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Asparaginase Associated Acute Pancreatitis—A Review

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Abstract: Drugs remain a leading cause of acute pancreatitis (AP) in children. Asparaginase is a known cause of AP with reported incidence of up to 19%. The exact pathophysiology of asparaginase-associated pancreatitis (AAP) is unknown. Risk factors include age (older children/adolescents and adults), intermediate risk/high risk acute lymphoblastic leukemia (ALL) and presence of genetic mutations which appear to be an additive risk. It is associated with severe AP with increased morbidity and mortality. Management is usually supportive and first involves stopping the medication, and then management of AP. Incidence of AAP upon rechallenge is high and should be avoided when possible.

Key words: Acute Lymphoblastic Leukemia, Asparaginase, Acute Pancreatitis, Children

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1. Introduction

The knowledge and awareness of pediatric acute pancreatitis (AP) has continued to improve over the past few decades.[1] Drugs are a common cause of AP in children.[2] Leukemias are the most common cancers in children and acute lymphoblastic leukemia (ALL) is the most common pediatric leukemia. Although it is not common in adults, trends have continued to increase.[3]

The use of asparaginase in the treatment of ALL has revolutionized pediatric ALL, improving long term survival to over 90%.[4] Asparaginase depletes circulating amino acid asparagine by converting it to aspartate and ammonia making it difficult for malignant cells to thrive.[5] Despite its benefits, the drug has several side effects including pancreatitis.[6] Reported incidence of asparaginase-associated pancreatitis (AAP) varies across studies but may be up to up to 19%.[7] All commercial formulations of

Abbreviations: AP, acute pancreatitis; AAP, asparaginase-associated pancreatitis; ALL, acute lymphoblastic leukemia; DM, diabetes mellitus; AGA, American Gastroenterology Association; NASPGHAN, North American Society of Pediatric Gastroenterology, Hepatology and Nutrition; INSPPIRE-2, International Study group of Pediatric Pancreatitis: In search for a cure-2; ARP, acute recurrent pancreatitis; CP, chronic pancreatitis; SNP, single nucleotide polymorphisms

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asparaginase available in the United States including pegylated forms of L-asparaginase (derived from *Escherichia coli)* PEG-asparaginase, Calaspargase pegol and lastly Erwinia derived asparaginase (from *Erwinia chrysanthemi*) are associated with pancreatitis.[8,9]

Several decades ago, a method was proposed for estimating adverse drug reactions.[10] However, given the nuance of re-exposing patients with severe AP to the same etiology to implicate the drug, drug induced pancreatitis is often underdiagnosed.[11] Specifically, AAP can be underdiagnosed since the symptoms of pancreatitis maybe often unrecognized as they can mimic common side effects of chemotherapy. AAP usually occurs early in the course of therapy, often within weeks of first dose of asparaginase.[12]

Unfortunately, many cases of AAP are severe with an associated morbidity and mortality. Severe AP incidence in AAP varies across studies. In a single center retrospective study in the USA, almost 40% of AAP episodes were severe.[13] While, in a multicenter observational study from the Ponte di Legno Toxicity Working Group study out of Denmark, out of 465 patients identified with AAP, investigators reported that slightly over a quarter of the patients (26%, N=109) developed pseudocyst and a mortality rate of 2% (N=7).[14] In another single institutional study in Taiwan, although incidence of AAP was low at nearly 5%; 78% developed moderately severe to severe AP.[15]

Recurrence of AP is common with rechallenge of asparaginase in AAP in up to 63% of cases.[12] Although some authors advocate avoiding asparaginase after AAP, some argue that rechallenge of asparaginase after an episode of APP though increases risk of pancreatitis recurrence, does not worse AP severity. In a cohort of 7640 children (from infancy to 18 years) with ALL treated under the Chinese Children Cancer Group ALL 2015 protocol, rechallenge of AAP cases with asparaginase increased AAP rates to 20.8% from 2.2% in the low-risk group and 33.8% from 5.8% in the intermediate/ high risk groups but did not worsen AP severity. A failure to rechallenge AAP cases with asparaginase was an independent risk factor for poor survival.[16] As of 2020, an expert could not offer clear recommendations on re-challenging patients with severe AAP with asparaginase until more prospective data is available.[17]

