Research Report

Medical Outcomes of Acute Aspirin Single Substance Poisoning in Pediatric Patients

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Abstract

Background: A consensus guideline on salicylate poisoning recommends referring patients to the emergency department if they ingested 150 mg/kg of aspirin. The dose of aspirin associated with severe poisoning in pediatric patients has not been investigated. **Objective:** This study aims to associate medical outcomes with aspirin overdoses in patients 5 years old and younger. **Methods:** A retrospective review of data on pediatric patients with single substance aspirin exposures reported from poison centers across the country was conducted. The primary endpoint was to associate aspirin doses with medical outcomes. Secondary endpoints included evaluation of the signs, symptoms, and treatments of ingestion and their association with medical outcomes. **Results:** There were 26 488 included exposures with aspirin exposures resulting in no effect (92.5%), minor effect (6.0%), moderate effect (1.4%), major effect (0.2%), and death (0.02%). There were 8921 cases with available weight-based dosing information. Median doses associated with no effect, minor effects, moderate effects, major effects, and death ranged between 28.4 and 40.9 mg/kg, 52.5 and 82.3 mg/kg, 132.1 and 182.3 mg/kg, 132.3 and 172.8 mg/kg, and 142.2 and 284.4 mg/kg, respectively. Minor effect and moderate effect exposures were more likely to have alkalinization documented compared to no effect exposures (odds ratio [OR] = 1.75, 95% confidence interval [CI] = 1.41-2.17; OR = 1.79, 95% CI = 1.12-2.86). There was no difference in rates of alkalinization between minor and moderate exposures (OR = 1.02, 95% CI: 0.61-1.7). **Conclusions and relevance:** Reevaluation of the current recommendation of 150 mg/kg for referral to a healthcare facility is necessary for pediatric acute salicylate overdoses.

Keywords

aspirin, clinical toxicology, clinical pharmacy, clinical practice, pediatrics

Introduction

It is known that young children are particularly vulnerable to unintentional exposure to prescription or over-the-counter medications, especially if they are not stored properly. Children under 5 years of age can easily reach medications on tables, in purses, and in drawers, and are more likely to put the objects they find in their mouths.[1] In addition, the sweet flavor of certain formulations make medications attractive to children. These ingestions are often described as unintentional exploratory ingestions, since the intent is not self-harm.[2]

Aspirin is a widely available over-the-counter medication used for its analgesic, antipyretic, and antiplatelet properties. Since 1981, the use of aspirin in children has been discouraged due to concerns for Reye's syndrome.[3] Despite the decline in its therapeutic use in pediatric patients, the 2019 Annual Report of the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) reported 2713 single substance aspirin exposures involving children 5 years old and younger.[4] These ingestions of aspirin can be particularly concerning, since severe intoxications may cause noncardiogenic pulmonary edema, cerebral edema, coma, and death.[5]

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The exact dose of aspirin associated with severe poisoning has not been investigated. In an attempt to unify recommendations across poison centers, a working group made up of several experts in the field of toxicology published recommendations for referring patients to a healthcare facility (HCF) after aspirin ingestions. For acute unintentional ingestions in adult and pediatric patients, a referral threshold was set at 150 mg/kg or 6.5 g of aspirin, whichever is less. The panel assessed the level of evidence as Grade C, based on expert opinion and general consensus.[6] To date there has been no validation of this recommendation, especially in pediatric patients. Therefore, this study aims to use NPDS data to associate medical outcomes with doses of aspirin in patients 5 years old and younger to determine if the current cutoff of 150 mg/kg is an appropriate dose for referral of pediatric patients to health care facilities.

Materials and Methods

This is a retrospective, descriptive, database study using the NPDS of aspirin exposures in patients <6 years old. The primary endpoint was to associate severity of medical outcomes with reported doses of single-substance exposures to aspirin. Associations between medical outcomes and doses of aspirin were further evaluated based on age group (<6 months, 6 months to 1 year, >1 year). Secondary endpoints included an evaluation of the signs, symptoms, and treatments associated with aspirin ingestions and their association with medical outcomes. Additionally, we evaluated the single-substance aspirin exposures per year. Cases were included if they were acute, single-substance aspirin exposures occurring from January 1, 2000 through December 31, 2018; age was 5 years old and younger; and the case was followed to a known medical outcome. For evaluation of dosing, only cases with both weight provided and a dose provided as milligrams, grams, or number of tablets and product strength were included. These were utilized in order to define a mg/kg dose associated with levels of toxicity.

