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Incidence and Clinical Associations of Childhood Acute Pancreatitis

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Short title: Incidence of acute pancreatitis

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Abbreviations:
AP: Acute pancreatitis
BAPS: British Association of Paediatric Surgeons
BPSU: British Paediatric Surveillance Unit
CI: confidence interval
INSPPIRE: International Study Group of Paediatric Pancreatitis: In Search for a Cure
MMR: measles, mumps and rubella
RCPCH: Royal College of Paediatrics and Child Health

What's Known on This Subject: Acute pancreatitis in childhood is a relatively rare but potentially serious condition. In the past, trauma and mumps have been the commonest associations. No study has ever estimated incidence within a childhood population on a prospective basis.

What This Study Adds: Acute pancreatitis has a childhood incidence in the UK of 0.78 per 100,000/year (95%CI 0.62-0.96). Gallstones and drug therapy are now the most commonly identified associations whilst mumps and trauma are identified rarely. Children of Pakistani heritage are disproportionately affected.

Contributors' Statements:

Abdalmonem Majbar: Dr Majbar helped with designing the data collection instruments, collected the data, conducted all analyses, drafted the initial manuscript, and approved the final manuscript as submitted.

Eleri Cusick and Paul Johnson: Ms Cusick and Professor Johnson contributed to study conceptualization and design, took part in data interpretation, critically reviewed the manuscript, and approved the final manuscript as submitted.

Richard Lynn: Mr Lynn contributed to study conceptualization and design, critically reviewed the manuscript, and approved the final manuscript as submitted.

Linda Hunt: Dr Hunt supported and contributed to the statistical analysis, critically reviewed the manuscript, and approved the final manuscript as submitted.

Julian Shield: Professor Shield conceptualized and designed the study, supervised and assisted data collection and analyses, critically reviewed the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: To establish the UK incidence and clinical associations of acute pancreatitis (AP) in children aged 0–14 years.

Methods: Monthly surveillance of new cases of AP in children under 15 years of age through the British Paediatric Surveillance Unit conducted from April 2013 to April 2014 (inclusive) followed by one year administrative follow-up for all valid cases.

Results: 94 cases (48 boys) fulfilled the diagnostic criteria. The median age at diagnosis was 11.2 years (range 1.3–14.9). White children accounted for 61% of the cases compared to 28% from Asian and 5% from African ethnicities. Pakistani children accounted for 18 of 26 (69%) Asian patients and 19% of the total cohort. The incidence of AP in children in the UK was 0.78 per 100,000/year (95%CI 0.62–0.96). The incidence in Pakistani children (4.55; 95%CI 2.60-7.39) was 7-fold greater than White children (0.63; 95%CI 0.47-0.83). Of the 94 cases: 35 (37%) were idiopathic or associated with drugs 18 (19%), gallstones 12 (13%), hereditary 7 (7%), organic acidaemias 7 (7%), anatomical anomalies 5 (5%), viral infections 3 (3%), systemic diseases 2 (2%) and trauma 1 (1%). The most common drug associations were asparaginase (28%), azathioprine (17%) and sodium valproate (17%).

Conclusions: Whilst still relatively uncommon in the UK, on average there is more than one case of childhood AP diagnosed every week. The associations of AP have changed significantly since the 1970/80's. Over-representation of Pakistani children is worthy of further investigation.

INTRODUCTION:

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas with variable involvement of peri-pancreatic tissues and/or distant organ systems.[1] AP is uncommon in children, but leads to significant morbidity in the short, medium and long-term. Recently, an increase in the number of paediatric AP cases in single institutions has been reported by centres in the USA,[2-5] Australia,[6] and Mexico.[7] However, these studies are retrospective reviews and the incidence of AP is usually reported as an absolute number of cases per centre per year at individual referral institutions.

There is no recent UK data on AP in childhood and no robust estimate of incidence. Sibert conducted a retrospective review of all pancreatitis cases (acute and chronic) admitted to hospital in the Newcastle area and Wales between 1968 and 1975 and estimated the annual rate of diagnosis of pancreatitis in children under 16 years at approximately 1/400,000 in Newcastle and 1/250,000 in Wales.[8] Until now, no national population-based study has been conducted, either prospectively or retrospectively, to investigate the frequency of this condition in children, in the UK or elsewhere.