AAP can lead to both short term and long-term complications. Short term complications include all complications associated with AP.[18] Long term complications include the development of chronic pancreatitis, prediabetes/diabetes, exocrine pancreatic insufficiency and poor quality of life.[19] Diabetes mellitus (DM) requiring insulin therapy may begin during AP hospitalization and persist in the long term. In the multicenter institutional cohort study in Denmark, investigators observed that DM requiring insulin persisted even up to 8 years after episode of AAP.[14] The risk of DM in AAP is further complicated by an increased risk of hyperglycemia in children receiving asparaginase.[6]

Given the inarguable benefit of asparaginase in improving ALL survival, several questions come to mind in patients with ALL: (i) Should a patient with AAP be rechallenged with asparaginase? (ii) Are there risk factors to consider before asparaginase rechallenge after AAP episode? (iii) Should AAP severity affect decision to rechallenge? (iv) Any prophylactic medications or supportive measures to consider before starting asparaginase, during AAP, or before a rechallenge to decrease risk or severity of AAP? In this review, we will present available evidence with an attempt to answer some of these questions.

2. Clinical Management

Management of AAP is supportive. Asparaginase should be discontinued first.[20] Supportive management follows the American Gastroenterology Association (AGA) guidelines[21] and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) consensus recommendations.[22] Intravenous fluid hydration, pain control and early enteral nutrition are key management strategies.

3. Disease Mechanisms and Potential Therapies

Pathophysiological Basics

The exact pathophysiologic mechanism of AAP is unknown.[23] Potential mechanisms that have been proposed include acinar cell stress stimulation by rapid depletion of asparagine and glutamine in serum caused by asparaginase therapy.[24]

Transcriptomic data shows retinoids (vitamin A) may reverse certain gene signatures induced by asparaginase and analysis of a large electronic health database showed decreased risk of AAP with simultaneous vitamin A exposure.[25] In a recent study, investigators showed through a longitudinal lipidomic and proteomic profiling of pediatric AAP cases and controls, that an imbalance in the IL-18 and lysophasphatidylcholine signature is associated with AAP.[26]

Interventions

Potential therapies that have been trialed as prophylaxis to prevent AAP include octreotide thought to work by reducing pancreatic enzyme secretion and inflammation of the pancreas. In a single center retrospective study of 184 children with ALL, the incidence of AAP was ~10% (N=18). 13 of those who developed AAP were rechallenged with asparaginase and 12 (92%) received prophylactic octreotide, 4 (33.3%) out of these 12 patients developed AAP on re-exposure.[27] No patient developed severe AP. Other prophylactic measures including asparaginase dose reductions were undertaken by treatment physicians to prevent

recurrence.[27] Further, in a single institutional case series, investigators found that administration of a combination of protease inhibitors (gabexate mesilate, ulinastatin, and octreotide) and broad-spectrum antibiotics via continuous regional arterial infusion decreased severity of AP in children who developed AAP.[28]

Interventions

In a multinational study of patients aged 1-45 years with ALL, adolescents (10-17.9 years) and adults (18-45.9 years) had increased risk of AAP compared to young children (1-9.9 years). Further, adolescents were at an increased odds of both acute and chronic complications.[24] Adults were at an increased odds of chronic complications.[24] Further, in Chinese children treated under the Chinese Children Cancer Group ALL 2015 protocol, children who were older and those with intermittent or high risk ALL status were risk factors for AAP.[16] A systematic review evaluating risk factors for AAP showed that asparaginase formulation (particularly pegylated asparaginase), older age (>10 years), and high-risk ALL were associated with an increased risk of AAP.[8] Further, although the International Study group of Pediatric Pancreatitis: In search for a cure-2 (INSPPIRE-2) observational cohort study reported that asparaginase was an implicated medication in 23% of the acute recurrent pancreatitis (ARP) cohort cases of drug induced pancreatitis and 33.3% of the chronic pancreatitis (CP) cohort cases; other pancreatitis risk factors were present in many of these children suggesting an additive effect rather than isolated medication risk factor may be present. Overweight and obesity are also recognized risk factors for AP and for asparaginase toxicities.[29]

