles capped
			4 ^b	14	88.5 ± 1.29		Yes	
			4 ^b	28	86.2 ± 1.40		Yes	
			4 ^b	56	79.5 ± 2.06		Yes	
		Stored in glass vial	4 ^b	7	94.2 ± 2.60		No	
			4 ^b	14	87.4 ± 1.36		Yes	
			4 ^b	28	83.6 ± 1.22		Yes	
			4 ^b	56	76.7 ± 1.95		Yes	
	0.7	Stored in plastic syringe	4 ^b	7	98.5 ± 1.98		No	
			4 ^b	14	96.8 ± 1.38		No	
			4 ^b	28	94.0 ± 3.69		No	
			4 ^b	56	94.6 ± 6.47		No	
		Stored in glass vial	4 ^b	7	99.2 ± 0.27		No	
			4 ^b	14	98.3 ± 0.55		No	
			4 ^b	28	98.3 ± 1.06		No	
			4 ^b	56	97.8 ± 1.42		No	
Kerddonfak [24]	1	Prepared under laminar flow hood	20	30	101.40 ^a	Clinical significance: < 90% or > 110% of labelled dose remaining	No	No other signs of degradation noted in samples; norepinephrine not detected in any sample; brown particles found at needle cap in some syringes; solutions were pink-brown at 4 months
			20	60	102.68 ^a		No	
			20	90	101.19 ^a		No	
			20	30	101.36 ^a		No	
		Prepared in open air	20	60	99.31 ^a		No	
			20	90	101.09 ^a		No	
			20				No	
			20				No	

Table 2 (continued)

Study	Concentration of epinephrine (mg/mL)	Variable conditions	# of samples in study arm	Time period of storage (24 h days)	Mean percent of initial (or labeled ^a) dose remaining (%)	Significance test used	Significant degradation of epinephrine concentration? (yes/no)	Notes
Zenoni [11]	0.1	Storage at room temperature (20–24 °C)	2 ^c	7	90 ± 1.2	Statistical significance: one-way ANOVA; Clinical significance: < 90% of labelled dose remaining	Statistically yes (compared to refrigerated storage, p < 0.002); clinically no	No other signs of degradation noted: no degradation products detected, no changes in color or clarity visualized
			2 ^c	14	91 ± 0.3			
			2 ^c	28	91 ± 0.5			
			2 ^c	56	98 ± 0.5			
			2 ^c	168	96 ± 0.7			
		Storage at 2–8 °C	2 ^c	7	104 ± 0.1		No	
			2 ^c	14	105 ± 0.1			
			2 ^c	28	102 ± 1.0			
			2 ^c	56	110 ± 1.0			
			2 ^c	168	104 ± 3.8			

^a Study measured percent of manufacturer's labeled dose^b 4 samples were obtained from 2 syringes or vials tested in duplicate^c 2 samples were obtained from 1 syringe tested in duplicate

Table 3 Sterility of epinephrine in prefilled syringes

Study	Concentration of epinephrine (mg/mL)	Type of epinephrine container used	Total # of samples tested	Sterility tests performed	Testing methods	Time at which sterility tested	Results
Donnelly [22]	0.1	Plastic syringe	None	None	N/A	N/A	N/A
	0.7	Glass vial					
		Plastic syringe					
		Glass vial					
Kerddonfak [24]	1	1-mL disposable syringe, prepared under laminar flow hood	6 syringes (2 per time point)	Tests for gram-negative bacteria, gram-positive bacteria, and fungal cultures	Syringes (1 mL each) tested for bacteria on blood agar incubated at 35 °C in air and for fungal cultures on brain heart blood agar incubated at 37 °C and sabouraud dextrose agar incubated at 37 °C	At each time point (after 1, 2, and 3 months of storage) for both conditions	No aerobic bacterial or fungal growths in any sample
		1-mL disposable syringe, prepared in open air	6 syringes (2 per time point)				No aerobic bacterial or fungal growths in any sample
Zenoni [11]	0.1	1-mL polycarbonate syringes	6 syringes (2 at time zero, 2 stored at room temperature, and 2 stored at 2–8 °C)	Tests for sterility, absence of bacterial endotoxin, and the rate of particle contamination	Particulate test according to European Pharmacopeia, limulus amoebocyte lysate (LAL) test for the presence of endotoxin, visual examination of the solution	At time zero and after 4 weeks	All tests negative: bacterial contamination absent, endotoxin levels < 0.125 EU/mL, no visually detectable changes in color or clarity of solution, invisible particle count (< 10 µm and < 25 µm) below detectable limits

