



A systematic review of epinephrine degradation with exposure to excessive heat or cold

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ABSTRACT

Background: Epinephrine is a lifesaving drug in the treatment of anaphylaxis and cardiac resuscitation. Current US storage recommendations are for controlled room temperature (20°C–25°C), with excursions permitted from 15°C to 30°C. Maintaining epinephrine within this required range is challenging, particularly for patients carrying autoinjectors and during storage in emergency vehicles.

Objective: To study epinephrine degradation with extreme temperature exposure for epinephrine concentrations used in anaphylaxis and cardiac resuscitation.

Methods: We searched the literature for all studies of epinephrine in sealed syringes, vials, or ampules in concentrations between 1:1,000 and 1:10,000, that measured epinephrine in samples exposed to temperatures above and/or below the recommended storage temperature compared with control samples.

Results: Nine studies were included. Heat exposure resulted in epinephrine degradation but only with prolonged exposure. Constant heat resulted in more degradation. None of the studies that evaluated epinephrine exposure to extreme cold found significant degradation. None of the studies evaluating the effects of real-world temperature fluctuations detected significant degradation. Only 2 small studies (1 evaluating heat and 1 freezing) involved autoinjectors, and all 40 devices tested fired correctly.

Conclusion: Temperature excursions in real-world conditions may be less detrimental than previously suggested. Freezing and limited heat excursions did not result in epinephrine degradation. Refrigeration of epinephrine appears to reduce degradation. However, the effect of extreme temperatures, particularly freezing, on autoinjectors is not sufficiently well established. More research is needed at clinically relevant high temperatures, with limited exposure to heat, and involving autoinjector devices.

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Introduction

Epinephrine is a lifesaving medication for the treatment of anaphylaxis.¹ Individuals with known food or insect sting allergies must have fully functional epinephrine autoinjectors (EAI) with them at all times so that they can receive treatment as soon as possible should they have an anaphylactic reaction. According to prescribing information available from the EAI manufacturers, all EAI available in the United States and Canada must be kept at room temperatures to remain fully functional. However, in many regions these temperature requirements are difficult to follow, especially during hot summer or cold winter months. This systematic review was performed to identify and

evaluate all published studies on the stability of epinephrine under extreme temperature conditions.

Methods

A thorough search of the literature was performed. The databases Ovid, PubMed, and Embase were searched for the keywords *epinephrine* and *adrenaline* in combination with the keywords *drug packaging*, *drug stability* or *drug storage*, *temperature*, *cold temperature*, *freezing*, *hot temperature*, *transition temperature*, *time*, *time factors*, *autoinjector*, *auto injector*, *EpiPen*, *Auvi-Q*, *Allerject*, *Anapen*, *Twinject*, *Adrenaclick*, and *intramuscular injections*. Searches were limited to articles published from January 1990 through July 2015. In addition, the National Guideline Clearinghouse was searched for the terms *epinephrine* and *adrenaline*. The titles and abstracts of all studies found were reviewed, and for all potentially relevant studies, the article was reviewed in full. Potentially relevant articles in other languages

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were translated into English using Google Translate. In addition, all included studies were searched forward in Web of Science to find newer sources in which the original ones were cited. The references of all included studies were also reviewed to search for additional relevant studies.

Inclusion Criteria

We included all studies that evaluated epinephrine in concentrations between 1:1,000 and 1:10,000, provided the samples remained in a sealed glass container as sold by the manufacturer, whether inside an EAI, vial, ampule, or factory-sealed syringe. Although EAI's currently marketed in North America are only available in 2 concentrations, Pharmacopeia (USP) 1:1,000 (1 mg/mL) for use in adults and children who weigh 30 kg or more and a USP 1:2,000 concentration (0.5 mg/mL) for use in children who weigh 15 to 30 kg, we also included studies of epinephrine as dilute as 1:10,000, which is the concentration used for cardiac resuscitation. Because we anticipated possible variation of results by concentration, studies for each concentration of epinephrine were analyzed separately. We included all studies in which the temperatures studied exceeded the excursion limits of the recommended storage range of epinephrine, based on prescribing information, and could be compared with control samples maintained within recommended room temperatures ranges during the same study period. We included studies in which temperature was the only variable that affected the degradation of epinephrine (other than the slight degradation expected with the passage of time), in which the epinephrine concentration after exposure was reported as the percentage of the control dose, or in which this outcome measure could be calculated from reported data. Additional inclusion criteria were that epinephrine was the only active ingredient in the vial, ampule, or syringe (other than drug stabilizers, such as sodium bisulfite or sodium metabisulfite; simple buffers, such as hydrochloric acid; and salts such as sodium chloride). Exclusion criteria were that the concentration of epinephrine was unknown or not reported, the study tested a mixed solution of epinephrine and another active ingredient (eg, lidocaine with epinephrine), the epinephrine expired before or during the study, the epinephrine was drawn up from the original container into a new vial or syringe (potentially exposing it to oxygen, which also contributes to epinephrine degradation), or there was concomitant exposure of the epinephrine to air, light, or pressure, in addition to heat.