The NPDS is a data warehouse with information collected from calls to poison centers from the public and healthcare providers. Specialists in Poison Information (SPI) at various poison centers collect information to enter into the NPDS as they are triaging calls. Data collected on each case includes patient demographics, substance, quantity of the substance, reason for exposure, clinical effects, and treatments. Additionally, specialists code a medical outcome as per standard definitions.[7]

Medical outcomes and definitions per the NPDS coding manual include no effect (patient developed no symptoms as a result of the exposure); minor effect (patient developed signs and symptoms that were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement); moderate effect (patient exhibited signs and

symptoms that were more pronounced, more prolonged, or more systemic in nature than minor signs and symptoms); major effect (patient exhibited signs and symptoms that were life-threatening or resulted in significant residual disability or disfigurement); and death (patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication).[7] It is generally understood that cases with no effect and minor effect do not require treatment at a HCF, but those with at least moderate effects do require treatment at a HCF.

Age related standards using references decided at individual poison centers were applied when describing vital signs for pediatric patients. The NPDS coding user's manual defines an electrolyte abnormality as an imbalance in any of the electrolytes, including sodium, potassium, bicarbonate, chloride, calcium, magnesium, and phosphate. The specific type of electrolyte abnormality was not recorded in the database. The NPDS coding user's manual defines acidosis as bicarbonate < 20 mEq/L, pH <7.35, or elevated lactate levels. A definition of elevated lactate was not provided in NPDS coding user's manual.[7]

Dose assessment is performed by the SPI based on information provided. This includes the stated dose, along with certainty of the estimate. Dose certainty includes estimate, exact, and maximum possible. Doses listed as maximum possible represent the upper extreme of what the ingested dose could have been. It is possible that in these situations the actual dose is less than the numerical amount reported. The true amount ingested is equal to the maximum possible amount times an unknown probability, which ranges from 0 to 1. Previous studies have multiplied reported doses coded as maximum possible by 0.5, as this more likely reflects the population as a whole.[8] However, in practice, doses coded as maximum possible are not adjusted to determine if intervention or referral to a health care facility is needed. In order to mirror clinical practice, it is also worthwhile to examine doses as they are reported. Therefore, in this study, the data were analyzed using both the adjusted and nonadjusted doses of cases coded as maximum possible. In dose analysis, extreme outliers were reported that could potentially be impractical (>2400 mg/kg or <20 mg). Therefore, the data were evaluated with outliers included and excluded. The institutional review board determined this study to be exempted from review, since the study was retrospective and involved no patient contact.