navigate successfully [41]. The use of a syringe and needle to deliver epinephrine is an inexpensive alternative in these cases [7] and also allows for customizable doses and needle lengths, which may benefit patients for whom the standard needle length of an auto-injector is too short (resulting in subcutaneous injection) or too long (resulting in injection into bone) [42]. However, a patient or caregiver may be unable to quickly and correctly draw up a dose of epinephrine during the stress and time constraints of an anaphylactic reaction [12, 43].

Prefilled syringes can be prepared in advance, either in clinic or in a pharmacy, for the patient to take home. Transferring epinephrine from an ampule or vial into the syringe potentially exposes the epinephrine to oxygen, which could accelerate degradation. The medication also potentially risks contamination during transfer. Although evidence is limited, the results of this systematic review suggest that epinephrine prefilled syringes, in concentrations typically used in anaphylaxis, appear to be a viable alternative to EAI. Under recommended storage conditions, 1 mg/mL epinephrine is stable in a syringe for at least 3 months [24] and 0.7 mg/mL epinephrine is stable in a syringe for at least 8 weeks [22]. An additional study by Rawas-Qalaji et al., excluded from this review based on prolonged high heat exposure, showed similar stability of epinephrine. In this study, syringes containing 1 mg/mL epinephrine and stored at 38 °C still delivered at least 90% of the label dose after 2 months of storage in low humidity or 3 months in high humidity [25]. These results are especially notable because high storage temperatures are expected to accelerate degradation of epinephrine compared to room temperature storage [44].

Donnelly's study was the only one which compared the stability between two different concentrations of epinephrine stored in prefilled syringes [22]. This study found that 0.7 mg/mL epinephrine remained stable for the full 8 weeks of the study, while 0.1 mg/mL epinephrine showed clinically significant degradation by 14 days. These results suggest that higher concentrations of epinephrine are more stable in syringes over time. The stability of 1 mg/mL epinephrine in Kerddonfak's study further supports this idea [24]. However, another study did not find any clinically significant degradation of 0.1 mg/mL epinephrine in prefilled syringes over 24 weeks [11], indicating that different storage conditions may have an impact on stability of epinephrine regardless of concentration.

Each study stored the epinephrine-filled syringes in a slightly different way, which may have contributed to the variation seen in the results. In Donnelly's study, in which the 0.1 mg/mL epinephrine samples demonstrated significant degradation past 7 days of storage, capped needles were attached to the epinephrine

prefilled syringes during storage. The needle allowed air exposure during storage that may have contributed to the degradation of epinephrine seen in this study [22]. In Zenoni's study, which also tested 0.1 mg/mL epinephrine, the syringes were stored without needles attached, sealed with a plastic cap, and kept inside a sealed, light-proof plastic container. In this study, no significant degradation of epinephrine was detected over 24 weeks of storage [11]. This more rigorous storage process may have reduced air exposure and minimized the impacts of light, moisture, and oxygen on the degradation of epinephrine.

Zenoni additionally compared storage of 0.1 mg/mL epinephrine at room temperature to storage in a refrigerator (2–8 °C) [11]. Storing epinephrine prefilled syringes at 2–8 °C resulted in significantly higher concentrations of epinephrine compared to the syringes stored at room temperature over the course of the 24-week study, although neither group showed clinically significant degradation (epinephrine concentration below 90%) by 24 weeks. Although epinephrine is recommended for storage at room temperature in the United States, studies on epinephrine stored in cold temperatures, including freezing, have found no significant degradation, even up to a full year of storage [44].

Neither of the two studies testing for bacterial growth [11, 24] nor the one study testing for fungal growth [24] identified any contamination. In addition, another study demonstrated that prefilled syringes containing 1 mg/mL epinephrine remained sterile after storage in contaminated soil, whereas epinephrine ampules, needles, and syringes stored separately in the same contaminated soil before combining them for use resulted in contamination of six out of 10 solutions [45]. Prefilled syringes may offer a more sterile solution in the community than providing an ampule, needle, and syringe. However, the testing performed in these studies was on a very limited number of samples (Table 3) and only up to 3 months of storage, and therefore cannot be extrapolated to the long-term sterility of all epinephrine syringes. Any prefilled syringes distributed to patients or used in the hospital setting would need to be properly tested for sterility as would be expected for a commercial product distributed under national guidelines.