In adults, the most common causes of AP are alcohol and gallstones,[9,10] but in children it is associated with a wide variety of potential aetiologies, including abdominal trauma, drug therapy, infections, systemic diseases and congenital anatomical anomalies.[2,11] Trauma and mumps were the commonest associations reported in the UK in the 1970/80's.[8,12,13] However, there has been no effort to re-examine the associated agents of this disease in the UK in the last three decades. The last study conducted within the UK was performed in Scotland in the 1990s on retrospective data from 1978-1992, where mumps (39%) and trauma (14%) were the most frequent associations.[13]

Several changes in population characteristics, including the introduction of the MMR vaccine in 1988 and an increase in the prevalence of obesity-associated gallstones among children,[14] may have changed the incidence and causative agents responsible for this relatively rare condition in childhood. Therefore, the aims of this study were to conduct the first prospective examination of the incidence of AP in UK children and to determine its current clinical associations.

METHODS

We conducted a prospective monthly surveillance of over 3,700 consultant paediatricians and paediatric surgeons in the UK and Ireland using the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health (RCPCH) to detect all new cases of AP in 0- to 14-year-old children. The BPSU is an active reporting system where an orange card containing a list of conditions is sent monthly, by post or electronically, to all consultant paediatricians and other specialists where appropriate. Respondents report cases they have seen in the previous month for conditions named on the card, or to tick a "Nothing to report" box. Following the return of the card to the BPSU, the research team are informed of the reporting clinicians' details who receive a short proforma asking for clinical details, this is returned to the researcher for analysis.[15,16] AP in children under 15 years of age was included on the card for 13 months (April 2013 to April 2014 inclusive). The orange card return compliance was 95.3% during the study period. To identify children directly referred to surgical departments, the British Association of Paediatric Surgeons (BAPS) supported this study and paediatric surgeons received the orange card. Almost all paediatricians belong to the RCPCH and thus receive 'orange cards'. The vast majority of paediatric surgeons are members of BAPS or RCPCH. No general or emergency physicians in the UK manage children with AP without referral to one of the above.

Clinicians were asked to report any child under the age of 15 years seen in the previous month with a new diagnosis of AP. Diagnosis of AP required at least two of the three following features: (1) Acute onset of upper abdominal pain; (2) Serum amylase and/or lipase raised ≥3 times the upper limit of normal local range; and (3) Imaging findings characteristic of AP. These criteria for diagnosis of AP were adapted according to revised Atlanta criteria,[17] and a consensus of the "International Study Group of Paediatric Pancreatitis: In Search for a Cure" (INSPPIRE).[18]

Reporting clinicians were contacted with an initial study questionnaire to collect information about the patient, clinical presentation, diagnostic details, consultant at discharge and again at one year post diagnosis. Upon receipt of a completed initial study questionnaire, the eligibility of the patient and case status was determined. This included the age of the child, time of diagnosis and fulfilment of the study case definition. The clinicians' diagnoses were reviewed by the study investigators (A.A.M., J.H.S., P.J. and E.C) in light of the questionnaire data supplied. Clinical associations were accepted after the investigators' review and special considerations. For example, viral infection and hereditary pancreatitis were only recorded, as an association if a confirmatory serology test or genetic testing, were conclusive. Associations were updated at the end of the follow-up period. Cases with no identifiable association were then classified as idiopathic. If a child had more than one episode of AP during the study period, only the first episode was included as a new case.

Ethics approval

The study was approved by The National Research Ethics Service (NRES) Committee South West – Central Bristol – (REC reference 11/SW/0132) and was granted Section 251 of the National Information Governance Board for Health and Social Care (NIGB) permission by NIGB Ethics and Confidentiality Committee (ECC) under reference ECC 6-02(FT12)/2012.