Statistical Analysis

Univariate statistics were used to describe the study data. The relationships between dose and medical outcomes were evaluated using the Kruskal-Wallis test. For the post-hoc test for multiple comparisons, the Mann-Whitney U test for between-group comparisons with Bonferroni correction
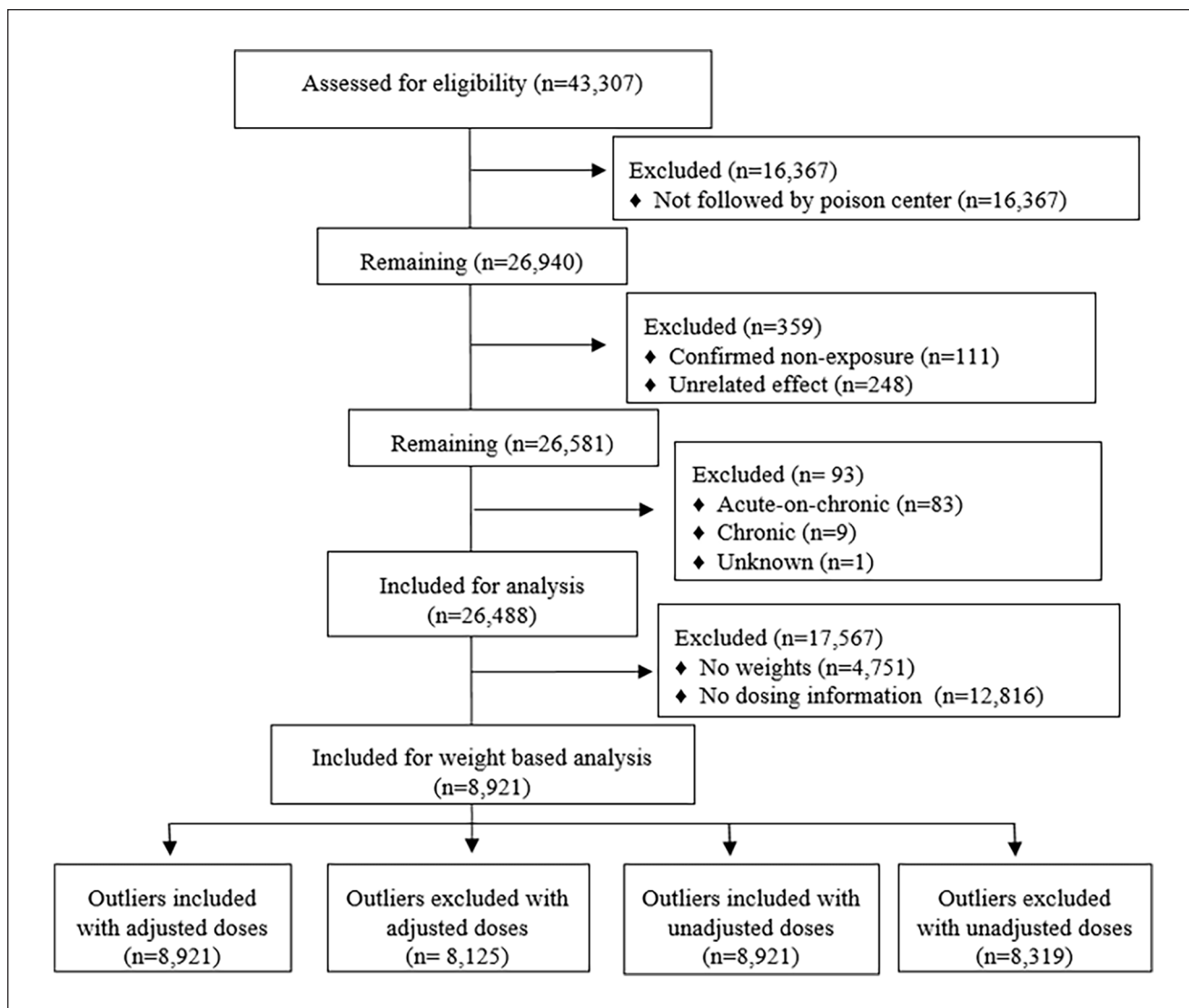
Figure 1. Process of inclusion of patients for the study.

was used. The adjusted p-values were computed from Bonferroni correction. Chi-square and Fisher's exact tests were used to check associations between medical outcomes and alkalinization. A simple logistic regression was performed to present the magnitude of the associations using odds ratios. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) and R (R Core Team, 2021).

Results

There were 26 488 exposures identified for inclusion in the analysis of the entire group. For the dose analysis, 8921 cases were identified for inclusion, which included outliers (Figure 1). The median age for the entire group was 2 years old (inter quartile range [IQR]: 1.6, 2 years) and approximately 48% (n = 12 788) were female. About 58% (n = 15 278) of

the patients were managed in a non-health care facility. Thirty-six percent (n = 9579) of patients were managed in the emergency department, 3% (n = 702) of patients admitted to the floor, and 2% (n = 466) admitted to the intensive care unit (ICU). The group used for the dose analysis was reflective of the whole population with similar age and sex. However, more patients were treated in a non-healthcare facility and fewer patients were treated in the emergency department (Table 1).

Aspirin exposures in children 5 years old and younger stayed relatively stable throughout the study period with an average of 3625 ± 274 (standard deviation) exposures per year (Figure 2). Most of the included exposures in the entire group resulted in no effect (n = 24 489; 92.5%) followed by minor effect (n = 1577; 6.0%), moderate effect (n = 377; 1.4%), major effect (n = 39; 0.2%), and death (n = 6;

Table 1. Baseline Characteristics for All Patients.

	Entire group (n = 26 488)	Dose analysis group (n = 8921)
Age, median (IQR), m	24 (19, 24)	24 (18, 24)
Female, n (%)	12 788 (48.3)	4276 (47.9)
Weight, median (IQR), kg	13 (11.3, 15)	3.2 (11.3, 15.5)
Medical outcome, n (%)		
No effect	24 489 (92.5)	8415 (94.3)
Minor effect	1577 (6)	418 (4.7)
Moderate effect	377 (1.4)	83 (0.9)
Major effect	39 (0.2)	4 (0.04)
Death	6 (0.02)	1 (0.01)
Place of management, n (%)		
ICU	466 (1.8)	108 (1.2)
ED	9579 (36.2)	1931 (21.7)
Floor	702 (2.7)	181 (2)
Non healthcare facility	15 278 (57.7)	6609 (74.1)
Other/unknown	463 (1.8)	92 (1)