One author (H.G.P.) reviewed all study titles and abstracts to identify potentially relevant studies. These studies were reviewed by 2 authors (H.G.P. and J.C.B.) independently to determine eligibility. Any discrepancies were resolved through discussion. For studies in which inclusion was dependent on information missing from the published report, attempts were made to contact the study authors.

Data were collected from the included studies independently by 2 researchers. Any discrepancies were resolved through discussion. When relevant study details were missing from included studies, attempts were made to contact the respective authors of these studies to obtain these details. When the percentage or concentration of epinephrine remaining was unspecified but presented graphically and the study's authors could not be reached or could not provide additional information, the values were estimated from the graphs provided.

The concentration of epinephrine remaining could be obtained for all studies as a mean percentage relative to the control dose. When this was not reported by the study authors, it was calculated by dividing the percentage of labeled dose of the test sample by the percentage of labeled dose of the control sample.

Results

Searches using Ovid, PubMed, and Embase resulted in 378 total studies, including 46 duplicates. Of the 332 studies initially identified, 315 were excluded on first review by one author based on titles, abstracts, or articles that clearly indicated nonrelevance, leaving 17 potentially relevant studies.^{2–18} One additional study was found as a result of communication with experts in the field.¹⁹ These 18 potentially relevant articles underwent further review by both authors, and 7 of these studies were determined to be eligible for inclusion.^{2–7,19} These 7 eligible studies were then searched forward in Web of Science, yielding 26 new studies. Of these, 24 were excluded on first review by one author and 2 were further reviewed by both authors,^{20,21} resulting in the inclusion of 1 additional study.²⁰ Two authors then reviewed the references of the 8 included studies, which yielded 3 more potentially relevant studies.^{22–24} These were reviewed by both authors, and 1 more study was included.²³ The 2 studies found through Web of Science and their references were also searched forward in Web of Science, yielding no additional relevant studies. The National Guideline Clearinghouse search yielded 43 studies, none of which was considered relevant on first review. Ultimately, 9 studies were determined to be eligible for inclusion in this systematic review (Fig 1).^{2–7,19,20,23}

Three potentially eligible studies were published in German.^{22–24} These articles were translated from German to English using Google translate, and an additional physician author bilingual in English and German and medically trained in Germany (C.S.B.) joined the research team to assist with review of these articles. Three authors (H.G.P., J.C.B., and C.S.B.) assessed these studies for eligibility and abstracted the data. One German study was determined to be eligible for inclusion.⁶ There were no differences to resolve regarding study eligibility or data abstraction.

Three studies evaluated epinephrine 1:1,000 exposed to heat, with varying amounts of degradation relative to the control (Table 1). The samples were exposed to at least 100 hours of heat, either at a very high temperature (70°C) or for a prolonged period

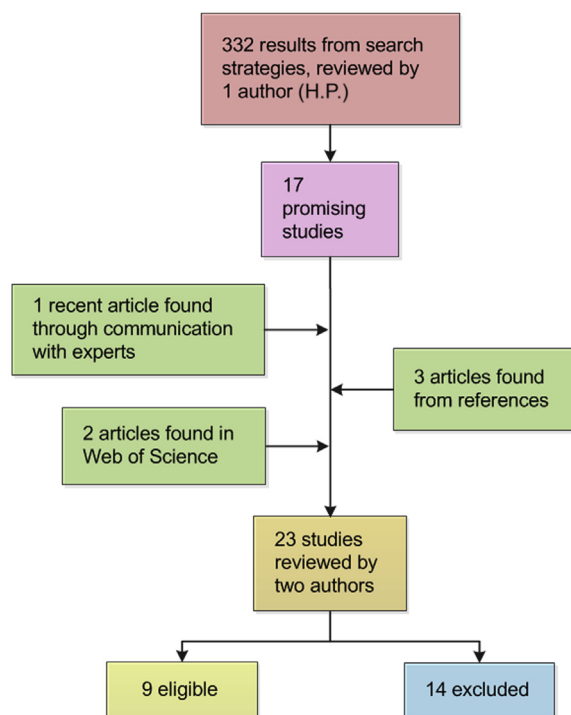


Figure 1. Flowchart of Study Selection.

