

Drug-associated acute pancreatitis in paediatric versus adult reports: a disproportionality analysis of FAERS

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Abstract

Background

While drug-associated acute pancreatitis is proportionally more prevalent in children than adults, large-scale, age-stratified pharmacovigilance data remain limited. This study addresses this gap by analysing paediatric-specific signals to improve early recognition and safety monitoring.

Objectives

This study aimed to identify drugs associated with acute pancreatitis in children compared with adults and explored age-related differences in reporting patterns using the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods

A retrospective disproportionality analysis was conducted on 29,349 reports (November 1970–February 2026) from the FAERS. The dataset included 2,138 (7.3%) paediatric cases (0–17 years). Suspected active ingredients were identified, and reporting patterns were compared between age groups [chi-squared tests, reporting odds ratio (ROR), proportional reporting ratio (PRR), multivariate regression analysis].

Results

Reporting increased over time, with tenfold more reports in adults. The top ten suspected drugs in children were: methotrexate, pegaspargase, asparaginase, dexamethasone, acetaminophen, prednisone, vincristine sulfate, cytarabine, valproic acid and mercaptopurine. Paediatric cases were primarily linked to oncologic and immunomodulatory treatments, whereas adult reports were mainly linked to antidiabetic and cardiovascular agents. Seven active ingredients (dexamethasone, acetaminophen, prednisone, tacrolimus, lamivudine, didanosine, furosemide) showed significantly higher reporting proportions in children ($p < 0.01$). Dexamethasone, tacrolimus, and didanosine were showed positive interaction terms with serious outcomes in adjusted models. Serious outcome and consumer-reporting were more common in neonates and infants.

Conclusions

Distinct age-dependent patterns were identified. These findings support paediatric-specific pharmacovigilance assessment and caution against direct extrapolation of adult spontaneous-reporting patterns to children. A clinically useful list of drugs with the highest reporting frequencies in children has been generated.

What's known

- *Drug-associated acute pancreatitis is proportionally more prevalent in children.*
- *The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) can be used to analyse and explore age-dependent patterns.*

What's new

- *The top ten suspected drugs in children were: methotrexate, pegaspargase, asparaginase, dexamethasone, acetaminophen, prednisone, vincristine sulfate, cytarabine, valproic acid and mercaptopurine, linked to oncology and immunomodulation.*
- *Seven drugs (dexamethasone, acetaminophen, prednisone, tacrolimus, lamivudine, didanosine, furosemide) showed significantly higher reporting proportions in children. Dexamethasone, tacrolimus, and didanosine were associated with serious outcomes.*

Introduction

The incidence rate of acute pancreatitis in children is between 3.6 and 13.2 per 100,000 per year. In adults, it is 40 per 100,000 with an increase over the years of approximately 3.1% in the full population and 5.4% per year in children [1]. Acute pancreatitis is less commonly fatal in children compared to adults. However, it is an important reason for hospitalisation and may result in severe complications, particularly because a substantial portion of paediatric patients experience recurrent episodes [1, 2]. Gallstone obstruction and ethanol[3] are the most common causes in adults, while genetics, drug-induced, anatomically, infection, metabolism, auto-immune or trauma are most common in children [4]. This etiological divergence underscores the importance of age-stratified pharmacovigilance analyses rather than extrapolating adult data to paediatric populations.

Acute pancreatitis is commonly diagnosed using the INternational Study Group of Paediatric Pancreatitis In Search for a CuRE (INSPPIRE) criteria [2/3 criteria present, clinical (epigastric pain, or vomiting), biochemical (three times upper limit of normal of amylase and/or lipase), and imaging (contrast-enhanced CT, MRI/MRCP, or transabdominal ultrasonography) [1, 5, 6]. Since infants and toddlers cannot easily express stomach pain, vomiting is the most important presenting symptom of acute pancreatitis in this population [1].

Overall, less than 5% of acute pancreatitis is caused by drugs [2, 5, 7], while in children drug-induced pancreatitis is responsible for up to 25% of acute pancreatitis. For example, valproic acid (anti-epileptic and mood stabilizer) [8], asparaginase, clofarabine and vincristine (used in treatment of lymphocytic leukaemia(ALL) [7] and immunomodulators such as thiopurines, mesalamine and prednisone [9] are some of the more commonly reported drugs associated with pancreatitis in children. To diagnose drug-induced acute pancreatitis, all other frequent causes must first be considered and excluded. Thereafter, all suspected drugs have to be stopped or switched. If pancreatitis is resolved by doing so, the drug is most likely the cause of the acute pancreatitis [5].

Data on the most commonly reported associations between specific drugs and acute pancreatitis helps to faster suspect and identify the implicated drug enabling timely discontinuation and reducing the risk of severe complications through supportive care and mitigation [2, 5, 7]. Unfortunately, large-scale studies are lacking with only a few event reports for each drug [2].

At present, pharmacovigilance studies already exist for the full population, without a separate discussion or analysis concerning the patterns on children to adults [10]. This study therefore aims to generate a clinically useful overview on individual drugs which are most commonly associated with acute pancreatitis in children, compared with patterns in adults by analysis of the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) (recently renamed to AEMS). We hereby hypothesized that drug-acute pancreatitis associations differ between children and adults due to age-dependent pharmacokinetic and pharmacodynamic factors, or pharmaco-epidemiological differences.