Abbreviations: ED, emergency department; ICU, intensive care unit; IQR, interquartile range; m, months.
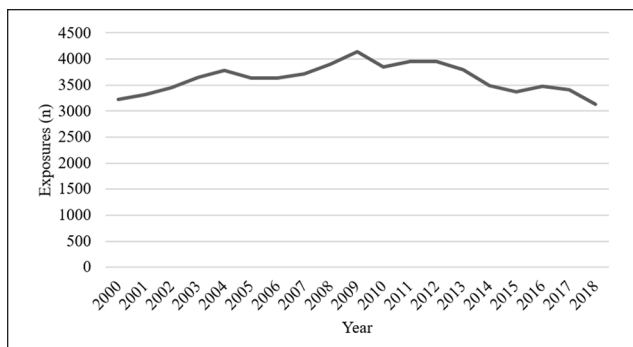

Figure 2. Aspirin exposures per year for pediatric patients under 6 years old from 2000 to 2018.

0.02%) (Table 1). Table 2 displays median doses of aspirin across medical outcomes based on whether outliers were included or not and whether cases coded as maximum possible were adjusted or not. When the data were analyzed with outliers included and unadjusted doses, median doses associated with medical outcomes were 40.9 mg/kg for no effect, 82.3 mg/kg for minor effects, 182.3 mg/kg for moderate effects, 172.8 mg/kg for major effects, and 284.4 mg/kg for death. When the data were analyzed with outliers excluded and adjusted doses, median doses associated with medical outcomes were 28.4 mg/kg for no effect, 52.5 mg/kg for minor effects, 132.1 mg/kg for moderate effects, 132.3 mg/kg for major effects, and 142.2 mg/kg for death. Refer to Table 2 for further data comparisons.

There was an association between dose and medical outcome ($P < 0.0001$), regardless of dose analysis method used (adjusted dose; unadjusted dose; outliers included; outliers excluded). Pairwise comparisons were conducted to calculate the effect sizes between medical outcomes. Effect sizes were large when comparing doses with no effect with doses with moderate effects, regardless of analysis method. When outliers were excluded, effect sizes were large when comparing doses with minor effects with doses with moderate effects. When outliers were included, effect sizes were medium when comparing doses with minor effects with doses with moderate effects (Table 2).

An age based analysis was conducted to examine doses associated with medical outcomes in patients <6 months old, 6 months to 1 year old, and > 1 year old. When examining patients <6 months old, median doses that produced moderate and major effects were >150 mg/kg. There were no deaths in this age group. Effect sizes were significant for all comparisons. When examining patients 6 months to 1 year old, median doses producing moderate effects and major effects were <150 mg/kg. Death was associated with a median dose of 142 mg/kg when the dose was adjusted and 284.4 mg/kg when the dose was unadjusted. Differences between medical outcomes were not significant. When examining patients >1 year old, median doses that produced moderate effects were <150 mg/kg. There were no doses producing major effects or death. Comparisons between no effect and minor effects were not significant. All other comparisons including minor to moderate effects were significant (Table 3).

The patient who died was an 11-month-old male weighing 8 kg who reportedly ingested a maximum of 2275 mg (~284 mg/kg) of aspirin. He was given activated charcoal, IV fluids, and sodium bicarbonate but, unfortunately, died prior to being transferred to a HCF where hemodialysis could be performed.

Table 2. Comparison of Dose Across Medical Outcomes.