The idea of using prefilled syringes to treat anaphylaxis is not new: a paper published in 1975 describes kits containing antihistamine tablets and a preloaded syringe of epinephrine available by prescription [46]. While an epinephrine prefilled syringe was recently approved by the United States Food and Drug Administration and brought to market in clinical settings [47], general inaccessibility of affordable epinephrine devices has led to "off-label" use of epinephrine prefilled syringes in many allergists' offices

of the United States (personal communication), and in community and hospital environments around the world. In countries where diluted (0.1 mg/mL) solutions of epinephrine are unavailable, stock epinephrine may be routinely diluted and stored in syringes as ready-to-use preparations in the hospital setting [11]. While there are United States Pharmacopeia standards for compounded medications allowing only 1–3 days of storage (depending on conditions) after compounding [48, 49], we are unaware of any industry standards specific to drawing up epinephrine or other medications without compounding or dilution, and intended for intramuscular use. There have been reports of infections associated with medications stored in syringes and then delivered intravenously [50], but we are unaware of any infections associated with intramuscular use of syringes. There has, however, been one reported Clostridial infection following an EpiPen injection in a thigh [14], suggesting that this potential exists.

Prefilled syringes are inexpensive and allow the provider to tailor the dose and needle length to meet the patient's needs. However, prefilled syringes might be most valuable in pre-hospital and hospital settings, where the high costs of EAI has resulted in increased use of epinephrine in syringes, most commonly drawn up from ampules or vials at the time of use [9, 10, 51]. Epinephrine prefilled syringes may be a better alternative to drawing up epinephrine at the time of need, as drawing up doses using an ampule and syringe under time pressure is prone to errors even among medical professionals [12]. Thus, stocking prefilled syringes in the medical setting, ideally with a range of weight-based doses, might minimize errors and potentially reduce the time taken to get epinephrine to a patient experiencing anaphylaxis. Storing resuscitation medications in color-coded prefilled syringes has been shown to reduce administration time and errors among emergency medical professionals [52].

To date, there is no definitive evidence to suggest how long 1 mg/mL epinephrine prefilled syringes are stable or sterile, as the current research has only indicated stability and sterility for up to 3 months. This potentially limited time to expiration may be problematic particularly in the community setting, where patients might not reliably change out their medication on time. Prefilled syringes also require protection from light exposure and must be stored in a container that prevents the syringe plunger from being unintentionally depressed prior to use, limitations that must be addressed before prefilled syringes can be a feasible storage mechanism for ready-to-use epinephrine.

Limitations of the research

In order to find every potential study, we did not limit the results of the literature search to English. We used Google

Translate to translate the six non-English studies found in the search. We did not verify that our translations were correct with someone fluent in each language, so we may have missed pertinent information from these six studies. However, we do not believe that this is probable, given that none of these studies appeared relevant or remotely likely to be eligible for inclusion in this review.

In one study, mean storage room temperatures measured between 8 and 9 a.m. were 26 ± 3 °C [24]. Daily temperatures could have exceeded recommended room temperature ranges (20–25 °C, with excursions allowed up to 30 °C but a 24-h mean of no more than 25 °C) [14–21]. Since no 24-h mean temperature was provided in the study or was available after personal communication with the author, we decided that we did not have sufficient evidence that the mean daily temperatures exceeded those allowed under manufacturer recommended storage temperatures, and concluded that this study was eligible for inclusion. Fortunately, the possible heat exposure in this study does not appear to have impacted study conclusions. If the epinephrine had been exposed to excessive heat during the study, it would have been expected to cause increased degradation of epinephrine, which was not seen.

All three of the authors we attempted to contact replied (Benjaponpitak, Invernizzi, Donnelly), and two (Invernizzi and Donnelly) were able to provide additional information. However, no study was excluded based on lack of information.

Only three studies were eligible for this systematic review, and only one eligible study tested epinephrine at the 1 mg/mL concentration that would be appropriate in an epinephrine prefilled syringe for use in anaphylaxis [24]. Only a small range of different syringe brands were tested; results could vary by syringe type and storage conditions. Only two studies tested samples for bacterial contamination and one for fungal contamination. One of these studies tested 12 syringes total [24] and the other tested 6 syringes total [11]. These small sample sizes may have been insufficient to detect rare contamination events. Therefore, the implications of this systematic review are limited due to the small number of relevant studies.