Table 1

Exposure of Epinephrine 1:1,000 to Heat

Study	Type of epinephrine container used	Environment	Temperature tested, °C	Constant/cyclical; cycle of heating periods	No. of samples in study arm	Period of exposure (24-hour days)	Total duration of temperature exposure, h	Mean control dose remaining, %	Significance test used	Significant degradation of epinephrine concentration	Other signs of degradation noted
Grant et al, ² 1994	Ampules	Laboratory	70	Cyclical; 6 h heated, 2 h left to cool, 16 h room temperature	5	28	224		One-way ANOVA and comparison of individual means using the Tukey test ($P < .05$ significant)	No	No discoloration or precipitation
	Ampules	Laboratory	70	Cyclical; 6 h heated, 2 h left to cool, 16 h room temperature	5	56	448			No	No discoloration or precipitation
	Ampules	Laboratory	70	Cyclical; 6 h heated, 2 h left to cool, 16 h room temperature	5	84	672			No	Increase in concentration of degradation product; no discoloration or precipitation
Zeisel et al, ²³ 1998	Ampules	Laboratory	40	Constant	20	365	8,760	93.4	Statistical significance: nonparametric Mann-Whitney and Kruskal-Wallis tests ($P < .05$ significant, $P < .01$ highly significant); clinical significance: <90% of labeled dose remaining	Highly statistically significant but not clinically significant per the study author	
Rachid et al, ¹⁹ 2015	Epinephrine autoinjectors (EpiPens 0.3 mg)	Laboratory	70	Cyclical; 20 h heated, 4 h room temperature	5	5	100	81.9	ANOVA and comparison of individual means using the Tukey test ($P < .05$ significant)	Yes	For all study arms: no discoloration or precipitates on visual inspection, no metabolites detected on chiral analysis
	Epinephrine autoinjectors (EpiPens 0.3 mg)	Laboratory	70	Cyclical; 20 h heated, 4 h room temperature	5	5	100	81.1		Yes	
	Epinephrine autoinjectors (EpiPens 0.3 mg)	Laboratory	70	Constant	5	5	120	76.4		Yes	
	Epinephrine autoinjectors (EpiPens 0.3 mg)	Laboratory	70	Constant	5	10	240	60.4		Yes	

Abbreviation: ANOVA, analysis of variance.

Table 2
Exposure of Epinephrine 1:10,000 to Heat

Study	Type of epinephrine container used	Environment	Temperature tested, °C	Constant/cyclical; cycle of heating periods	No. of samples in study arm	Period of exposure (24-hour days)	Total duration of temperature exposure, h	Mean control dose remaining, %	Significance test used	Significant degradation of epinephrine concentration	Other signs of degradation noted
Johansen et al, ³ 1993	Abboject syringe	Laboratory	70	Cyclical; 4 h heated, 2 h room temperature, 4 h heated, 14 h room temperature	3	2	16	98.9 (est)	One-way ANOVA ($P < .05$ significant)	No	No significant difference in chemical structure
Church et al, ⁴ 1994	USP injectable cartridges	Laboratory	65 (range, 63–68)	Cyclical; 8 h heated, 16 h room temperature	...	3	24	124 (est)	...	...	Epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (range, 63–68)	Cyclical; 8 h heated, 16 h room temperature	...	7	56	77.4 (est)	...	...	Epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (range, 63–68)	Cyclical; 8 h heated, 16 h room temperature	...	9	72	72 (est)	...	...	Epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (range, 63–68)	Cyclical; 8 h heated, 16 h room temperature	...	12	96	40 (est)	...	...	Epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (range, 63–68)	Cyclical; 8 h heated, 16 h room temperature	...	21	168	43	...	...	Epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (range, 63–68)	Cyclical; 8 h heated, 16 h room temperature	...	28	224	65.5 (est)	...	...	Epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (range, 63–68)	Cyclical; 8 h heated, 16 h room temperature	...	84	672	31	...	...	Epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (range, 63–68)	Constant	...	1	24	90 (est)	...	...	Epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (range, 63–68)	Constant	...	3	72	46 (est)	...	...	Dark brown discoloration (adrenochrome); epinephrine sulfonic acid
	USP injectable cartridges	Laboratory	65 (63–68)	Constant	...	4	96	10 (est)	...	...	Dark brown discoloration (adrenochrome); epinephrine sulfonic acid
Grant et al, ² 1994	Carpject syringes	Laboratory	70	Cyclical; 6 h heated, 2 h left to cool, 16 h room temp	5	28	224	88 (est)	ANOVA and comparison of individual means using the Tukey test ($P < .05$ significant)	No	No discoloration or precipitation
	Carpject syringes	Laboratory	70	Cyclical; 6 h heated, 2 h left to cool, 16 h room temperature	5	56	448	53 (est)		Yes	Decreased strength of BP increase in rats; no discoloration or precipitation
	Carpject syringes	Laboratory	70	Cyclical; 6 h heated, 2 h left to cool, 16 h room temperature	5	84	672	36		Yes	Decreased strength of BP increase in rats; no discoloration or precipitation
Gill et al, ⁵ 2004	Autoinjector-style syringes	Laboratory	Varies; half of sites exceeded 40, total range from 6.5 to 52 ^a	Varied based on field conditions	3 per location ^a	5, 10, 15, 30, or 45	Varies ^a	From 94 to 103 ^a	Drug defined as stable if remaining concentration >90% of original concentration without color changes or precipitation	No	No color change, precipitation, or turbidity

Abbreviations: ANOVA, analysis of variance; BP, blood pressure; est, estimated.

^aEpinephrine was stored in Advanced Life Support vehicles and exposed to natural heating cycles. Fifteen locations were studied, including a laboratory control.