Medical outcome	Outliers included with adjusted dose n = 8921	Outliers excluded with adjusted dose n = 8125	Outliers included without adjusted dose n = 8921	Outliers excluded without adjusted dose n = 8319
No effect	n = 8415	n = 7649	n = 8415	n = 7840
Dose, median (IQR), mg/kg	30.8 (15.5, 66.2)	28.4 (14.3, 52.8)	40.9 (21.4, 95.3)	35.8 (20.4, 78.6)
95% CI	(29.7 to 31.5)	(27.4 to 38.7)	(39.6 to 42.1)	(35.7 to 37.6)
Minor effect	n = 418	n = 394	n = 418	n = 398
Dose, median (IQR), mg/kg	59.5 (24.6, 131.6)	52.5 (23.9, 107.3)	82.3 (28.6, 164.2)	73.9 (27.5, 157.6)
95% CI	(50.9 to 70.7)	(44.6 to 64)	(68.6 to 97.5)	(63.6 to 87)
Moderate effect	n = 83	n = 77	n = 83	n = 76
Dose, median (IQR), mg/kg	148.5 (89.2, 239)	132.1 (89.1, 213.2)	182.3 (121.1, 257.5)	178.3 (116.9, 237.1)
95% CI	(120.3 to 182.3)	(108 to 173.7)	(162 to 207.4)	(152.7 to 205.4)
Major effect	n = 4	n = 4	n = 4	n = 4
Dose, median (IQR), mg/kg	132.3 (50.2, 225.6)	132.3 (50.2, 225.6)	172.8 (100.4, 225.6)	172.8 (100.4, 225.6)
95% CI	(19.3 to 267.7)	(19.3 to 267.7)	(38.6 to 267.7)	(38.6 to 267.7)
Death	n = 1	n = 1	n = 1	n = 1
Dose, median (IQR), mg/kg	142.2 (19.3 to 267.7)	142.2 (142.2, 142.2)	284.4 (284.4, 284.4)	284.4 (284.4, 284.4)
95% CI	142.2	142.2	284.4	284.4
P value	<0.0001	<0.0001	<0.0001	<0.0001
Pairwise comparison				
No effect vs. Minor				
Effect size (Cliff's delta)	Small (−0.272)	Small (−0.313)	Small (−0.256)	Small (−0.304)
95% CI	(−0.329 to −0.214)	(−0.374 to −0.249)	(−0.313 to −0.196)	(−0.365 to −0.241)
Adjusted *P* value	<0.0001	<0.0001	<0.0001	<0.0001
No effect vs. Moderate				
Effect size (Cliff's delta)	Large (−0.680)	Large (−0.737)	Large (−0.661)	Large (−0.731)
95% CI	(−0.764 to −0.575)	(−0.824 to −0.616)	(−0.747 to −0.554)	(−0.821 to −0.606)
Adjusted *P* value	<0.0001	<0.0001	<0.0001	<0.0001
Minor vs. Moderate				
Effect size (Cliff's delta)	Medium (−0.469)	Large (−0.502)	Medium (−0.462)	Large (−0.485)
95% CI	(−0.577 to −0.345)	(−0.615 to −0.368)	(−0.572 to −0.337)	(−0.600 to −0.351)
Adjusted *P* value	<0.0001	<0.0001	<0.0001	<0.0001

For the pairwise comparison, no effect, minor effect, and moderate effects were the only medical outcomes included due to the small sample size of major effect and death.
Abbreviations: CI, confidence interval; IQR, interquartile range.

The most common signs and symptoms reported in the dose analysis group (n = 8921) were tinnitus (n = 1443; 16.2%), vomiting (n = 1402; 15.7%), nausea (n = 1067; 12%), tachycardia (n = 800; 9%), abdominal pain (n = 598; 7%), tachypnea (n = 517; 5.8%), electrolyte abnormality (n = 483; 4%), acidosis (n = 358; 4%), dizziness (n = 209; 2.3%), and lethargy (n = 170; 1.9%).

Table 4 describes the various treatments for aspirin poisonings according to medical outcome. The most common treatments limited to a HCF in the weight-based analysis group were intravenous fluids (n = 2139; 24%), alkalinization (n = 1865; 20.9%), and single dose activated charcoal (n = 1635; 18.3%). Of the cases coded as "no effect," 6332 (75.2%) received a wide variety of treatments.

Medical outcomes were also compared to see if they correlated with the likelihood of getting alkalization. A minor effect patient was 75% more likely to have alkalinization compared to a no effect patient (odds ratio [OR] = 1.75, 95% confidence interval [CI] = 1.41 to 2.17; *P* < 0.001). A moderate effect patient was 79% more likely to have alkalinization compared to a no effect patient (OR = 1.79, 95% CI = 1.12 to 2.86; *P* = 0.01). A moderate effect patient was 2% more likely to have alkalinization compared to a minor effect patient (OR = 1.02, 95% CI = 0.61 to 1.7; *P* = 0.8). However, this was not statistically significant.

Discussion

The purpose of the 2007 Clinical Toxicology Guideline was to provide recommendations on when to refer ingestions of aspirin to a HCF.[6] There is consensus that cases with at least moderate effects require treatment at a HCF. Therefore, it is important to identify doses that could produce at least moderate effects. Our study showed that there was a wide range

Table 3. Comparison of Dose Across Medical Outcomes Based on Age.