Conclusions

EAI is the preferred method for epinephrine administration during an anaphylactic event, and the ideal solution to their current inaccessibility is making the devices affordable and widely available in a range of doses and needle lengths that meet the needs of all patients with allergies. Epinephrine prefilled syringes for intramuscular delivery might offer an alternative when EAI is not an option. They might also have a

valuable role in prehospital and hospital care. Prefilled syringes have the potential to reduce dosing errors and decrease time to drug administration when compared with the traditional ampule, needle, and syringe method. Commercially-produced prefilled syringes may offer an even better alternative, if they remain affordable.

Syringes filled with 1 mg/mL epinephrine, the concentration typically used for anaphylaxis, have been shown by one study to be stable and sterile for at least 3 months [24]. One study has demonstrated that syringes containing 0.7 mg/mL epinephrine remain stable for at least 8 weeks [22], while the two studies examining 0.1 mg/mL epinephrine syringes show varied results [11, 22]. No study testing for sterility has found bacterial or fungal contamination of the prefilled syringes after storage for up to 3 months [11, 24], although this testing was limited to a small number of samples and may not reflect long-term sterility of all epinephrine prefilled syringes. More research is needed on the duration of stability and sterility of 1 mg/mL epinephrine prefilled syringes, as only one study thus far has examined this concentration of epinephrine that is relevant for the intramuscular treatment of anaphylaxis. If used, epinephrine prefilled syringes should be stored with sealed caps in light-blocking containers that prevent the syringe plungers from depressing, either at room temperature or refrigerated. They should be stored along with an appropriately sized needle in a sterile package, ideally along with alcohol swabs and gauze. As EAI's remain unaffordable and inaccessible for many patients, there may be an increasing place for these epinephrine prefilled syringes in the treatment of anaphylaxis.

Abbreviations

EAI: epinephrine auto-injector; EMS: emergency medical services.

Authors' contributions

HP reviewed all study titles and abstracts, reviewed full studies for inclusion, extracted data, and wrote the manuscript. JM performed the literature search to retrieve articles for review. JB reviewed studies for inclusion, extracted data, and assisted in writing and revising the manuscript. All authors read and approved the final manuscript.

Authors' information

HP has a Bachelor of Science in Biology and Public Health and is a Research Assistant at Seattle Children's Hospital. She has previously published a systematic review on epinephrine exposed to temperatures outside of the recommended range as first author. She has an additional work-in-progress on epinephrine auto-injector injuries reported to the Washington Poison Center.

JM is a Librarian at Seattle Children's Hospital. She is a skilled information specialist with over 30 years of experience in searching the biomedical literature databases to support patient safety, research, and publication in both health care delivery systems and the pharmaceutical industry.

JB is Co-Director of research for the Division of Emergency Medicine at Seattle Children's Hospital and is experienced in clinical research. She is/has been the lead investigator in a number of pediatric emergency department clinical studies. She is the 1st author on 13 peer-reviewed articles and 4 book chapters covering topics relative to pediatric emergency practice, most recently focusing on anaphylaxis and the use of auto-injectors. She has many

additional works-in-progress, including the development and validation of a new clinical score for anaphylaxis. She led a multi-disciplinary team at her hospital through a rigorous clinical standard work process to standardize and improve anaphylaxis care. She was recently accepted for membership to the American Academy of Asthma, Allergy and Immunology. She actively pursues social media avenues for education and research, including Pinterest pages (324 followers) which focus on allergies and auto-injectors, the creation of over two dozen YouTube videos about epinephrine auto-injectors (over 380,000 views), and Twitter posts (nearly 1000 mostly allergy parent, allergist, and emergency provider followers). She uses social media as a platform to improve emergency care of anaphylaxis, and to lobby for improved epinephrine auto-injector quality, affordability, and access.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

This review is a secondary analysis of data from other studies. When needed, corresponding authors were contacted for additional information as described in the study methods. The data that support the findings of this article are available from the respective corresponding author of each included study.