Materials and Methods

Data source

The FAERS database is a worldwide publicly available database. The FAERS does not provide incidence rates or establish causality but is suitable for signal detection and disproportionality analysis. We hereby followed the REporting of A Disproportionality Analysis for DrUg Safety Signal Detection Using Individual Event Safety Reports in PharmacoVigilance (READUS-PV) guidelines [11].

Data extraction from the FAERS database

In the FAERS database, we searched for reports coded with the MedDRA preferred terms 'acute pancreatitis', 'increased lipase' and 'increased amylase' reported in children. Since increased lipase and amylase three times the upper limit of normal are one of the three INSPPIRE criteria for acute pancreatitis by children [12]. Furthermore, serum lipase has a higher sensitivity and specificity than serum amylase [1, 10]. This approach was chosen to align the main case definition more closely with clinically interpretable acute pancreatitis reports.

The selected data were extracted from the FAERS database as Microsoft Excel file by the first author on 20/02/2026. This is since the start of reporting (1969), to ensure that all existing event reports can be included in the analysis. However, the oldest report regarding acute pancreatitis is from 01/11/1970. As a result, the extraction includes all data from 01/11/1970 until 19/02/2026 (latest update version in FAERS at the time of data extraction). Event records in the FAERS database can contain multiple drug observations for a single patient. Therefore, observations were cleaned to remove duplicate drug records within each patient case. All analyses were carried out using R studio, version R-4.5.1 software.

Event report inclusion and exclusion criteria

Patient age was a critical factor for inclusion and stratification. Reports lacking age information were therefore omitted. When age was reported in other time indications than years, it was converted to years. Reports in which age was stated in decennia and equal to one were excluded to prevent age misclassification, as these did not allow differentiation between < 18 years (child) and $\geq$ 18 years (adults).

The following criteria lead to exclusion:

- Event reports directly linked to overdose, including: 'accidental exposure to product, completed suicide or suicide attempt, intentional self-harm unspecified, drug abuse or substance abuse, drug use disorder, intentional overdose and overdose and poisoning deliberate, intentional product misuse, intentional product use issue, or intentional self-injury'.
- Event reports describing exposure as fetus or neonate, including maternal exposure during pregnancy or maternal drugs affecting the fetus.

Definitions and stratification

In this study, children were defined as aged 0–17 years (inclusive), and adults as individuals aged 18–101 years. This stratification aligns with broader pharmacological classifications, where the European Medicines Agency (EMA) further categorizes paediatric populations into neonates (0–27 days), infants (28 days – 23 months), children (2–11 years), and adolescents (12–17 years) [13]. An event is defined by the FDA as 'serious' if the adverse event included any of the following: "death", "life threatening", "hospitalized", "disabled" or "congenital anomaly" [14].

Data analysis

The number of reports (annual) was extracted separately for children and adults, while the geographical distribution of event reports was visualized. Event reports are reported in the FAERS by a health care professional or consumer, and this was also described. To identify drugs associated with acute pancreatitis, only unique active pharmaceutical ingredients were considered per event report, and the top 25 active ingredients for children and adults were extracted. A similar effort was done for the clinical indication, unless this was not mentioned in the event reports.

Disproportionality analysis between children and adults, reporting odds ratio (ROR), proportional reporting ratio (PRR) and multivariate analysis

Disproportionality analysis was performed on shared suspected active ingredients across the top 25 lists for events reported in both children and adult samples. This analysis examines the difference in reporting rate of specific suspected active ingredients between children and adult. The chi-squared test was applied to assess the association between age group and drug-specific reporting frequency. The Benjamini-Hochberg FDR is used as adjusted p-value, to correct for false positive p-values.

The Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR) were calculated to quantify disproportionate reporting.

Reporting Odds Ratio (ROR): The ROR was calculated as $(a/b)/(c/d)$. In this formula:

- a = paediatric reports containing drug X.
- b = paediatric reports not containing drug X.
- c = adult reports containing drug X.
- d = adult reports not containing drug X.

An ROR significantly greater than one indicates that the suspect product active ingredient is reported significantly more frequently in children compared to adults.

PRR was calculated as $(a/(a+b))/(c/(c+d))$, using analogous definitions for a , b , c , and d as in the ROR calculation.

The PRR indicates the significance of the proportion of reporting. Confidence intervals for both ROR and PRR were calculated at the 0.05 and 0.95 levels using log normalization, accounting for the skewed distribution of the odds ratio.

Finally, a multivariate analysis was performed for the active ingredients common to the top 25 reported drugs in both children and adults, with focus on differences in seriousness. The following logit regression model was estimated:

$$Y_{serious} = \beta_0 + \beta_{drug} X_{drug} + \beta_{child} X_{child} + \beta_{drug \times child} X_{drug} X_{child} + [controls] + \epsilon$$

The variables in this model are:

- $Y_{serious}$ is a binary indicator equal to 1 if the outcome is serious and 0 otherwise.
- X_{drug} is a binary indicator equal to 1 if the specific drug is present in the report and 0 otherwise.
- X_{child} is a binary indicator equal to 1 if the reported age is < 18 and 0 otherwise.
- $X_{drug} X_{child}$ signifies the interaction term between X_{drug} and X_{child} .
- Control variables included reporter type, patient sex and reporting country.