Statistics

The incidence rate was calculated using the valid cases from the first 12 consecutive months and the population denominator obtained from "Population Estimates Summary for the UK, mid-2013" table, published by the Office for National Statistics.[19] Ethnicity specific incidence rates of AP were calculated for English and Welsh children only using the "Ethnic group by age in England and Wales 2011" data.[20] The ethnic groups by age were only available for these two countries. 95% confidence intervals for rates were calculated using an 'exact' method for Poisson. Poisson regression models were used to compare the rates for the main ethnic groups. The statistics software SPSS (Version 21.0. Armonk, NY: IBM Corp) and Stata vs 12.1 (StataCorp LP, Texas, 1985-2011) were used for analysis. A 5% level of significance was used.

RESULTS

220 case notifications were received over the 13 months of the study. Of these, 202 (92%) responses to the initial study questionnaire were received and the remaining 18 cases had no response. 133 episodes met the diagnostic criteria for AP during the study period; 95 were newly confirmed cases (94 from the UK and 1 from Ireland), 20 were duplicates and 18 were recurrent episodes. Sixty-nine cases were excluded because they did not fulfil the case definition or were diagnosed outside the study period. 94 UK newly confirmed cases were included in the final analysis and 88 of these, who had been diagnosed in the first 12 consecutive months of the study period, were used in the calculation of the incidence.

Of the 94 UK cases, 46 were girls; the female to male ratio was approximately 1:1. The median age at diagnosis was 11.2 years, (range 1.3 to 14.9 years). The cases were evenly distributed throughout the year, with no discernible seasonal trend. White children accounted for 61% of cases compared to 28% from Asian and 5% from African ethnic groups. Children of Pakistani origin accounted for the majority (18 of 26; 69%) of Asian heritage cases and 19% of the total

cohort. Eighty-eight of ninety-four cases (94%) were screened using amylase, eighteen (19%), had amylase and lipase levels measured and six cases were screened using lipase alone. Twelve children developed AP whilst in hospital during management for other conditions. In only one case was diagnosis made in intensive care unit.

Incidence rates

The estimated UK population under 15 years of age in mid-2013 was 11,307,400, giving a national incidence of AP in children aged 0–14 years of 0.78 per 100,000/year (95%CI 0.62-0.96). The specific incidence rates of AP in different ethnic groups in England and Wales are shown in Table 1.

Table 1. Ethnicity specific incidence rates for acute pancreatitis in 0-14 years olds in England and Wales

Group	Ethnicity	Population	No of cases	Rate per 100,000[a]	95% CI
	All Ethnicities	**9,891,138**	**83**	**0.84**	**0.67-1.04**
1	**White: Total**	**7,781,925**	**49**	**0.63**	**0.47-0.83**
2	**Mixed: Total**	**523,782**	**2**	**0.38**	**0.05-1.38**
	White and Asian	154,176	1	0.65	0.02-3.61
	Other Mixed	114,303	1	0.88	0.02-4.87
3	**Asian: Total**	**979,148**	**24**	**2.45**	**1.57-3.65**
	Indian	255,892	2	0.78	0.10-2.82
	Pakistani	351,384	16	4.55	2.60-7.39
	Bangladeshi	146,817	3	2.04	0.42-5.97
	Other Asian	178,704	3	1.68	0.35-4.91
4	**Black: Total**	**478,863**	**4**	**0.84**	**0.23-2.14**
	African	281,495	4	1.42	0.39-3.64
5	**Other: Total**	**127,420**	**1**	**0.79**	**0.02-4.37**
	Ethnicity not known		3		

[a] Poisson regression was used to compare the rates for the 5 main groups (labelled 1 to 5 in the first column). There were significant differences between the 5 groups (P<0.001 overall). Group 3 was significantly higher than group 1 (P<0.001) whereas the other groups 2, 4 and 5 were not significantly different from 1 (min P=0.49).

Clinical associations

The main clinical associations of AP in the 94 children are listed in Table 2. Thirty-five cases (37%) had no reported associated agents and were classified as idiopathic. The most common associations identified were drug therapy (19%) and gallstones (13%). The majority of the 35 idiopathic cases were in older age groups: 17 (49%) cases in the 10–14 age group and 14 (40%) in the 5–9 age group, compared to only 4 (11%) in the 0–4 group (2 were under 3 years). Of the 12 gallstone-associated cases, five were boys; body weight of 5 cases was above the 91st centile (4 were above the 98th centile) and 2 cases had chronic haemolytic disease (hereditary spherocytosis and sickle cell disease). Overall, 6 of 7 organic acidaemia cases (86%) and 3 of 5 asparaginase (leukaemia treatment)-associated cases (60%) were of Pakistani ethnicity. One child had recessive familial hypertriglyceridaemia. The triglyceride level, after fluid therapy, was 4.8 mmol/L (normal range 0.4-2.1 mmol/L).