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Expired Epinephrine Maintains Chemical Concentration and Sterility

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EXPIRED EPINEPHRINE MAINTAINS CHEMICAL CONCENTRATION AND STERILITY

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ABSTRACT

Objectives: Epinephrine shortages affect nearly all American emergency medical services (EMS) systems. Utilization of expired epinephrine could mitigate this situation in daily EMS operations. Concerns about using expired medications include sterility, potency, and potential harmful chemical decay byproducts. There are no cross-platform analyses of sterility and chemical purity of multiple samples of expired parenteral epinephrine. We hypothesized that epinephrine injections will remain sterile and will retain their active ingredient's content for more than 30 months past expiration. **Methods:** Six parenteral epinephrine prefilled syringes, 1 mg/10 mL, with an expiration date of January 1, 2012 had been stored in the climate controlled setting of a hospital inpatient pharmacy where they remained until they were taken for chemical or microbial analysis 30 months after expiration. An unexpired parenteral epinephrine prefilled syringe content was used as a control. Contents of three separate syringes with expired content from the same lot and one control underwent ultra-high pressure liquid chromatography-mass spectrometry (UHPLC-MS) and nuclear magnetic resonance (NMR) to determine epinephrine content and stability. In parallel, contents of another three expired epinephrine syringes were analyzed for sterility by plating on aerobic, anaerobic, and fungal media in a hospital microbiology laboratory. The aerobic plates were checked for growth in 3 days, the anaerobic

in 5 days, and the fungal in 28 days. **Results:** UHPLC-MS and NMR showed that content of epinephrine present in the original sample remained unchanged compared to the control. There was no statistical difference in the UHPLC-MS and NMR signal amplitudes between the control and the expired samples. No chemical degradation byproducts were detected using NMR. There was no growth of any bacteria or fungus. **Conclusion:** Recurrent epinephrine shortages impact EMS and hospital operations in the United States. Individual administrators may be hesitant to authorize use of expired pharmaceuticals due to perceived potential complications or fear of litigation. This study shows that the original parenteral epinephrine remains sterile and detectably pure more than 2.5 years after expiration. Further study of the sterility and chemical integrity of expired medications that had been subjected to the conditions of EMS vehicles may be a future research endeavor based on the aforementioned paradigm. **Key words:** expired epinephrine; sterility; chemical concentration

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INTRODUCTION

Medication shortages have become increasingly problematic over the last decade. Following a maximum of 267 new shortages in 2011, there has been an average of 180 new drug shortages annually through 2015. Within that same time period, there have been up to 320 active drug shortages per quarter (1). While certain drug shortages have been more severe than others in extent and duration, impact on patient care is the greatest concern. For example, many shortages affect medications that primarily treat non-acute diseases. Other shortages pertain to therapies utilized to manage lower complexity disease states or less critical symptoms. Beyond those considerations, in many shortage situations there have been pharmacotherapeutic alternatives that have allowed for patient care to proceed with minimal or no compromise.

The most concerning shortages involve medications utilized for acute, critical conditions where alternate therapies with equivalent efficacy, safety, or clinical experience are not available. An example of this is parenteral epinephrine for the treatment of anaphylaxis or cardiac arrest (2,3). Also complicating the case of epinephrine are the various formulations available, intended for emergent administration by healthcare personnel or ease of administration by

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patients and family members (i.e., prefilled syringes, automatic injection devices, etc.). Situations may arise when epinephrine is available, but not in an optimal formulation for critical therapeutic contexts. We therefore decided to examine the stability of expired injectable epinephrine. If there were a future significant shortage of injectable epinephrine, the overall risk-versus-benefit ratio at that time could shift such that administration of expired product may be more prudent than denying a patient life-saving therapy. If such a shortage were to occur, knowing the extent of the physiochemical and microbiological stability of epinephrine could be of high value.

METHODS

Materials

Six epinephrine prefilled 1 mg/10 mL syringes (McKesson Packaging Services Business Unit of McKesson Corporation) from the same batch, with an expiration date of January 1, 2012, were stored at room temperature in a climate-controlled setting at the Carle Foundation Hospital inpatient pharmacy. In July 2014, which was 30 months after expiration and 48 months after production, three of each were submitted to the Carle Foundation Hospital microbiology laboratory and the University of Illinois at Urbana-Champaign chemistry laboratories. Each medication package was intact and the epinephrine solution within the syringes was clear and colorless. One epinephrine prefilled 1 mg/10 mL syringe, with an expiration date of August 1, 2015, was used as a controlled comparator solution for the chemical analysis. All epinephrine samples were purchased from Sigma-Aldrich Corporation (St. Louis, Missouri).