Medical outcome	<6 months old				6 months to 1 year old				>1 year old			
	Outliers included with adjusted dose	Outliers excluded with adjusted dose	Outliers included without adjusted dose	Outliers excluded without adjusted dose	Outliers included with adjusted dose	Outliers excluded with adjusted dose	Outliers included without adjusted dose	Outliers excluded without adjusted dose	Outliers included with adjusted dose	Outliers excluded with adjusted dose	Outliers included without adjusted dose	Outliers excluded without adjusted dose
	n = 406	n = 383	n = 406	n = 384	n = 854	n = 804	n = 854	n = 802	n = 7659	n = 6937	n = 7659	n = 7131
No effect	n = 29	n = 25	n = 29	n = 27	n = 813	n = 766	n = 813	n = 763	n = 7571	n = 6857	n = 7571	n = 7048
Dose, median, mg/kg	25.5	21.7	34.5	25.5	31.1	28.8	35.8	35.6	30.7	27.9	42.2	36.7
(IQR)	(12.7, 59.5)	(11.8, 27.1)	(12.9, 62.6)	(12.7, 59.5)	(16.2, 48.7)	(16.2, 42.3)	(25, 68.1)	(23.8, 57.3)	(15.2, 68.6)	(14.0, 53.7)	(21.1, 97.6)	(20.4, 81.8)
95% CI	(17.2 to 40.3)	(12.7 to 25.6)	(20.7 to 59.5)	(19.8 to 54.2)	(28.6 to 32.6)	(27.5 to 31.2)	(34.2 to 36.2)	(32.8 to 35.8)	(29.7 to 31.9)	(27.4 to 28.7)	(40.8 to 44.1)	(35.7 to 38.8)
Minor effect	n = 310	n = 295	n = 310	n = 294	n = 37	n = 34	n = 37	n = 35	n = 71	n = 65	n = 71	n = 69
Dose, median, mg/kg	71.4	66.7	100.5	89.2	32.5	31.8	37.6	37.6	33.2	29.8	55.6	53.6
(IQR)	(26.4, 146.5)	(25.4, 128.4)	(32.4, 167.8)	(29.7, 162.2)	(21.0, 71.5)	(20.9, 62.3)	(28.6, 85.9)	(25.5, 85.6)	(18.8, 97.6)	(17.8, 68.9)	(23.8, 144.7)	(23.8, 131.6)
95% CI	(59.2 to 81.1)	(53.5 to 78.4)	(82.2 to 119.2)	(74.2 to 111.4)	(28.6 to 54.2)	(25.5 to 46.9)	(32.5 to 65.1)	(31.1 to 62.3)	(27.5 to 55.6)	(26.8 to 43.0)	(32.5 to 78.5)	(29.8 to 78.4)
Moderate effect	n = 64	n = 60	n = 64	n = 60	n = 2	n = 2	n = 2	n = 2	n = 17	n = 15	n = 17	n = 14
Dose, median, mg/kg	158.1	150.6	190.7	183.5	120.4	120.4	120.4	120.4	121.1	108	140.8	125.9
(IQR)	(93.0, 228.6)	(91.5, 212.3)	(145.9, 253.3)	(141.2, 241.7)	(108.6, 132.2)	(108.6, 132.2)	(108.6, 132.2)	(108.6, 132.2)	(40.5, 272.5)	(31.1, 257.5)	(81, 272.5)	(47.6, 235.3)
95% CI	(122.1 to 191.5)	(120 to 182.3)	(178.1 to 216.1)	(162.5 to 207.4)	(108.6 to 132.2)	(108.6 to 132.2)	(108.6 to 132.2)	(108.6 to 132.2)	(40.5 to 272.5)	(31.1 to 257.5)	(81 to 272.5)	(47.6 to 257.5)
Major effect	n = 3	n = 3	n = 3	n = 3	n = 1	n = 1	n = 1	n = 1	n = 0	n = 0	n = 0	n = 0
Dose, median, mg/kg	183.5	183.5	183.5	183.5	19.3	19.3	38.7	38.7	-	-	-	-
(IQR)	(81, 267.7)	(81, 267.7)	(162, 267.7)	(162, 267.7)	-	-	-	-	-	-	-	-
95% CI	(81 to 267.7)	(81 to 267.7)	(162 to 267.7)	(162 to 267.7)	-	-	-	-	-	-	-	-
Death	n = 0	n = 0	n = 0	n = 0	n = 1	n = 1	n = 1	n = 1	n = 0	n = 0	n = 0	n = 0
Dose, median, mg/kg	-	-	-	-	142.2	142.2	284.4	284.4	-	-	-	-
(IQR)	-	-	-	-	-	-	-	-	-	-	-	-
95% CI	-	-	-	-	-	-	-	-	-	-	-	-
P value	<0.0001	<0.0001	<0.0001	<0.0001	0.1	0.2	0.3	0.2	0.0003	0.0002	0.0001	0.0002
Pairwise comparison												
No effect vs. Minor												
Effect size (Cliff's delta)	Medium (−0.384)	Large (−0.554)	Medium (−0.366)	Medium (−0.431)	-	-	-	-				
95% CI	(−0.574 to −0.155)	(−0.678 to −0.400)	(−0.555 to −0.142)	(−0.598 to −0.228)								
Adjusted P value	0.002	<0.0001	0.003	0.0006					0.4	0.3	0.3	0.07
No effect vs. Moderate												
Effect size (Cliff's delta)	Large (−0.692)	Large (−0.877)	Large (−0.683)	Large (−0.778)	-	-	-	-	Large (−0.529)	Large (−0.568)	Large (−0.552)	Large (−0.548)
95% CI	(−0.847 to −0.431)	(−0.948 to −0.722)	(−0.834 to −0.440)	(−0.886 to −0.591)					(−0.740 to −0.225)	(−0.787 to −0.221)	(−0.748 to −0.269)	(−0.767 to −0.215)
Adjusted P value	<0.0001	<0.0001	<0.0001	<0.0001					0.0006	0.0003	<0.0001	0.001