Results

Data extraction

After extracting, there were 36,315 cases. Table 1 shows the process of cleaning this dataset. 6,809 reports were omitted due to unavailable patient age, three because the patient's age was recorded in decennia and was equal to one. Furthermore, 152 records were removed due to direct involvement in an overdose. In addition, two reports were omitted because the exposure occurred in a fetus or neonate. The final dataset contains 29,349 event reports of which 2,138 concerning children.

Table 1
Sample selection procedure

Initial dataset size	Leave out	Total
Pancreatitis Acute + Amylase Increased + Lipase Increased		36,315
Leave out observations where patient age is unavailable	-6,809	29,506
Leave out observations where patient age is expressed in decennia, and is equal to 1	-3	29,503
Leave out observations where patient was directly involved in overdose	-152	29,351
Leave out observations where patient was exposed as foetus/during pregnancy	-2	29,349
Final dataset size		29,349
(of which < 18-year-old / child patient observations)		(2,138)

Number of reports per year

The number of reports per year (01/11/1970 to 20/02/2026) is shown in **supplemental Fig. 1**. We observed an increasing trend in event reports in both children and adults. This suggests that the adverse event “acute pancreatitis” occurs more frequently. Alternatively, adverse events are more recognised or reported over time. Furthermore, we observed about ten times more event reports per year in adults than in children, with some fluctuation over time.

Distribution of event reports by country

The distribution of event reports by country is shown in **supplemental Fig. 2**. The USA was most commonly involved, followed by France, Great Britain, Germany, Canada, India and China. More countries reported cases in adults than in children.

Descriptive statistics on seriousness and reporter characteristics

The distribution of the adverse event outcomes of the observations and reporter characteristics is shown in Table 2. This shows that there are more outcomes qualified as serious in neonates (89.9%) and infants (79.6%) than in other (paediatric) age subgroups. Furthermore, there are clearly more self-reported cases and less reported cases by the professionals in neonates than other subgroups. In the other paediatric subgroups, there are more reported cases by the professionals than by the patient or relatives of the patient.

Table 2
Descriptive Statistics related to seriousness, and reporter characteristics

Class	Subclass	Count	Male	Serious Outcome	Reporter Self	Reporter Professional
Adult		27,211	13,781 (50.6%)	21,178 (77.8%)	4,387 (16.1%)	21,103 (77.6%)
Child		2,138	1,080 (50.6%)	1,661 (77.7%)	256 (12%)	1,705 (79.8%)
	Newborn infant (0–27 days)	59	38 (64.4%)	53 (89.8%)	23 (39%)	24 (40.7%)
	Infants and toddlers (28 days – 23 months)	103	56 (54.4%)	82 (79.6%)	12 (11.7%)	74 (71.8%)
	Children (2–11 years)	924	455 (49.2%)	713 (77.2%)	96 (10.4%)	756 (81.8%)
	Adolescents (12–17 years)	1,052	533 (50.7%)	815 (77.5%)	126 (12%)	851 (80.9%)
Notes:						
* Serious Outcome is defined as a reported adverse outcome of a patient including any of the following: “Death”, “Life Threatening”, “Hospitalized”, “Disabled”, and “Congenital Anomaly”.						

Drug-associated acute pancreatitis was fatal in 7.4% of children and 8.9% of adults. In contrast, events were classified as life threatening in 9.7% of paediatric and 7.7% of adult cases. Hospitalization rates were comparable between children and adults (60% and 59.9%) (**supplemental table 1**).

Top 25 suspected drugs in children and adults

Table 3, 4 and supplemental table 2 are case-based, whereas Table 6 is drug-observation-based after within-case deduplication of repeated active ingredients; therefore, denominators differ across analyses. The top 25 suspected product active ingredients associated with acute pancreatitis in children and adults respectively are listed in Table 3. These data reflect reporting frequency (cases, and %), not relative risk.

Table 3
Suspect Product Active Ingredients Top 25 in children and adults respectively.

Child			Adult		
Suspect Product	Cases	%	Suspect Product	Cases	%
Active Ingredients			Active Ingredients		
Vincristine/Vincristine Sulfate	209	9.78%	Metformin Hydrochloride	1309	4.81%
Methotrexate	182	8.51%	Liraglutide	813	2.99%
Pegaspargase	165	7.72%	Acetaminophen	807	2.97%
Asparaginase	150	7.02%	Exenatide	805	2.96%
Dexamethasone	133	6.22%	Atorvastatin/Atorvastatin Calcium	792	2.91%
Acetaminophen	128	5.99%	Sitagliptin Phosphate	705	2.59%
Prednisone	122	5.71%	Hydrochlorothiazide	563	2.07%
Mercaptopurine	112	5.24%	Didanosine	455	1.67%
Cytarabine	111	5.19%	Quetiapine Fumarate	451	1.66%
Valproic Acid	108	5.05%	Simvastatin	433	1.59%
Sulfamethoxazole	106	4.96%	Lamivudine	412	1.51%
Trimethoprim	106	4.96%	Prednisone	403	1.48%
Cyclophosphamide	102	4.77%	Semaglutide	392	1.44%
Tacrolimus	93	4.35%	Ritonavir	379	1.39%
Cyclosporine	92	4.30%	Stavudine	378	1.39%
Prednisolone	75	3.51%	Furosemide	376	1.38%
Zidovudine	71	3.32%	Tacrolimus	375	1.38%
Divalproex Sodium	66	3.09%	Nivolumab	352	1.29%
Lamivudine	58	2.71%	Dulaglutide	339	1.25%
Mycophenolate Mofetil	57	2.67%	Olanzapine	335	1.23%
Didanosine	57	2.67%	Dexamethasone	318	1.17%
Furosemide	54	2.53%	Ramipril	314	1.15%
Infliximab	52	2.43%	Ibuprofen	309	1.14%
Daunorubicin	51	2.39%	Lisinopril	302	1.11%
Levetiracetam	50	2.34%	Sulfamethoxazole	301	1.11%
Notes:					
* The total number of individual case observations for Children is equal to 2,138; the total number of individual case observations for adults is equal to 27,211.					