Table 3
Exposure of Epinephrine 1:1,000 to Cold

Study	Type of epinephrine container used	Environment	Temperature tested, °C	Constant/cyclical; cycle of cooling periods	No. of samples in study arm	Period of exposure (24-hour days)	Total duration of temperature exposure, h	Mean control dose remaining, %	Significance test used	Significant degradation of epinephrine concentration	Other signs of degradation noted
Grant et al, ² 1994	Ampules	Laboratory	2.5	Cyclical; 2 h cooled, 6 h left to warm up, 16 h room temperature	5	28	224	...	ANOVA and comparison of individual means using the Tukey test ($P < .05$ significant)	No	No discoloration or precipitation
	Ampules	Laboratory	2.5	Cyclical; 2 h cooled, 6 h left to warm up, 16 h room temperature	5	56	448	...		No	No discoloration or precipitation
	Ampules	Laboratory	2.5	Cyclical; 2 h cooled, 6 h left to warm up, 16 h room temperature	5	84	672	...		No	No discoloration or precipitation
De Winter et al, ⁶ 2013	Ampules	Laboratory	2–8	Constant	2	31	744	100.5	Comparison of the slopes of the regression lines of test samples vs room temperature controls using F tests ($P < .05$ significant)	No	...
	Ampules	Laboratory	2–8	Constant	2	59	1,416	101.1		No	...
	Ampules	Laboratory	2–8	Constant	2	120	2,880	101.5		No	...
	Ampules	Laboratory	2–8	Constant	2	181	4,344	105.8		No	...
	Ampules	Laboratory	2–8	Constant	2	243	5,832	103.0		No	...
	Ampules	Laboratory	2–8	Constant	2	304	7,296	104.3		No	...
	Ampules	Laboratory	2–8	Constant	2	365	8,760	106.5		No	...
Rachid et al, ⁷ 2015	Epinephrine autoinjectors (EpiPens 0.3 mg)	Laboratory	–25	Cyclical; 20 h cooled, 4 h room temperature	5	5	100	100.5	ANOVA and comparison of individual means using the Tukey test ($P < .05$ significant)	No	All solutions clear with no precipitates on visual inspection, no metabolites detected on chiral analysis
	Epinephrine autoinjectors (EpiPens 0.3 mg)	Laboratory	–25	Constant	5	5	120	99.3		No	
	Epinephrine autoinjectors (EpiPens 0.3 mg)	Laboratory	–25	Constant	5	10	240	96.8		No	
	Epinephrine autoinjectors (EpiPens 0.3 mg)	Laboratory	4	Constant	5	10	240	100.2		No	

Abbreviation: ANOVA, analysis of variance; est, estimated.

Table 4
Exposure of Epinephrine 1:10,000 to Cold

Study	Type of epinephrine container used	Environment	Temperature tested, °C	Constant/cyclical; cycle of cooling periods	No. of samples in study arm	Period of exposure (24-hour days)	Total duration of temperature exposure, h	Mean control dose remaining, %	Significance test used	Significant degradation of epinephrine concentration	Other signs of degradation noted
Johansen et al, ³ 1993	Abboject syringe	Laboratory	–20	Cyclical; 4 hrs cooled, 2 h room temperature, 4 h cooled, 14 h room temperature	3	2	16	105.7 (est)	ANOVA ($P < .05$ significant)	No	No significant difference in chemical structure
Grant et al, ² 1994	Carpject syringes	Laboratory	2.5	Cyclical; 2 h cooled, 6 h left to warm up, 16 h room temperature	5	28	224	...	ANOVA and comparison of individual means using the Tukey test ($P < .05$ significant)	No	No discoloration or precipitation
	Carpject syringes	Laboratory	2.5	Cyclical; 2 h cooled, 6 h left to warm up, 16 h room temperature	5	56	448	...		No	No discoloration or precipitation
	Carpject syringes	Laboratory	2.5	Cyclical; 2 h cooled, 6 h left to warm up, 16 h room temperature	5	84	672	...		No	No discoloration or precipitation

Abbreviation: est, estimated.

Table 5
Exposure of Epinephrine 1:1,000 to Heat and Cold

Study	Type of epinephrine container used	Environment	Temperature tested, °C	Constant/cyclical; cycle of cooling periods	No. of samples in study arm	Period of exposure (24-hour days)	Total duration of temperature exposure, h	Mean control dose remaining, %	Significance test used	Significant degradation of epinephrine concentration	Other signs of degradation noted
Zeisel et al, ²³ 1998	Ampules	Emergency vehicles	–10.4 to 50.8 ^a	Varied based on field conditions	60	365	Unknown	98.4	Statistical significance: non-parametric Mann-Whitney and Kruskal-Wallis tests ($P < .05$ significant, $P < .01$ highly significant); clinical significance: <90% of labeled dose remaining	No	...
	Ampules	Clinics	–10.4 to 50.8 ^a	Varied based on field conditions	20	365	Unknown	98.4		No	...
De Winter et al, ⁶ 2013	Ampules	Emergency vehicles	–8 to 9.8; mean, 3.2	Varied based on field conditions	2	31	Unknown	100.6	For all study arms: comparison of the slopes of the regression lines of test samples vs room temperature controls using F tests ($P < .05$ significant)	No	...
	Ampules	Emergency vehicles	–8 to 13.6; mean, 3.2	Varied based on field conditions	2	59	Unknown	100.6		No	...
	Ampules	Emergency vehicles	–8 to 26.9; mean, 9.8	Varied based on field conditions	2	120	Unknown	100.5		No	...
	Ampules	Emergency vehicles	–8 to 35.8; mean, 16.8	Varied based on field conditions	2	181	Unknown	102.0		No	...
	Ampules	Emergency vehicles	–8 to 35.8; mean, 18	Varied based on field conditions	2	243	Unknown	99.0		No	...
	Ampules	Emergency vehicles	–8 to 35.8; mean, 18	Varied based on field conditions	2	304	Unknown	101.5		No	...
	Ampules	Emergency vehicles	–8 to 35.8; mean, 10.3	Varied based on field conditions	2	365	Unknown	104.1		No	...