(continued)

Table 3. (continued)

	<6 months old				6 months to 1 year old				>1 year old			
	Outliers included with adjusted dose	Outliers excluded with adjusted dose	Outliers included without adjusted dose	Outliers excluded without adjusted dose	Outliers included with adjusted dose	Outliers excluded with adjusted dose	Outliers included without adjusted dose	Outliers excluded without adjusted dose	Outliers included with adjusted dose	Outliers excluded with adjusted dose	Outliers included without adjusted dose	Outliers excluded without adjusted dose
Medical outcome	n = 406	n = 383	n = 406	n = 384	n = 854	n = 804	n = 854	n = 802	n = 7659	n = 6937	n = 7659	n = 7131
Minor vs. Moderate												
Effect size (Cliff's delta)	Medium (−0.470)	Large (−0.506)	Medium (−0.469)	Large (−0.514)	-	-	-	-	Medium (−0.438)	Medium (−0.471)	Medium (−0.458)	
95% CI	(−0.590 to −0.331)	(−0.629 to −0.359)	(−0.593 to −0.324)	(−0.642 to −0.359)					(−0.677 to −0.117)	(−0.720 to −0.114)	(−0.682 to −0.155)	
Adjusted P value	<0.0001	<0.0001	<0.0001	<0.0001					0.02	0.01	0.01	0.08

For the pairwise comparison, no effect, minor effect, and moderate effects were the only medical outcomes included due to the small sample size of major effect and death. If the P value is >0.05, effect sizes are not needed. Therefore, a pairwise comparison was not completed for the 6 months to 1 year old group.

Abbreviations: CI, confidence interval; IQR, interquartile range.

Table 4. Health Care Facility Treatments for Aspirin Poisonings Based on Medical Outcomes for Patients in the Dose Analysis Group.

	Medical outcome					
	No effect (n = 8415)	Minor effect (n = 418)	Moderate effect (n = 83)	Major effect (n = 4)	Death (n = 1)	Total (n = 8921)
IV Fluids, n (%)	1958 (23.3)	154 (36.8)	24 (28.9)	2 (50)	1 (100)	2139 (24)
Charcoal single dose, n (%)	1503 (17.9)	114 (27.3)	16 (19.3)	1 (25)	1 (100)	1635 (18.3)
Alkalinization, n (%)	1708 (20.3)	129 (30.9)	26 (31.3)	1 (25)	1 (100)	1865 (20.9)
Cathartic, n (%)	364 (4.3)	44 (10.5)	4 (4.8)	0	0	412 (4.6)
Charcoal multiple doses, n (%)	305 (3.6)	32 (7.7)	6 (7.2)	1 (25)	0	344 (3.9)
Antiemetics, n (%)	377 (4.5)	22 (5.3)	2 (2.4)	0	0	401 (4.5)
Lavage, n (%)	117 (1.3)	10 (2.4)	1 (1.2)	0	0	128 (1.4)

Abbreviation: IV, intravenous.

of doses that produced at least moderate effects, including doses that were < 150 mg/kg. Although median doses for moderate effects ranged between 132 to 182 mg/kg, the interquartile ranges show doses in the 25th percentile as low as 89 mg/kg for adjusted data, regardless of the inclusion or exclusion of outliers. Median unadjusted doses producing moderate effects in the 25th percentile were 121 mg/kg when outliers were included and 117 mg/kg when outliers were excluded. The age-based analysis showed that moderate effects were associated with median doses <150 mg/kg in patients ≥6 months old. This suggests that the dose cutoff of 150 mg/kg for referral to a health care facility may miss patients who require treatment, especially in this age group. However, this wide range of doses producing moderate effects also included doses > 150 mg/kg, especially when examining doses in the 75th percentile. Additionally, moderate and major effects were associated with median doses > 150 mg/kg in patients < 6 months old. Therefore, these data support the notion that more research is needed to determine an appropriate dose cutoff for referral in pediatric patients.