Table 2. Clinical associations of acute pancreatitis in 94 children < 15 years old in the UK

Clinical association		No (%)
Idiopathic		**35 (37)**
Drugs		**18 (19)**
Asparaginase	5	
Azathioprine	3	
Sodium valproate	3	
Methylprednisolone	1	
Mercaptopurine	1	
Mesalazine	1	
Carbamazepine	1	
Clarithromycin	1	
Opiates	1	
Calcium carbonate/Alfacalcidol	1	
Gallstones		**12 (13)**
Hereditary		**7 (7)**
SPINK1 gene positive	5	
PRSS1 gene positive	2	
Organic acidaemias		**7 (7)**
Propionic acidaemia	4	
Methylmalonic acidaemia	2	
Isovaleric acidaemia	1	
Anatomical anomalies		**5 (5)**
Pancreas divisum	3	
Choledochal cyst	2	
Viral Infections		**3 (3)**
Mumps	1	
EBV & CMV	1	
Rotavirus	1	
Systemic diseases		**2 (2)**
Systemic lupus erythematosus	1	
Henoch Schonlein Purpura	1	
Trauma		**1 (1)**
Handle bar injury	1	
Others		**4 (4)**
Cystic Fibrosis	2	
Hypertriglyceridaemia	1	
Alpha 1-antitrypsin deficiency	1	

Abbreviations: SPINK1, Serine Peptidase Inhibitor, Kazal Type 1; PRSS1, Protease, Serine, 1 (Trypsin 1); EBV, Epstein–Barr virus; CMV, Cytomegalovirus.

DISCUSSION

This study demonstrates that childhood AP remains an uncommon disease in the UK: the incidence of AP in children under 15 years old was 0.78 per 100,000/year (95%CI 0.62-0.96). To the best of our knowledge, this is the first prospective, nationally based estimation of childhood AP worldwide. Only one previous retrospective study has been conducted in the UK, but it was primarily designed to examine the aetiology, complications and outcomes of pancreatitis in children. It also estimated the incidence in only two regions[8]. Although the previous study included all cases of pancreatitis and children up to age 16 years, our incidence rate is double that estimated in Wales (0.4/100,000/year) and three-fold higher than Newcastle (0.25/100,000/year).[8] This apparent increase in the UK incidence might be due to an increase in clinical awareness or to the change in its clinical associations, which was reflected by an increase in the proportion of some previously known associations, such as drugs, and the appearance of new associations not previously reported, such as organic acidaemias.

We were unable to compare our incidence findings with Europe as no data exists. The rate of childhood AP reported here for the UK was lower than that reported for Australia (2.5/100,000 in 1993 and 3.6/100,000 in 2002),[6] and the USA (2.4/100,000 in 1993 and 13.2/100,000 in 2004).[3] However, both of these studies were retrospective reviews conducted at major paediatric referral centres and the cases of AP were detected by either reviewing hospital laboratory databases,[6] or hospital discharge records.[3] The retrospective nature, referral bias and variation in the diagnostic criteria and age groups of these studies may explain these differences. In addition, the Australian study had a higher number associated with trauma (36%) and systemic disease (22%),[6] than our study (1% for trauma and 2% for systemic diseases), which might also have led to a higher incidence in Australia than the UK .

More than a quarter of our patients were of Asian or British Asian origin (28%). Interestingly, Pakistani children alone accounted for about one fifth (19%) of the cohort, although they constitute only 3.6 % of the population < 15 years of age in England and Wales.[20] As a result, the incidence in Pakistani children (4.55; 95%CI 2.60-7.39) was seven-fold higher than in White children (0.63; 95%CI 0.47-0.83) (data for England and Wales only). All seven of the organic acidaemia cases, which represent disorders caused by inherited inborn errors of metabolism, were of Asian heritage and the majority of these (6 out of 7) were Pakistani. This may reflect the tradition for first-degree marriage amongst this ethnic group and may in part explain the overrepresentation of Pakistani children in our data. As three of five asparaginase-associated cases were of Pakistani heritage, further investigation to determine whether Pakistani children have a higher incidence of leukaemia or are more sensitive to asparaginase than others is warranted.