Sample Preparation

For UHPLC-MS, a standard epinephrine stock solution was first prepared in dimethyl sulfoxide (DMSO) at 200 mg/mL of epinephrine. The as a stock solution was and serially diluted into concentrations (0.05–1.00 µg/mL) with solvent A (95/5 Acetonitrile/50 mM Ammonium Acetate). Expired epinephrine samples were diluted into 1 µg/mL with solvent A. Standard addition method was used to build the calibration curve in which samples were spiked with standard solution at various concentrations. Each sample was mixed thoroughly on a vortex between dilutions. Finally, 4 µL of solution was loaded on the system for measurement and six duplicate measurements were carried out for each solution. For NMR experiments, the epinephrine solution samples were used without any dilution.

Chemical Analysis

UHPLC-MS

Epinephrine was measured by UHPLC-MS and NMR. The EVOQ ultra-high performance liquid chromatography mass spectrometer (UHPLC-MS) system equipped with a hydrophilic interaction liquid chromatography (HILIC) column (100 × 2.1 mm, 2.6 mm) on-line hyphenated to EVOQ triple quad mass spectrometer (all Bruker Daltonics) was used for analyte separation and detection. HPLC solvent A is 95/5 Acetonitrile/50 mM Ammonium Acetate pH 4, and solvent B is 50/40/10 Acetonitrile/water/50 mM Ammonium Acetate pH 4. Multiple reaction monitoring (MRM) in positive mode was used to analyze all solutions. Epinephrine-containing solutions were analyzed with multiple reaction monitoring (MRM) approach using heated electrospray ionization conducted in positive mode. Electrospray voltage was set to +4500V, cone and heated probe temperature were 150°C and 450°C, respectively. Cone gas flow and probe gas flow were 10 and 15, respectively. Nebulizer gas flow was 60. Three transitions are monitored – m/z 184.2 → 79.4 as quantifier, 184.2 → 166 and 184.2 → 150.9 as qualifiers. Information on epinephrine signal area is collected and statistically processed using Microsoft Excel with mean and standard deviation for six independent measurements of each sample presented. Multiple reaction monitoring (MRM) in positive mode was used to analyze all solutions.

¹H-NMR

The Agilent VNMRS 750 MHz spectrometer with a 5 mm indirect-detection probe equipped with X,Y,Z-gradient capability was used for structural and quantitative analysis of epinephrine solutions. A total of 128 scans were used, each with a 60 degree pulse angle and 4.7 second repetition time between scans. A continuous low power (2 s) helped to saturate the water signal. The chemical shifts were referenced to water peak at 5.01 ppm. The proton spectra of three expired epinephrine solution and one control epinephrine solution samples in their native buffer condition (citric acid and sodium citrate) were collected at 4°C. The proton spectrum of the epinephrine standard (0.2 mg/mL) in deuterated dimethyl sulfoxide (DMSO) was conducted at 25°C. Sample concentrations were calculated by comparing the integration values of epinephrine solution samples with those of the epinephrine standard.

Microbiological Analysis

Using standard clinical microbiology laboratory techniques, 0.5 mL of epinephrine from each of three

expired prefilled syringes was plated onto standard aerobic, anaerobic, and fungal culture media. These cultures were maintained in the microbiology laboratory under appropriate temperature and atmospheric conditions for the culture type. Culture media were examined for growth daily for 3 days for aerobic bacteria, daily for 5 days for anaerobic bacteria, and weekly up to 28 days for fungi.

RESULTS

UHPLC-MS detected strong signals for all measured epinephrine transitions with good linearity of the calibration curve in 0–5 ppm range. Samples were diluted to achieve the best concentration for quantitation. Epinephrine concentrations (mean \pm standard deviation) determined in the expired samples 1–3 were 0.09 ± 0.02 mg/mL, 0.11 ± 0.02 mg/mL, and 0.10 ± 0.02 mg/mL, respectively, and concentration of unexpired epinephrine was 0.11 ± 0.04 mg/mL (Figure 1). No significant difference between data points was observed when technical replicates were taken into account.