It is worthwhile to note that in our data, more severe outcomes were not closely tied to increasing dose. This may have been due to inconsistencies in the way quantities were reported in patients included in the dose analysis. This could possibly explain why a large portion of cases coded as "no effect" was given treatments for aspirin ingestion. Based on the available data, we were not able to completely elucidate why they required treatment due to the lack of salicylate concentrations. In an effort to account for this, we examined if medical outcomes were tied to the need for alkalinization, a treatment that is more specific for aspirin toxicity. When compared to patients with no effect, patients with minor and moderate effects were more likely to get alkalinization. However, when comparing patients with minor and moderate effects, there was no significant difference in the need for alkalinization. This indicates that

patients with at least minor effects would require treatment specific for aspirin toxicity, which challenges the general idea that patients with minor effects generally do not need treatment. However, there may have been some inconsistency with distinguishing between minor and moderate effects, since the criteria is somewhat subjective, overlap categories, and the data to decide is by second-hand report. Additionally, because outcome is tied to symptoms, it is possible that therapies administered decreased the toxicity and less severe outcomes were coded.

The most common signs and symptoms reported were abdominal pain, nausea, vomiting, tinnitus, and tachycardia, which is to be expected with aspirin poisonings. It is also not surprising that the most common treatments are intravenous fluids, activated charcoal, and alkalization, since current recommendations suggest supportive care, decontamination therapy to prevent absorption, and alkalization to enhance renal elimination of aspirin.[9]

Even though aspirin poisoning is a common occurrence reported to poison centers across the country, this study showed that the occurrences of aspirin poisonings in children under 6 years old have stayed relatively stable over the study period with approximately 3600 exposures per year. However, this only represents single substance exposures and those reported to poison centers, so our numbers likely underrepresent the true burden of aspirin poisoning in children. This data is eye opening, since inadvertent exposure to aspirin in children remains high despite efforts to discourage its use and prevent exploratory ingestions. It is especially alarming that these exposures included patients under 6 months of age, since patients at this age are reliant on adults and can only access these medications if they are within reach or directly administered to the infant.

Limitations for this study include its retrospective nature, which may limit the quality and quantity of information reported. Not all cases had the combination of dose and

weight, meaning we had to use a subgroup of reported exposures. However, overall medical outcomes were similar between the 2 groups. Serum salicylate concentrations are recorded by poison centers, but not uploaded to NPDS, so we were unable to confirm the exposure. In general, minor effects are less likely to be identified, but we believe the most serious effects and invasive interventions are identified and coded.[10,11] The NPDS requires minimum coding of medical outcomes based on effects but does not limit SPIs from upcoding (eg, coding a more severe medical outcome than specific effects suggest). Poison center data collection is passive, and these data do not capture patients not reported to the poison center. Time of exposure was not reported so it could be possible that patients with no effect could have experienced effects prior to the poison center call and it was not recorded. A prospective, multicenter study with extensive investigation of history and serum concentration would address many of the limitations we identified.

Conclusion and Relevance

The current cutoff of 150 mg/kg does not capture some patients that require treatment, especially patients < 1 year old that are at greatest risk for worse outcomes. This study highlights the need for further prospective research and adjustment of the guideline to lower the dose recommendation for referral of pediatric patients < 6 years old with single-substance exposures to aspirin to HCFs. A suggested area of focus is to examine salicylate levels associated with doses of aspirin exposures in pediatric patients.

Disclaimer

The American Association of Poison Control Centers (AAPCC) maintains the National Poison Data System (NPDS), which houses de-identified case records of self-reported information collected from callers during exposure management and poison information calls managed by the country's poison control centers (PCCs). NPDS data do not reflect the entire universe of exposures to a particular substance as additional exposures may go unreported to PCCs; accordingly, NPDS data should not be construed to represent the complete incidence of U.S. exposures to any substance(s). Exposures do not necessarily represent a poisoning or overdose and AAPCC is not able to completely verify the accuracy of every report. Findings based on NPDS data do not necessarily reflect the opinions of AAPCC.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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