This study shows that childhood AP has a wide variety of clinical associations in the UK, as in other countries; however, more than one third of the cases (37%) were idiopathic. It should be noted that all idiopathic cases had imaging for gallstones, but only 20% were screened for genetic causes, as the policy in the UK seems to be to screen mainly in cases with a history of recurrent pancreatitis. We found that associations of AP in this country have changed significantly compared to data from the previous four decades. Medication (19%) and gallstones (13%) were the commonest associations, whilst trauma (1%) and mumps (1%) were uncommon in our patients. Despite recent advances in diagnostic techniques, including pancreatico-biliary imaging and genetic testing, we found a high proportion of idiopathic AP in UK children although this was within previously reported national ranges of 25–56%.[8,12,13] Idiopathic AP seems to be more common in children. It has been reported globally in a wide range of proportions in children, from 15 to 36% of total cases.[6,7,21-28] Lopez did not find

idiopathic pancreatitis in children under age 3,[5] but the present study supports Kandula's findings that idiopathic cases can be detected at this young age.[29]

In 19% of our cases, AP was associated with drug therapy. The majority of these drugs (asparaginase, azathioprine, sodium valproate, methylprednisolone, mercaptopurine and opiates) are a known association,[30] and others (mesalazine, carbamazepine and clarithromycin) are recognised as possible inducers of AP.[30,31] In one case, AP was associated with hypercalcaemia secondary to over-replacement of vitamin D/oral calcium (alfacalcidol and calcium carbonate); a similar case was reported recently in an adult patient from the UK.[32] Asparaginase, azathioprine and sodium valproate, which are used for treatment of leukaemia, inflammatory bowel diseases and epileptic disorders, respectively, were the most commonly associated medications in our series. This is similar to previous paediatric findings.[2,24,25] Asparaginase-associated pancreatitis has been reported in 6.7–18% of cases following leukaemia treatment in children,[33] but the risk was only 1.5% in children and young adults with acute lymphoblastic leukaemia in the UK.[34]

Gallstones were the second most frequent association, accounting for 13% of the total patients, compared to 4% in a previous study in Scotland,[13] and no cases in other UK series.[8,12] Gallstones were not exclusively associated with the overweight or haemolytic diseases, as 5 out of 12 cases had no recognised risk factors. The proportion of gallstone cases in our study (13%) was comparable to recent studies from France (13%),[23] and America (12%),[24] and higher than in Italy (6%),[25] but less than the 26% reported in another large American study.[4]

We found trauma and mumps, previously the most commonly reported associations in the UK, to have become uncommon. Mumps was previously responsible for 16–39% of AP cases in the UK,[8,12,13] but we found only one case. This probably reflects the introduction of the MMR vaccine in 1988. The most surprising finding in the present study was that only one case was

associated with trauma during the study period. Trauma accounted for 13–16% of UK cases in the past,[8,12,13] and has been reported in 8-59% of children with AP internationally.[2,4-6,21,23,24,29,35,36] One explanation might be that children these days are overly protected by their parents, less active, and spend more time sitting watching TV or playing electronic games than being outdoors. In addition, the younger age of our cohort may also be pertinent, as trauma is more common in older teenagers.