^aAmbient temperatures; storage container temperatures not reported.

Table 6
Exposure of Epinephrine 1:10,000 to Heat and Cold

Study	Type of epinephrine container used	Environment	Temperature tested, °C	Constant/cyclical; cycle of cooling periods	No. of samples in study arm	Period of exposure (24-hour days)	Total duration of temperature exposure, h	Mean control dose remaining, %	Significance test used	Significant degradation of epinephrine concentration	Other signs of degradation noted
Johansen et al, ³ 1993	Abboject syringe	Not specified	–20, 70	Cyclical; 4 h cooled, 2 h room temperature, 4 h heated, 14 h room temperature	3	2	16	105.3 (est)	ANOVA ($P < .05$ significant)	No	No significant difference in chemical structure
Gammon et al, ²⁰ 2008	Vial from EMS stock	No	54, –6	Cyclical; 12 h heated, 12 h cooled	1 (sampled 3 times)	7	168 (84 heat, 84 cold)	91.93	Statistical significance: descriptive, simple linear regression, and Pearson correlation tests ($R > 0.75$ significant); clinical significance: <90% of labeled dose remaining	No	...
	Vial from EMS stock	No	54, –6	Cyclical; 12 h heated, 12 h cooled	1 (sampled 3 times)	14	336	81.96		Not statistically significant, but clinically significant	...
	Vial from EMS stock	No	54, –6	Cyclical; 12 h heated, 12 h cooled	1 (sampled 3 times)	21	504	87.75		Not statistically significant, but clinically significant	...
	Vial from EMS stock	No	54, –6	Cyclical; 12 h heated, 12 h cooled	1 (sampled 3 times)	28	672	79.52		Not statistically significant, but clinically significant	...

Abbreviations: ANOVA, analysis of variance; EMS, emergency medical services; est, estimated.

(a full year). Degradation varied not only by duration of heat exposure but also by whether the heat exposure was constant or cyclic. The highest loss relative to control was in samples exposed to 240 hours of continuous heating at 70°C, where only 60.4% of the labeled dose remained.¹⁹

Four studies evaluated epinephrine 1:10,000 exposed to heat (Table 2). Results were again variable. In 2 experiments in which the duration of heat exposure was lower (16 and 24 hours), degradation was not seen.^{3,4}

None of the 3 studies that evaluated epinephrine 1:1,000 exposed to cold or the 2 studies that evaluated epinephrine 1:10,000 exposed to cold reported statistically significant epinephrine degradation, even though many samples were exposed to extreme freezing temperatures for prolonged periods (Table 3 and Table 4).

None of the 2 studies that evaluated epinephrine 1:1,000 exposed to variable heat and cold in field conditions or the 2 studies that evaluated epinephrine 1:10,000 exposed to alternating heat and cold reported statistically significant epinephrine degradation, even though the samples were all exposed to either extreme hot and cold temperatures or prolonged periods of exposure (Table 5 and Table 6).

Only 1 study involving heat and 1 study involving cold evaluated EAI. These studies were not powered to evaluate the functioning of the device mechanisms, and this was not the primary aim of these studies. However, the authors observed that all 20 devices exposed to heat and all 20 devices exposed to cold fired correctly.

Discussion

Because the incidence of allergies and anaphylaxis continues to increase worldwide, especially among children,^{1,25,26} so does the need for EAI. As more individuals with allergies are required to carry these devices, it is increasingly important that the requirements for their correct use are made as convenient and unrestricted as possible, without risking impaired function of the device or the medication it contains.

Storage requirements for epinephrine are based on standard storage temperature recommendations for all US Food and Drug Administration (FDA)–approved room temperature drugs. The allowed range of 20°C to 25°C with excursions permitted to 15°C to 30°C is considered controlled room temperature as standardized by the USP. These ranges are listed in the prescribing information for all currently FDA-approved EAI devices.^{27–29} The FDA room temperature recommendations also include temperature excursions up to 40°C, as long as the mean kinetic temperature still falls within the 20° to 25°C range, although this additional specification is missing from prescribing information for all 3 EAI.