Table 4
Clinical indications Top 25 in children and adults respectively.

Child			Adult		
Clinical indication	Cases	%	Clinical indication	Cases	%
Product Used for Unknown Indication / -	837	39.15%	Product Used for Unknown Indication / -	9,514	34.96%
Acute Lymphocytic Leukaemia	241	11.27%	Type 2 Diabetes Mellitus	2,696	9.91%
Prophylaxis	80	3.74%	Hypertension	2,518	9.25%
Hiv Infection	79	3.70%	Diabetes Mellitus	1,430	5.26%
Epilepsy	76	3.55%	Depression	935	3.44%
Seizure	76	3.55%	Hiv Infection	904	3.32%
Pain	60	2.81%	Pain	901	3.31%
Prophylaxis Against Graft Versus Host Disease	52	2.43%	Prophylaxis	774	2.84%
Colitis Ulcerative	52	2.43%	Hypercholesterolaemia	636	2.34%
Crohn's Disease	46	2.15%	Rheumatoid Arthritis	499	1.83%
Immunosuppressant Drug Therapy	37	1.73%	Dyslipidaemia	488	1.79%
Attention Deficit Hyperactivity Disorder	35	1.64%	Gastroesophageal Reflux Disease	442	1.62%
Infection Prophylaxis	31	1.45%	Hyperlipidaemia	412	1.51%
Pyrexia	28	1.31%	Anxiety	409	1.50%
B Precursor Type Acute Leukaemia	26	1.22%	Bipolar Disorder	387	1.42%
Bone Marrow Conditioning Regimen	26	1.22%	Chronic Myeloid Leukaemia	381	1.40%
Acne	25	1.17%	Crohn's Disease	379	1.39%
Antiviral Prophylaxis	25	1.17%	Schizophrenia	360	1.32%
Hypertension	24	1.12%	Insomnia	329	1.21%
Gastroesophageal Reflux Disease	24	1.12%	Hypothyroidism	313	1.15%
Depression	23	1.08%	Colitis Ulcerative	286	1.05%
Antibiotic Prophylaxis	21	0.98%	Back Pain	281	1.03%
Graft Versus Host Disease	21	0.98%	Atrial Fibrillation	280	1.03%
Autism Spectrum Disorder	20	0.94%	Hepatitis C	272	1%
Asthma	20	0.94%	Multiple Sclerosis	270	0.99%
Notes:					
* The total number of individual case observations for Children is equal to 2,138; the total number of individual case observations for adults is equal to 27,211. Clinical indications present in both children and adults in the top 25 are highlighted in bold.					

Top 25 clinical indications in children and adults

The top 25 clinical indications of drugs in children and adults are shown in Table 4. In 476 event reports for children, and in 5,006 event reports for adults, the clinical indication is not mentioned.

For children, the main indication associated with drug-related acute pancreatitis is ALL, which counts for 241 cases (14.5%). Another important clinical indication is prophylaxis against various pathologies. Since this reads diverse as indication, we listed the top 20 (70%) most commonly reported prophylaxis indications in **supplemental table 5**. Other clinical indications are Human Immunodeficiency Virus (HIV) infection, epilepsy, seizures, pain, ulcerative colitis and Crohn's disease.

For adults, the two main clinical indications for drug-related acute pancreatitis are type 2 diabetes mellitus and hypertension with respectively 2,696 cases (12.1%) and 2,518 cases (11.4%). Other important reasons are diabetes mellitus (unspecified type), depression, HIV infection, pain, prophylaxis, hypercholesterolaemia, rheumatoid arthritis, dyslipidaemia, gastroesophageal reflux disease, and hyperlipidaemia Table 4.

The six clinical indications that children and adults have in common are prophylaxis, HIV infection, pain, ulcerative colitis, gastroesophageal reflux disease, and depression.

Disproportionality analysis

We performed disproportionality analyses for the suspected product active ingredients that appeared among the top 25 in both paediatric and adult cases. Notably, we found statistically significant evidence that dexamethasone, acetaminophen, prednisone, tacrolimus, lamivudine, didanosine, furosemide were disproportionately reported in paediatric reports compared to adults (Table 5). These seven drugs have significantly higher occurrence rates for children.