Recent case series of AP in children from Italy, France and America indicated familial/hereditary AP in 6%, 8% and 1% of patients, respectively.[23-25] Seven of the children (7%) in our study who had recurrent episode/s were diagnosed with hereditary pancreatitis. Although AP is a known complication of organic acidaemias,[37,38] this was not reported in previous studies from this country. We found seven cases (7%), all of Asian origin, associated with these rare inherited disorders. In total, 5% of our cases were attributed to anatomical congenital anomalies (pancreas divisum and choledochal cyst); which is similar to the 5% reported in America,[24] but much lower than the 23% and 43% reported in Taiwan and Japan.[21,27] Anatomical anomalies, particularly choledochal cyst, are known to be more common in Asian than in Western children.[27]

Two cases in our study were associated with systemic diseases, namely systemic lupus erythematosus and Henoch Schonlein purpura. AP has been associated with systemic diseases in 2–53% cases in paediatric series.[2,4-6,21,23,24,26,29] This variation may be partly due to differences in the definition of AP and age of patients and to the variations in classification and assigning the associated agents. The changing incidence in Australia was attributed in part to an increase in cases associated with systemic illnesses.[6]

The main limitation of this study is the potential underestimation of incidence resulting from incomplete ascertainment inherent in the use of the BPSU methodology. Although the orange

card return compliance during the survey period and clinician responses for case information were high, at 95% and 92%, respectively, data collection solely through the BPSU may have resulted in incomplete ascertainment. In addition, it is possible that some mild cases or AP in those too young to exhibit classical abdominal pain were simply not diagnosed by clinicians caring for the children in primary or secondary care, and thus not reported. Despite this, the study provides the first epidemiological data on AP in children and its current associations.

CONCLUSION

This study shows that AP is an uncommon disease in young children in the UK, but is possibly becoming more frequent. Childhood AP has diverse clinical associations while more than one third of cases are idiopathic. The associations of childhood AP in the UK have changed significantly in the last four decades. Young patients of Pakistani ethnicity, with organic acidaemias or who are undergoing treatment with asparaginase, are at greater risk for developing AP and the diagnosis should be considered early in the management of abdominal symptoms. The over-representation of Pakistani children observed in this study merits further investigation.

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References

1. Bradley EL, 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg*. 1993;128(5):586-590

2. Werlin SL, Kugathasan S, Frautschy BC. Pancreatitis in children. *J Pediatr Gastroenterol Nutr*. 2003;37(5):591-595

3. Morinville VD, Barmada MM, Lowe ME. Increasing incidence of acute pancreatitis at an American pediatric tertiary care center: is greater awareness among physicians responsible? *Pancreas*. 2010;39(1):5-8

4. Park A, Latif SU, Shah AU, et al. Changing referral trends of acute pancreatitis in children: A 12-year single-center analysis. *J Pediatr Gastroenterol Nutr*. 2009;49(3):316-322

5. Lopez MJ. The changing incidence of acute pancreatitis in children: a single-institution perspective. *J Pediatr*. 2002;140(5):622-624

6. Nydegger A, Heine RG, Ranuh R, Gegati-Levy R, Crameri J, Oliver MR. Changing incidence of acute pancreatitis: 10-year experience at the Royal Children's Hospital, Melbourne. *J Gastroenterol Hepatol*. 2007;22(8):1313-1316.

7. Sanchez-Ramirez CA, Larrosa-Haro A, Flores-Martinez S, Sanchez-Corona J, Villa-Gomez A, Macias-Rosales R. Acute and recurrent pancreatitis in children: etiological factors. *Acta Paediatr*. 2007;96(4):534-537

8. Sibert JR. Pancreatitis in childhood. *Postgrad Med J*. 1979;55(641):171-175

9. Munsell MA, Buscaglia JM. Acute pancreatitis. *J Hosp Med*. 2010;5(4):241-250

10. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas*. 2006;33(4):323-330

11. Nydegger A, Couper RT, Oliver MR. Childhood pancreatitis. *J Gastroenterol Hepatol*. 2006;21(3):499-509

12. Moossa AR. Acute pancreatitis in childhood. A study of 16 cases and review of the literature. *Prog Pediatr Surg*. 1972;4:111-127

13. Haddock G, Coupar G, Youngson GG, MacKinlay GA, Raine PA. Acute pancreatitis in children: a 15-year review. *J Pediatr Surg*. 1994;29(6):719-722

14. Svensson J, Makin E. Gallstone disease in children. *Semin Pediatr Surg*. 2012;21(3):255-265

15. Hall SM, Nicoll A. The British Paediatric Surveillance Unit--a pioneering method for investigating the less common disorders of childhood. Report of a seminar held in June 1995. *Child Care Health Dev*. 1998;24(2):129-143