Existing room temperature requirements may be difficult to achieve in some environments, such as midsummer days in hot areas of the country or midwinter hikes on snowy days. It is difficult for families to know whether the device has exceeded the acceptable temperature range because there are no temperature indicators on any of these devices. Appropriate storage is similarly challenging in prehospital health care settings, such as ambulances, where medications are typically stored at ambient temperatures. In hot climates, vehicle temperatures frequently exceed recommended ranges. In a study of fire trucks servicing a desert region of Southeast California, temperature monitors in uncooled drug boxes reached temperatures as high as 52°C.³⁰ In a study of Advanced Life Support vehicles in New Jersey, uncooled drug boxes reached temperatures as high as 58°C in midsummer.³¹ In a British study of temperatures inside a physician's bag in various locations of a car left in an unshaded parking lot, temperatures reached as high as 80°C inside the bag in the back window of the car, with an ambient temperature of 24°C.³²

After even brief (4 hours) suspected exposures to temperatures exceeding allowed excursion ranges, customer service representatives of the largest EAI manufacturer (Mylan, Canonsburg, Pennsylvania who make EpiPen) may recommend exchanging the device, particularly for excursions below 15°C or above 42°C (oral communication, 2015). This is inconvenient and expensive for families (in the United States, the 2015 retail costs for EpiPen are frequently \$500–\$600 for a set of 2 devices and a trainer).³³ However, patients contacting Sanofi customer service to ask about heat excursions for their devices can be told verbally that tests have shown that Auvi-Q devices remained within specifications for up to 1 month at temperatures between 38°C and 42°C (personal communication). Physicians requesting information can receive a written letter from Sanofi providing these same facts, referencing data on file. Sanofi will return the license and development rights for Auvi-Q to kaléo, the developer, in late 2016,³⁴ so it is unclear whether these recommendations will continue after that transition.

This systematic review suggests that epinephrine may be more robust than the current prescribing information storage recommendations suggest. Even with freezing, no studies evaluating exposure to excessive cold temperature produced evidence of epinephrine degradation. In 1 study comparing refrigeration (recommended storage practice in Norway) with room temperature storage, there was significant degradation at room temperature compared with refrigerated temperature.⁶ However, only 1 study, of 0.3-mg EpiPen devices, tested the effect of freezing on EAI.⁷ Although the 20 devices exposed to extreme cold fired successfully, there is still insufficient information on the effect of temperature on autoinjector device mechanisms. Freezing is of particular concern because it has the potential to crack the device's glass syringe, and this would not be visible to the user. In a study of emergency vehicles in Germany, with a total exposure time of 279 hours below freezing, there were 2 cases of fine cracks in glass ampules, but these were not specified as epinephrine ampules.²⁴

At high temperatures, results were more variable, with some studies reporting significant degradation of epinephrine. This finding likely reflects differences among studies in the degree, pattern, and duration of exposure. Only the studies of 1:10,000 epinephrine included very limited heat exposure. In these studies, when heat exposure was cyclic and with a total exposure of 24 hours or less, there was no significant degradation. None of the studies of 1:1,000 epinephrine, a concentration that is more comparable to the concentration of epinephrine in autoinjectors, tested a similarly short duration of heat exposure.

Only 1 study compared degradation with heat exposure between concentrations of epinephrine.² In this study, epinephrine 1:10,000 degraded more rapidly with heat exposure than epinephrine 1:1,000. On the basis of these results, EAI may be less sensitive to heat exposure than 1:10,000 epinephrine used intravenously in cardiac resuscitation. In addition, epinephrine 1:2,000 used in the 0.15-mg autoinjectors designed for patients weighing less than 30 kg may degrade more significantly than the epinephrine 1:1,000 in the 0.3-mg counterpart, when exposed to the same temperature excursions. Separate testing and separate storage temperature recommendations for each concentration of epinephrine may be needed.

The pattern of exposure to extreme temperature also appears to be an important factor affecting epinephrine degradation. Constant heating degraded the epinephrine more than cyclical heat, as seen both within studies^{4,19} and between studies. In the study by Church et al,⁴ 164 hours of constant heating at 65°C led to complete degradation of all epinephrine, whereas 164 hours of cyclic heat alternating between 65°C and room temperature, distributed during 3 weeks, resulted in a 57% decrease in the epinephrine concentration.⁴ This finding may explain why degradation was

noted in the study by Rachid et al,¹⁹ with 20 hours at 70°C daily cycles of heat but not in the study by Grant et al,² with 6 hours at 70°C daily cycles of heat, even though the total duration of heat exposure in the study by Grant et al was higher.

In the laboratory studies, the amount of heat exposure likely exceeds what typically happens in real-world situations. Neither of the 2 studies that tested epinephrine in real-world environments, exposing the samples to natural variations in temperature, revealed significant degradation.

Many of the studies also measured levels of epinephrine degradation products (Tables 1–6). Importantly, these products may be present long before the epinephrine solution appears visibly discolored.^{2,4} The makers of EAls warn against using the autoinjector if the solution appears discolored, seems cloudy, or contains precipitates.^{27,28} However, significant degradation can occur even while the solution remains clear, colorless, and normal in appearance.^{2,19} In addition, epinephrine degradation products can appear and increase in concentration while the epinephrine concentration still exceeds 90% of labeled dose, which is the acceptable industry standard.^{2,4} The clinical significance of this finding is not yet known.¹⁹

Differences in additives between epinephrine products could also play a role in epinephrine degradation. All EAls approved for use in the United States and Canada contain an epinephrine solution that includes at least epinephrine, sodium chloride, and either sodium metabisulfite or sodium bisulfite.^{27–29} For example, EpiPen uses a solution of epinephrine, sodium chloride, sodium metabisulfite, hydrochloric acid, and water.²⁷ The presence of bisulfite as a preservative in epinephrine solutions may contribute to the degradation of the drug.^{4,35}

Limitations of the Research

Only 2 of the 7 authors we attempted to contact responded, both of whom provided additional information. However, we do not believe any excluded studies would have been included with additional information. In addition, we contacted manufacturers but we were not provided with any detailed study information, which we were informed was considered proprietary information. We may thereby have missed studies that would have met eligibility criteria.