Table 5
Disproportionality analysis

Suspect Product Active Ingredient	Occurrence rate		Pearson chi-squared test		
	Child sample	Adult sample	X ²	p-value	FDR-adjusted p-value
Acetaminophen	0.0599	0.0297	57.69	p < 0.001 ***	p < 0.001 ***
Lamivudine	0.0271	0.0151	17.32	p < 0.001 ***	p < 0.001 ***
Prednisone	0.0571	0.0149	196.90	p < 0.001 ***	p < 0.001 ***
Didanosine	0.0267	0.0167	10.85	p < 0.001 ***	p < 0.001 ***
Furosemide	0.0253	0.0139	16.73	p < 0.001 ***	p < 0.001 ***
Tacrolimus	0.0435	0.0138	109.70	p < 0.001 ***	p < 0.001 ***
Dexamethasone	0.0674	0.0131	345.40	p < 0.001 ***	p < 0.001 ***
Notes: The total number of observations for Children is equal to 2,138; the total number of observations for adults is equal to 27,211.					
** The disproportionality analysis examines the difference in the rate of occurrence of specific 'Suspect Product Active Ingredients' between the Child and the Adult samples. The analysis is limited to Suspect Product Active Ingredients that are shared across the top 25 in both the Child and Adult samples, i.e., acetaminophen, lamivudine, prednisone, didanosine, furosemide, tacrolimus, and dexamethasone.					
*** p-values are indicated as follows: *** at the 0.001 level, ** at the 0.01 level, and * at the 0.05 level.					
**** Benjamini-Hochberg FDR adjusted p-values are reported as 'FDR-adjusted p-value'					

ROR and PRR analysis

Asparaginase, pegaspargase, daunorubicin, vincristine, vincristine sulfate and mercaptopurine have an ROR > 10 and an PRR also > 10 (Table 6). There are significantly different reporting rates between children and adults (chi-squared). This suggests that reporting odds were > 10-fold higher in paediatric cases than in adult cases. The other drugs in the table are also more reported in children than in adults with significant signals. Didanosine is the exception, which is almost equally reported in children than in adults without a significant signal.

Multivariate analysis

The seven individual suspected product active ingredients (Table 5) were explored in a multivariate analysis (details are provided in **supplemental Tables 6.1–6.7**). For '*dexamethasone*', there is a significant interaction effect between children and dexamethasone, and apparently associated with serious outcome. This remains when including control variables. For '*acetaminophen*', there was a significant negative association with 'serious outcome', without interaction effects between children and acetaminophen. For '*prednisone*', a significant association with 'serious outcome' in general, with a significant negative association in children is documented, without interaction effect between children and prednisone. For '*tacrolimus*', a significant association with 'serious outcome' in general is also observed, be it with an interaction effect between children and tacrolimus. This appears to be associated with more serious outcomes in children, and this effect remains robust when including control variables. For '*lamivudine*', no significant associations (general, or specific to children) were observed. For '*didanosine*', there is a significant interaction effect between children and didanosine. This appears to be associated with serious outcome, and remains robust when control variables were included. Finally, for '*furosemide*', we observed a significant association between furosemide (general), but not in children, with neither interaction effects.

Table 6
Reporting odds ratio (ROR) and proportional reporting ratio (PRR) analysis of the suspect product active ingredients top 25 of the sample of children and adults.

Suspect Product Active Ingredient	Child cases	Total Child cases – a	Adult cases	Total Adult cases – c	ROR			PRR			χ^2
	a	b	c	d	value	CI	CI	value	CI	CI	
						5.00%	95.00%		5.00%	95.00%	
Asparaginase	150	5,665	51	57,463	29.83	21.69	41.04	29.09	21.20	39.92	1,027.78
Vincristine/Vincristine sulfaat	8	5,807	3	57,511	26.41	7.00	99.58	26.38	7.00	99.39	45.92
Pegaspargase	165	5,650	68	57,446	24.67	18.58	32.77	24.00	18.12	31.79	1,057.89
Daunorubicin	51	5,764	26	57,488	19.56	12.19	31.40	19.40	12.11	31.09	294.10
Mercaptopurine	112	5,703	83	57,431	13.59	10.22	18.07	13.35	10.06	17.70	540.37
Cytarabine	111	5,704	116	57,398	9.63	7.41	12.51	9.46	7.31	12.26	426.17
Methotrexate	182	5,633	237	57,277	7.81	6.42	9.49	7.60	6.27	9.20	589.36
Cyclosporine	92	5,723	160	57,354	5.76	4.45	7.46	5.69	4.41	7.34	223.27
Valproic Acid	108	5,707	192	57,322	5.65	4.46	7.16	5.56	4.40	7.03	256.74
Dexamethasone	133	5,682	318	57,196	4.21	3.43	5.16	4.14	3.38	5.06	222.19
Cyclophosphamide	102	5,713	247	57,267	4.14	3.28	5.22	4.08	3.25	5.14	166.67
Levetiracetam	50	5,765	125	57,387	3.98	2.87	5.53	3.96	2.85	5.49	76.80
Trimethoprim	106	5,709	290	57,224	3.66	2.93	4.58	3.62	2.90	4.51	145.66
Sulfamethoxazole	106	5,709	301	57,213	3.53	2.82	4.41	3.48	2.80	4.34	137.64
Zidovudine	71	5,744	217	57,297	3.26	2.49	4.27	3.24	2.48	4.22	81.18
Prednisone	122	5,693	403	57,111	3.04	2.48	3.73	2.99	2.45	3.66	123.73
Infliximab	52	5,763	176	57,338	2.94	2.15	4.01	2.92	2.15	3.98	49.31
Divalproex Sodium	66	5,749	224	57,290	2.94	2.23	3.87	2.91	2.22	3.83	62.77
Prednisolone	75	5,740	290	57,224	2.58	2.00	3.33	2.56	1.99	3.29	55.51
Tacrolimus	93	5,722	375	57,139	2.48	1.97	3.11	2.45	1.96	3.07	63.32
Mycophenolate Mofetil	57	5,758	264	57,250	2.15	1.61	2.86	2.14	1.61	2.84	27.42
Acetaminophen	128	5,687	807	56,707	1.58	1.31	1.91	1.57	1.30	1.89	22.58
Furosemide	54	5,761	376	57,138	1.42	1.07	1.90	1.42	1.07	1.89	5.52
Lamivudine	58	5,757	412	57,102	1.40	1.06	1.84	1.39	1.06	1.83	5.29
Didanosine	57	5,758	455	57,059	1.24	0.94	1.64	1.24	0.94	1.63	2.13