^1H -NMR detected six signals attributed to epinephrine in analyzed samples (Figure 2). One peak was under the water signal and was detected by two-dimensional correlation spectroscopy (2D COSY). The signals are consistent with the ^1H spectrum of epinephrine in the Human Metabolome Database (HMDB, http://www.hmdb.ca/spectra/nmr_one_d/1066). Peaks with chemical shifts of 2.71, 3.27, 4.94, 6.84, 6.93, and 6.94 ppm were observed. The two large peaks at 2.64 and 2.78 in our samples that are not present in HMDB were from the citric buffer (epinephrine in HMDB was in water). Therefore, for quantitative analyzes and as confirmation of our ability to detect epinephrine samples of compound's standard, expired, and current epinephrine injections are compared. Epinephrine concentrations measured by ^1H -NMR for the expired samples 1–3 were 0.088 mg/mL, 0.090 mg/mL, and 0.090 mg/mL, respectively, and

concentration of unexpired epinephrine sample was 0.090 mg/mL. Expired and control epinephrine samples have the same NMR spectral profiles. (Figure 2). Absence of new significant peaks or disappearance of observed ones in NMR spectra indicates stability of the compound and formulation. No norepinephrine or metanephrine was detected. However, differences in data acquisition temperature and chemical matrix (DMSO vs. water-containing buffer) between the samples and the standard likely resulted in small underestimation of epinephrine concentration.

Microbiological analysis revealed no growth of any organisms. A certified microbiology technician and a Pathologist determined there was no growth of aerobic bacteria after 3 days, no growth of anaerobic bacteria after 5 days, and no fungal growth after 28 days.

DISCUSSION

The use of expired medications has understandably been avoided. However, given the current shortages of critical resuscitation medications for which no proven substitute exists, the use of expired medications may be necessary. Epinephrine is a critical medication for treatment of anaphylaxis and for cardiac arrest resuscitation. Verified extension of expiration dates for medications may play a crucial role in alleviation of shortages. This study is the first to perform bioanalytical confirmations of preservation of active ingredients with parallel verification of sterility post expiration. Our study analyzed prefilled epinephrine that had been in the controlled environment of an inpatient pharmacy. The expiration date set by drug manufacturers is purposefully a conservative estimate of the product's stability (4,5).

Other studies have evaluated the chemical concentrations of EMS medications for a variety of environmental conditions such as sunlight, vibration, and temperature extremes. Many EMS medications were evaluated including atropine, ondansetron, hydro-morphone, diphenhydramine, fentanyl, midazolam, morphine, naloxone, tranexamic acid, diazepam, lorazepam, and midazolam (6–9). Results from Armenian et al. demonstrated different stability and sensitivity of the drugs to environmental factors with atropine be most unstable, becoming undetectable after 4 weeks of exposure to heat (6). Epinephrine degradation was also studied demonstrating relative stability of the compound at different conditions and concentrations (10–14). For example, 64% of the drug was degraded after 12 week regiment of elevated temperatures at lower concentration but no changes are noted in more concentrated solution (11). Not only environmental factors but composition of epinephrine formulations including pH and presence of different preservatives/stabilizers influences stability

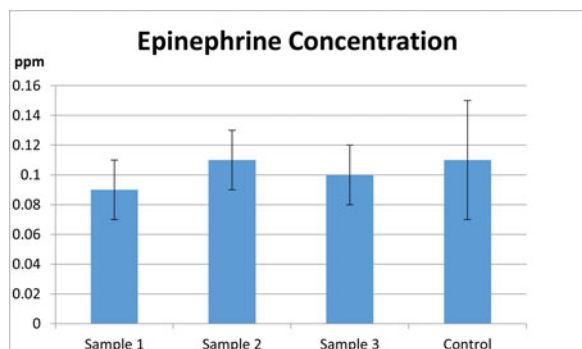


FIGURE 1. UHPLC-MS epinephrine concentration results for samples 1–3 and control.