In many of the studies, the temperature exposures were in extreme laboratory conditions and do not reflect typical real-world circumstances. Most of the studies involved frequent temperature excursions beyond recommended ranges but during short periods. Therefore, the results might not apply to less frequent and less extreme temperature excursions occurring episodically throughout a year.

Recommendations

Individuals and families should still aim to keep their EAls within the recommended storage temperature range of 20° to 25°C (68°F–77°F) whenever possible. However, the studies in this review uniformly indicate that extreme cold temperatures do not degrade epinephrine. Therefore, we encourage EAI manufacturers to seek FDA approval for revision of cold storage temperature recommendations for their devices. These recommendations should allow storage at lower nonfreezing temperatures, such as those typical of refrigeration. In the interim, we propose that individuals who own EAls do not need to replace them for brief excursions below 15°C that do not involve actual freezing.

More research needs to be performed on the stability of epinephrine at excessively high storage temperatures, particularly with limited exposure to heat, because most of the studies in this systematic review tested extreme temperatures for long periods. The studies that tested short exposure to extreme heat (<24 hours),

or real-world exposures, did not find significant degradation. We support previous recommendations that a single brief exposure to high temperatures exceeding recommendations does not warrant replacing an EAI.³⁶ We encourage pharmaceutical companies to conduct additional research to determine the storage temperature limitations of epinephrine based on pharmacokinetic properties and determine whether temperature recommendations could be liberalized from those based on standardized room temperature guidelines.

Better solutions to the challenges of temperature stability are needed. EAls could be manufactured with built-in or attached temperature indicators that provide clear evidence of when a device has been exposed to excessive heat. Newer devices are being developed that appear to have solved some of the issues of epinephrine stability. A device available only in Europe has a requirement to avoid freezing.³⁷ A device under development by Windgap Medical Inc (Boston, Massachusetts) that recently received a patent in the United States will have epinephrine that is stored as a powder and is expected to be more resistant to the effects of heat and cold.³⁸

The evidence based on available studies suggests that temperature excursions in real-world conditions may be less detrimental to epinephrine stability than previously suggested. Freezing and limited heat excursions did not result in epinephrine degradation. Refrigeration of epinephrine appears to reduce degradation. However, the effect of extreme temperatures, particularly freezing, on autoinjector devices and the glass syringes containing the drug is not sufficiently well established. More research is needed at clinically relevant high temperatures, with limited duration of heat exposure, and involving autoinjector devices.

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References

- [1] NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126:S1–S58.
- [2] Grant TA, Carroll RG, Church WH, et al. Environmental temperature variations cause degradations in epinephrine concentration and biological activity. *Am J Emerg Med*. 1994;12:319–322.
- [3] Johansen RB, Schafer NC, Brown PI. Effect of extreme temperatures on drugs for prehospital ACLS. *Am J Emerg Med*. 1993;11:450–452.
- [4] Church WH, Hu SS, Henry AJ. Thermal degradation of injectable epinephrine. *Am J Emerg Med*. 1994;12:306–309.
- [5] Gill M, Kislik A, Gore L, Chandna A. Stability of advanced life support drugs in the field. *Am J Health-Syst Pharm*. 2004;61:597–602.
- [6] De Winter S, Vanbrabant P, Vi NT, et al. Impact of temperature exposure on stability of drugs in a real-world out-of-hospital setting. *Ann Emerg Med*. 2013;62:380–387.e1.
- [7] Rachid O, Simons FER, Rawas-Qalaji M, Lewis S, Simons KJ. Epinephrine autoinjectors: does freezing or refrigeration affect epinephrine dose delivery and enantiomeric purity? *J Allergy Clin Immunol Pract*. 2015;3:294–296.
- [8] Abu-Reid IO, El-Samani SA, Hag Omer AI, et al. Stability of drugs in the tropics: a study in Sudan. *Int Pharm J*. 1990;4:6–10.
- [9] Carr RR, Decarie D, Ensom MHH. Stability of epinephrine at standard concentrations. *Can J Hosp Pharm*. 2014;67:197–202.
- [10] Hoellein L, Holzgrabe U. Ficts and facts of epinephrine and norepinephrine stability in injectable solutions. *Int J Pharm*. 2012;434:468–480.
- [11] Hogerzeil HV, De Goeje MJ, Abu-Reid IO. Stability of essential drugs in Sudan. *Lancet*. 1991;338:754–755.
- [12] Omer AIH, Stjernstrom NE. Stability of drugs in the tropics: a study in Sudan. *Trop Doct*. 1990;20:129.
- [13] Rudland SV, Annus T, Dickinson J, Langdon S. Adrenaline degradation in general practice. *Br J Gen Pract*. 1997;47:827–828.
- [14] Tantivesruangdet N. Stability of adrenaline in ambulance and drug storage room Narenthorn Center, Rajavithi Hospital. *J Med Assoc Thai*. 2013;96:S64–S68.
- [15] Zarghi A, Amini M, Alesahabfousl S. An ion-pair high-performance liquid chromatography method for stability studies of epinephrine acid tartrate in injectable solution. *Boll Chim Farm*. 2001;140:115–118.