Note
 * This table shows the result of the Reporting Odds Ratio (ROR) analysis for the top 25 Suspect Product Active Ingredients for the Child. The ROR is calculated as $\frac{(a/b)}{(c/d)}$ with * the number of child cases for the specific Suspect Product Active Ingredient, * the total number of child cases for the specific Suspect Product Active Ingredient, † the number of adult cases for the specific Suspect Product Active Ingredient, and ‡ the total number of adult cases for the specific Suspect Product Active Ingredient. An ROR significantly larger than one indicates that the Suspect Product Active Ingredient is significantly more frequently occurring with children compared to with adults.
 ** The number of individual drug observations for Child cases is equal to 5,815; the number of individual drug observations for adult cases is equal to 57,514. Event records in the FAERS database can contain multiple drug observations for a single patient. The observations are cleaned for duplicated drug records within the patient case.
 *** The table additionally shows the Proportional Reporting Rate (PRR) analysis for the top 25 Suspect Product Active Ingredients for both the Child and Adult cases. The PRR is calculated as $\frac{(a/c)}{(d/c+1)}$ with a, b, c, and d analogue to the ROR definitions. The PRR indicates the significance of the proportion of reporting, e.g., the Suspect Product Active Ingredient ‘Pegaspargase’ is about 24 times more likely to occur in a Child event compared to an adult event (within the subset of observations where either pancreatitis, increased amylase, or increased lipase is documented as an adverse event).
 **** The Confidence intervals are calculated at the 0.05 and 0.95 level using a log normalisation – since the distribution of the odds ratio is skewed.

The multivariate regression confirmed a robust association between dexamethasone, tacrolimus and didanosine and serious outcomes in children.

Discussion

Main findings relevant for paediatrics

We identified a fluctuating global increase in reports in both children and adults, potentially reflecting higher pharmacovigilance awareness or a rise in drug-associated cases. While the absolute number of event reports was higher in adults, a distinct paediatric pattern on suspected drugs and indications was described. Relevant for paediatric care, an overview of the top 25 drugs (Table 3) associated with drug-induced acute pancreatitis in children has been constructed. This provides clinicians a list when to suspect drug-induced pancreatitis in children.

Seriousness and age-dependent patterns

Drug-related acute pancreatitis is associated with a significant morbidity, evidenced by a 60% hospitalization rate. While paediatric mortality (7.4%) was lower than in adults (8.9%) - consistent with findings by Ahmed & Abu-El-Haija, 2025 [1]- life-threatening events were more prevalent in children (9.7% vs 7.7%). This vulnerability was highest in neonates (89.8%) and infants (79.6%), who experienced significantly higher rates of serious outcomes (**supplemental table 1**).

For children, the main indication associated with drug-related acute pancreatitis is ALL, which counts for 241 cases (14.5%). When further subdivided into paediatric age categories, In infants and toddlers, aspergillus infection and HIV infection accounts both for 7.8% and ALL accounts further accounts for 5.8% in infants and toddlers. In children and adolescents, ALL is the most prevalent clinical indication and accounts for respectively 13.6% and 10.3% (**supplemental table 4**).

The higher proportion of consumer/parental reporting in these youngest cohorts suggests that non-specific clinical signs, such as isolated vomiting, are often first recognized and reported by caregivers rather than healthcare professionals. This underscores the critical role of parental vigilance in the early detection of drug-induced pancreatitis in pre-verbal children, where classic symptoms like epigastric pain cannot be easily communicated.

High risk pharmacological agents

The top ten suspected drugs in children were: methotrexate, pegaspargase, asparaginase, dexamethasone, acetaminophen, prednisone, vincristine sulfate, cytarabine, valproic acid and mercaptopurine (Table 3). Specifically, acetaminophen, lamivudine, prednisone, didanosine, furosemide, tacrolimus and dexamethasone showed disproportionate reporting signals in children compared to adults (Table 5). Furthermore, asparaginase, pegaspargase, daunorubicin, vincristine and mercaptopurine have ROR and PRR values > 10, suggesting paediatric reporting rates are over ten times higher than in adults (Table 6).

Asparaginase is a cornerstone in ALL treatment. Wolthers et al. demonstrated that children included in their study developed acute pancreatitis within 50 days of exposure to asparaginase, with an incidence of 2–10%, depending on the cumulative dosage. Furthermore, re-exposure leads to recurrence of acute pancreatitis in 50% [15]. While asparaginase remains a cornerstone in paediatric ALL treatment, these findings underscore the potential association in the pathogenesis of acute pancreatitis. Similarly, our data aligns with the article of Buthler et al. Click or tap here to enter text.regarding the use of daunorubicin [16]. While utilized in adults and children for different oncological indications, it is associated with serious adverse events, most notably acute pancreatitis.