16. Knowles RL, Friend H, Lynn R, et al. Surveillance of rare diseases: a public health evaluation of the British Paediatric Surveillance Unit. *J Public Health (Oxf)*. 2012;34(2):279-286

17. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111

18. Morinville VD, Husain SZ, Bai H, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. *J Pediatr Gastroenterol Nutr*. 2012;55(3):261-265

19. Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2013. Office for National Statistics website. http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-322718. Accessed August 27, 2014

20. Ethnic group by sex by age in England and Wales 2011. Office for National Statistics website. http://www.nomisweb.co.uk/census/2011/LC2109EWLS/view/2092957703?rows=c_ethpuk11&cols=c_age. Accessed April 01, 2015

21. Chang YJ, Chao HC, Kong MS, Hsia SH, Lai MW, Yan DC. Acute pancreatitis in children. *Acta Paediatr*. 2011;100(5):740-744

22. Das S, Arora NK, Gupta DK, Gupta AK, Mathur P, Ahuja A. Pancreatic diseases in children in a north Indian referral hospital. *Indian Pediatr*. 2004;41(7):704-711

23. Fabre A, Petit P, Gaudart J, et al. Severity scores in children with acute pancreatitis. *J Pediatr Gastroenterol Nutr*. 2012;55(3):266-267

24. Lautz TB, Chin AC, Radhakrishnan J. Acute pancreatitis in children: spectrum of disease and predictors of severity. *J Pediatr Surg*. 2011;46(6):1144-1149

25. Minen F, De Cunto A, Martelossi S, Ventura A. Acute and recurrent pancreatitis in children: exploring etiological factors. *Scand J Gastroenterol*. 2012;47(12):1501-1504

26. Pezzilli R, Morselli-Labate AM, Castellano E, et al. Acute pancreatitis in children. An Italian multicentre study. *Dig Liver Dis*. 2002;34(5):343-348

27. Tomomasa T, Tabata M, Miyashita M, Itoh K, Kuroume T. Acute pancreatitis in Japanese and Western children: etiologic comparisons. *J Pediatr Gastroenterol Nutr*. 1994;19(1):109-110

28. Weizman Z, Durie PR. Acute pancreatitis in childhood. *J Pediatr*. 1988;113(1 Pt 1):24-29

29. Kandula L, Lowe ME. Etiology and outcome of acute pancreatitis in infants and toddlers. *J Pediatr*. 2008;152(1):106-110, 110 e101

30. Nitsche CJ, Jamieson N, Lerch MM, Mayerle JV. Drug induced pancreatitis. *Best Pract Res Clin Gastroenterol*. 2010;24(2):143-155

31. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol*. 2007;5(6):648-661

32. Pronisceva V, Sebastian J, Joseph S, Sharp E. A case report on over-replacement of oral calcium supplements causing acute pancreatitis. *Ann R Coll Surg Engl*. 2014;96(1):94E-95E

33. Raja RA, Schmiegelow K, Frandsen TL. Asparaginase-associated pancreatitis in children. *Br J Haematol*. 2012;159(1):18-27

34. Samarasinghe S, Dhir S, Slack J, et al. Incidence and outcome of pancreatitis in children and young adults with acute lymphoblastic leukaemia treated on a contemporary protocol, UKALL 2003. *Br J Haematol*. 2013;162(5):710-713

35. Tiao MM, Chuang JH, Ko SF, Kuo HW, Liang CD, Chen CL. Pancreatitis in children: clinical analysis of 61 cases in southern Taiwan. *Chang Gung Med J*. 2002;25(3):162-168

36. Schmittenbecher PP, Rapp P, Dietz HG. Traumatic and non-traumatic pancreatitis in pediatric surgery. *Eur J Pediatr Surg*. 1996;6(2):86-91

37. Kahler SG, Sherwood WG, Woolf D, et al. Pancreatitis in patients with organic acidemias. *J Pediatr*. 1994;124(2):239-243

38. Burlina AB, Dionisi-Vici C, Piovan S, et al. Acute pancreatitis in propionic acidaemia. *J Inherit Metab Dis*. 1995;18(2):169-172