- [16] Kerddonfak S, Manuyakorn W, Kamchaisatian W, Sasisakulporn C, Teawsomboonkit W, Benjaponpitak S. The stability and sterility of epinephrine prefilled syringe. *Asian Pac J Allergy Immunol*. 2010;28:53–57.
- [17] Rawas-Qalaji M, Simons FE, Collins D, Simons KJ. Long-term stability of epinephrine dispensed in unsealed syringes for the first-aid treatment of anaphylaxis. *Ann Allergy Asthma Immunol*. 2009;102:500–503.
- [18] Zenoni D, Priori G, Bellan C, Invernizzi RW. Stability of diluted epinephrine in prefilled syringes for use in neonatology. *Eur J Hosp Pharm Sci Pract*. 2012;19:378–380.
- [19] Rachid O, Simons FER, Rawas-Qalaji M, Lewis S, Simons KJ. Epinephrine doses delivered from auto-injectors stored at excessively high temperatures. *Drug Dev Ind Pharm*. 2016;42:131–135.
- [20] Gammon DL, Su S, Huckfeldt R, et al. Alteration in prehospital drug concentration after thermal exposure. *Am J Emerg Med*. 2008;26:566–573.
- [21] Kupper T, Schraut B, Rieke B, Hemmerling A, Schoffl V, Steffgen J. Drugs and drug administration in extreme environments. *J Travel Med*. 2006;13:35–47.
- [22] Muller C, Burghardt G, Wollmann H. The stability of norepinephrine hydrogen tartrate, epinephrine hydrogen tartrate and isoprenaline sulfate: the stability of drugs and preparations. *Pharmazie*. 1988;43:321–323.
- [23] Zeisel U, Bauer M, Tas P, Apfel C, Seifried P. Temperature stability of epinephrine under various storage conditions. *Anesthesiol Intensivmed*. 1998;39:139–145.
- [24] Castner T. *Temperaturbelastung von Medikamenten in der präklinischen Notfallmedizin*. Ulm, Germany: Dept of Anaesthesiology and Intensive Care, University of Ulm; 2000.
- [25] Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128:e9–e17.
- [26] Gupta RS, Springston EE, Smith B, Pongracic J, Holl JL, Warrier MR. Parent report of physician diagnosis in pediatric food allergy. *J Allergy Clin Immunol*. 2013;131:150–156.
- [27] EpiPen. Prescribing Information. www.epipen.com/en/prescribing-information#Patient. Accessed March 8, 2016.
- [28] Auvi-Q. Prescribing Information. <http://products.sanofi.us/Auvi-Q/Auvi-Q.html>. Accessed March 8, 2016.
- [29] Epineprine Auto-injector USP, Prescribing information. <http://www.epinephrineautoinject.com/pdf/Prescribing-Information.pdf>. Accessed March 11, 2016.
- [30] DuBois W. Drug storage temperatures in rescue vehicles. *J Emerg Med*. 2000;18:345–348.
- [31] Allegra J, Brennan J, Lanier V, Lavery R, MacKenzie B. Storage temperatures of out-of-hospital medications. *Acad Emerg Med*. 1999;6:1098–1103.
- [32] Rudland SV, Jacobs AG. Visiting bags: a labile thermal environment. *BMJ*. 1994;308:954–956.
- [33] Brown JC, Tuuri RE, Akhter S, et al. Lacerations and embedded needles caused by epinephrine autoinjector use in children. *Ann Emerg Med*. 2016;67:307–315.e8.
- [34] Sanofi US to Return Auvi-Q® (epinephrine injection, USP) Rights to kaléo [press release]. <http://www.news.sanofi.us/2016-02-23-Sanofi-US-to-Return-Auvi-Q-epinephrine-injection-USP-Rights-to-kal-o>. Accessed May 16, 2016.
- [35] Brustugun J, Kristensen S, Tonnesen HH. Photostability of epinephrine: the influence of bisulfite and degradation products. *Pharmazie*. 2004;59:457–463.
- [36] Lieberman P. Storage and stability of automatic epinephrine injectors. <http://www.aaaai.org/ask-the-expert/automatic-epinephrine.aspx>. Accessed December 15, 2015.
- [37] Emerade. Your adrenaline pen for emergency treatment of anaphylaxis. <http://www.emerade.com/adrenaline-auto-injector>. Accessed December 15, 2015.
- [38] Portable drug mixing and delivery system and method. <http://www.freepatentsonline.com/9199037.html>. Accessed December 15, 2015.