Disproportionality

Clinical indications differed sharply by age group (Table 4). In children, drugs associated with acute pancreatitis were primarily linked to ALL (241 cases or 14.5%). Other important reasons are prophylaxis, HIV, or epilepsy. In contrast, adult event reports were driven by diabetes type 2 (2,696 or 12.1%) and hypertension (2,518 or 11.3%). Other important reasons in adults are depression, HIV, or pain. Disproportionality analysis suggests that these drug-event combinations were reported disproportionately more often in paediatric than adult reports within FAERS, likely due to age-dependent pharmacokinetic and pharmacodynamic variations. Alternatively, these events are driven by differences in pharmacoepidemiology [17]. It is essential to expand clinical trials for children, as linear scaling based on weight or surface area fails to account for the pharmacodynamic and pharmacokinetic differences in children compared with adults, most pronounced in the first year(s) of life [18]

These factors reflect the necessity to perform age-specific clinical trials to mitigate the risks of both under- and overdosage in neonates and children (Pharmacology, 2003). [19]The multivariate regression confirmed a robust association between dexamethasone, tacrolimus and didanosine and serious outcomes in children. This emphasizes the need for heightened clinical vigilance when these specific agents are prescribed. The observed significant interaction between dexamethasone and serious outcomes in children ($p < 0.001$) may reflects its intensive use within paediatric oncology protocols, where synergistic toxicity with agents like L-asparaginase may exacerbate pancreatic injury.

Strengths and limitations

Pharmacovigilance is important to detect and explore post marketing issues with drugs, and provides real-world knowledge. The FAERS database is publicly available, and provides global information, in contrast to single centre, cohort or population databases. However, it is important to realize that events are reported, not necessary equal to reactions [20].

As with all spontaneous reporting systems, this analysis is subject to underreporting, reporting bias, and confounding by indication, which may influence observed patterns. It is often unclear whether an adverse event report of acute pancreatitis is attributable to the suspected drug, a concomitant [21]medication, an underlying pancreatic condition, or other concurrent factors (event versus reaction) [22]. For example, patients with Crohn's disease or ulcerative colitis have both a higher incidence of autoimmune pancreatitis and are frequently treated with immunosuppressive agents or corticosteroids, which may complicate causal interpretation[21]. Event reports are reported by healthcare professionals, consumers and pharmaceutical industry, without external control. Therefore, there are possibly duplicates or incompleteness in the event reports.

Recommendations and future approaches

Based on the distinct reporting patterns identified, clinicians should maintain a high index of suspicion for acute pancreatitis in paediatric patients treated with oncologic or immunomodulatory agents, even when symptoms are non-specific (e.g., isolated vomiting in infants). Future research should move beyond spontaneous reporting to prospective multicentre registries to capture denominators to calculate true incidence rates. Additionally, mechanistic studies are needed to determine if the high RORs for drugs like dexamethasone and tacrolimus in children are due to unique paediatric pharmacodynamic sensitivities or cumulative toxicity within complex treatment protocols. Integrating FAERS data with electronic health records (EHR) through machine learning could further refine early signal detection and help develop age-specific automated safety alerts.

Conclusions

This study provides a clinically relevant overview of the top 25 drugs associated with acute pancreatitis in children, offering a clinical useful tool for paediatricians when to suspect drug-induced pancreatitis. Twenty-four of the top 25 identified drugs show significantly higher reporting rates in children weighted to adults, and relate to ALL or immunotherapy, instead of cardiovascular and metabolic diseases in adults. The robust association between dexamethasone, tacrolimus, and didanosine and serious paediatric outcomes warrants closer clinical monitoring. These findings underscore the need for age-specific risk assessment to improve patient safety and early intervention in paediatric drug-induced pancreatitis.

Abbreviations

ALL: acute lymphatic leukaemia

ATC: Anatomical Therapeutic Classification

EMA: the European Medicines Agency

EHR: electronic health records

FAERS: the U.S. Food and Drug Administration Adverse Event Reporting System

GVP: Guidelines on Good Pharmacovigilance Practices

HIV: human immunodeficiency virus

PRR: proportional reporting ratio

READUS-PV guidelines: The REporting of A Disproportionality Analysis for DrUg Safety Signal Detection Using Individual Event Safety Reports in PharmacoVigilance

ROR: Reporting Odds Ratio

USA: the United States of America

Declarations

Conflict of Interest Statement

Karel Allegaert is member of the editorial board of European Journal of Paediatrics. He has not taken part in the review or selection process of this article. None of the authors has a conflict of interest relevant to the content of this article.

Author contributions

Methodology and Protocol: AV, KA; Statistical analysis: AV, NY; Resources: AV, KA; Writing - original draft preparation: AV, KA ; Writing - review and editing: NY, KVH, PDB. All authors have read and agreed to the published version of the manuscript.

Ethics approval

Not applicable.

Data availability statement

The dataset generated for this analysis is based on publicly available information. Researchers interested in using the data can contact the corresponding author.