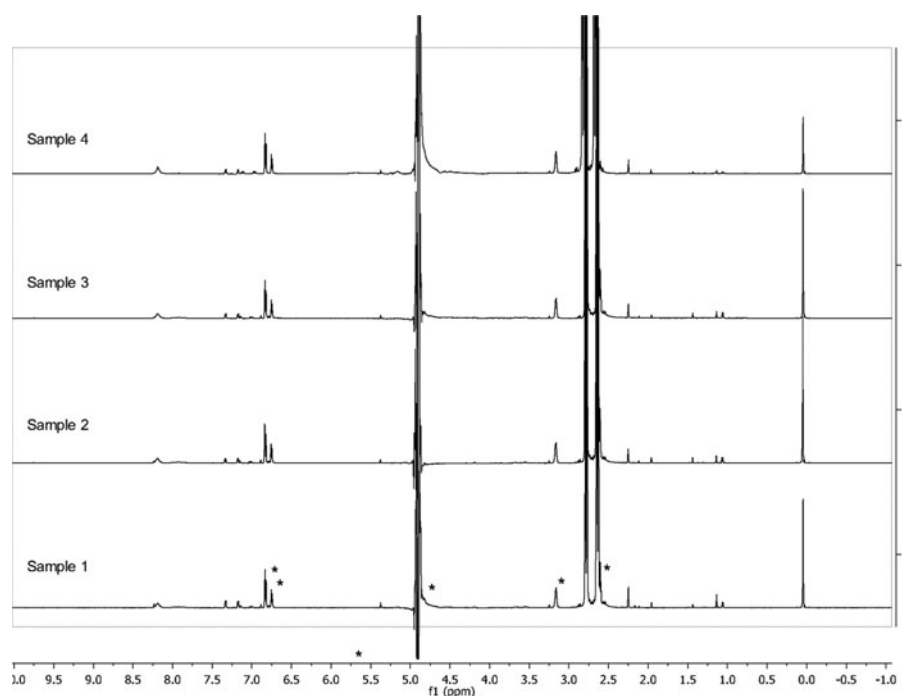


FIGURE 2. ^1H -NMR spectra of samples 1–3 and control (sample 4). The * refers to the peaks from epinephrine. The peak at 4.94 ppm under water was detected by 2D COSY spectrum (homonuclear correlation spectroscopy).

of the drug (13, 15–18). These results indicate that epinephrine can be classified as a thermo-labile drug in certain formulations (6–9).

The demand for epinephrine is increasing as it appears that the incidence of anaphylaxis is increasing (19). States are expanding scope of practice to allow EMT-Basics to inject epinephrine for anaphylaxis (19). Some states require school staff and law enforcement officers to administer epinephrine. Other states, like Illinois, are mandating training of police to recognize anaphylaxis with the option to administer epinephrine. Price increases follow the increasing demand for epinephrine as supply may be limited. When faced with a shortage, temporary authorization of expired medication may not be unsafe and may be preferable to death or disability from a critical illness such as anaphylaxis or cardiac arrest. Furthermore, the increased prevalence of epinephrine in schools and among law enforcement officers may increase the likelihood that an emergency responder or a lay person is faced with using an expired medication or not treating a potentially deadly illness. We believe this research shows there is some reasonable expectation that expired parenteral epinephrine maintains chemical stability and sterility many months beyond its labeled expiration date.

Our results are consistent with the majority of previously published data on epinephrine dosages stability (10) where epinephrine content demonstrated preservation for more than 8,500 hours at 40°C at laboratory settings (20). As our results

show, stability of injectable epinephrine for 2.5 years beyond expiration date provides compelling evidence that the safe shelf life for prefilled syringes may extend well beyond the date listed by the manufacturer.

Our data have additional support from results of the Shelf Life Extension Program (SLEP), which has also shown that many medications are viable past their labeled expiration dates (5). The SLEP is a federal program to extend the expiration date of medications for use by the Department of Defense and the Strategic National Stockpile by routinely testing samples from the appropriate medication lots. Over 50% of the medications tested by the SLEP have their expiration date extended by at least a year but the program has found a significant amount of lot-to-lot variability for any specific medication (5).

Private entities are currently not allowed to participate in the SLEP and the data collected by the program is not readily available for public use, which justifies studies such as ours to further evaluate the potential role of expired medications. Strengths of our study include the use of multiple samples and testing in independent certified laboratories. A limitation of our study is that the medications were stored under ideal conditions within the hospital. Others have reported that conditions in EMS vehicles frequently deviate from recommended storage conditions, which complicates direct application of these results to expired medications that were stored within EMS vehicles (21–23). This presents an opportunity for future

research using expired medications that were subjected to the real-world environment of prehospital medicine.

CONCLUSION

This study shows expired epinephrine maintains chemical purity and sterility more than 30 months after the manufacturer's listed expiration date. Therefore, if there were a future significant shortage of injectable epinephrine, the overall risk-versus-benefit ratio at that time could shift such that administration of expired product may be more prudent than denying a patient life-saving therapy.

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