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Figures

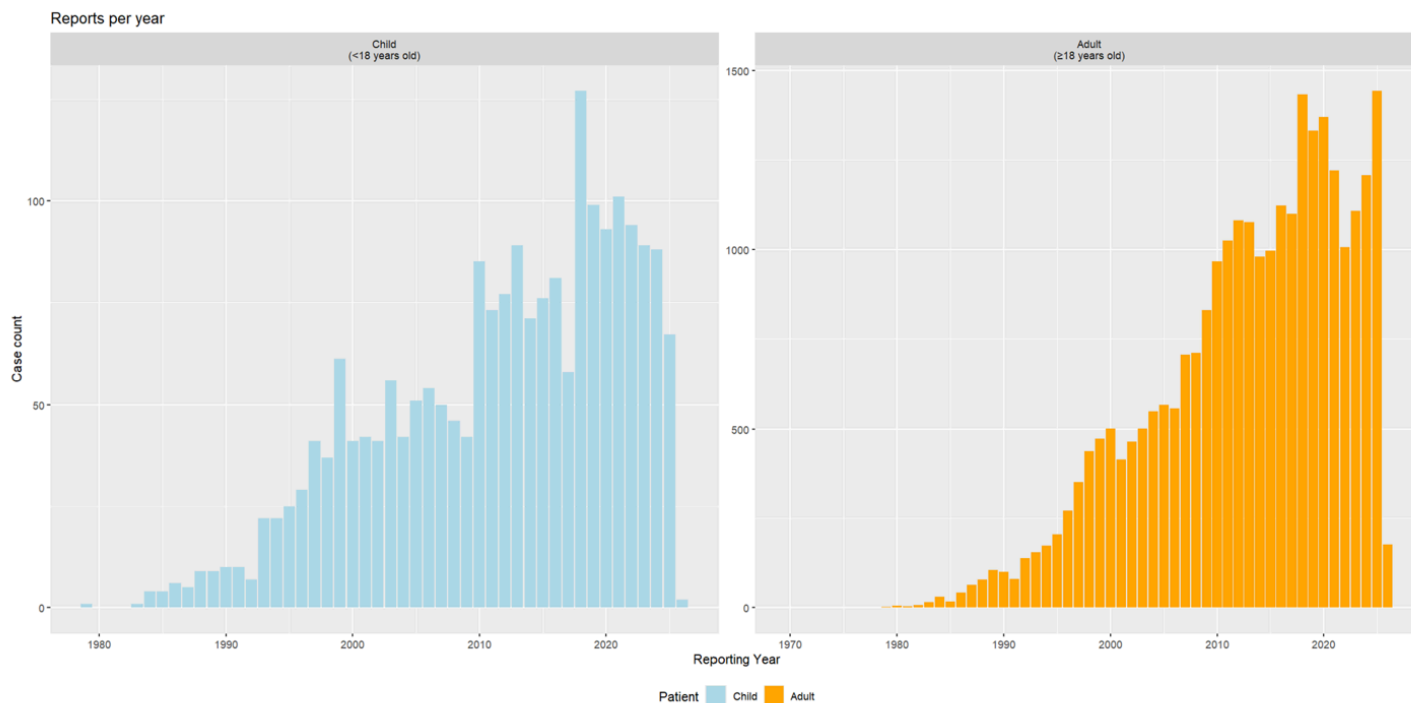


Figure 1

Number of reports per year – split by children and adults

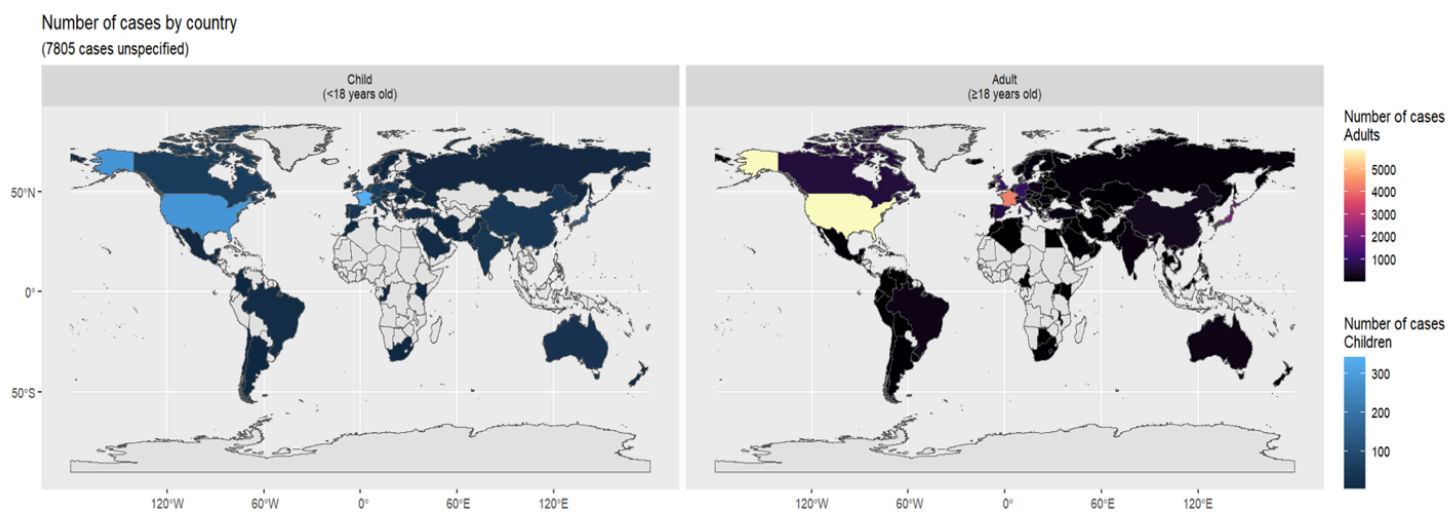


Figure 2

Number of cases reported per country (excl. 7,805 cases without country observation)

Supplementary Files

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