Some investigators have looked at the use of machine learning utilizing sex, age and inclusion of 30 single nucleotide polymorphisms (SNP) to predict risks of AAP in children undergoing ALL treatment with an ROC-AUC of 0.80.[30] The risks most predictive were younger age of 1-7 years, and certain PRSS1/PRSS2, CTRC, EPHB2, GALNTL6 mutations.[30] In another observational cohort study using data from ten international pediatric ALL groups, presence of SNP in *PRSS1-PRSS2* gene was associated with an increased risk of AAP.[31]

4. How I approach children with first time episode of suspected AAP?

It is important to note that oncologists frequently use the Common Terminology Criteria for Adverse Events (CTCAE) for grading severity of AAP and management.[32,33] A consensus accepted by both pancreatologists and oncologists is lacking.

Therefore, the information below solely reflects the opinion of the authors on the management of children with AAP.

Key information form history, physical exam, and labs

Children are diagnosed with AP using the INSPPIRE definition of pediatric AP requiring at least 2/3 criteria using a combination of symptoms: abdominal pain compatible with pancreatitis, laboratory testing of serum amylase or lipase of at least 3x the upper limit of normal, and imaging findings compatible with AP.[34] It is important to note that younger children may have nonspecific symptoms including non-localized abdominal pain, vomiting, fussiness, irritability, poor appetite. Further, many chemotherapeutic agents may cause nausea, vomiting, abdominal pain, poor appetite and symptoms of pancreatitis may be missed. Therefore, maintaining a high index of suspicion of acute pancreatitis in children with ALL who have been exposed to asparaginase is important and obtaining imaging if needed to make appropriate AP diagnosis. AP severity is classified using the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition classification.[18]

Risk Stratification

A multidisciplinary management and shared decision making including the patient or child, the family, oncologist, the pancreatologist/gastroenterologist and or advanced endoscopist and pharmacist should be involved in all children with AAP. It is important to weigh the risks of AAP, short- and long-term complication risks against the risk of ALL relapse or poor ALL prognosis when making the decision to withhold further asparaginase treatments or a rechallenge.

Risk modification is important and could be considered even prior to first dose asparaginase.

- A detailed family history screening for family history of pancreatitis or pancreatic cancer.
- Given emerging data suggesting increased risk in patients with vitamin A deficiency, consider obtaining vitamin A levels prior to starting asparaginase therapy, and consider starting supplementation if vitamin A levels are low or deficient.

For children with history of AAP, prior to rechallenge; clinicians could consider:

- Genetic testing for hereditary pancreatitis if family history of pancreatitis or pancreatic cancer is present.
- Lifestyle modifications including weight loss if overweight/obese to decrease risk of recurrence.
- Switching any medications that could also cause drug induced pancreatitis when possible.

The risk modification strategies presented above are suggestions for consideration given the limited evidence available in this area. Although important, limitations and barriers to implementation may be present. Interdisciplinary prospective studies are needed to adequately identify risk factors for AAP. Further, large multi-institutional randomized controlled trials are needed to investigate the role of prophylactic vitamin A supplementation in preventing or decreasing AAP severity.

We also present a table below comparing the CTCAE AAP grading severity, the NASPGHAN AP severity classification and the INSPPIRE AP definition. A child would have to meet INSPPIRE definition of AP for AP to be graded using the NASPGHAN AP severity classification. However, CTCAE neither relies on INSPPIRE AP definition nor does it use NASPGHAN AP severity classification. This presents a unique opportunity for a multidisciplinary collaboration between oncologists and pancreatologists to develop consensus AAP definition, classification and management.

CTCAE severity grading[32,33]	**NASPGHAN AP severity classification[18]**	**INSPPIRE AP definition[34]**
Grade 1: Asymptomatic elevation in pancreatic enzymes more than 1.5 times ULN or imaging findings of pancreatitis.	Mild AP: Meets definition for AP per INSPPIRE definition[34] without any complications (local/pancreatic or systemic) or exacerbation of comorbid conditions.	Meets at least 2 out of these 3 criteria: 1. Presence of symptoms of AP including epigastric pain 2. Elevated pancreatic enzymes: amylase or lipase at least 3 times ULN 3. Radiologic findings consistent with AP
Grade 2: Enzyme elevation or radiologic findings with symptoms (moderate).	Moderately Severe AP: Meets definition for AP per INSPPIRE definition[34] with local/pancreatic or systemic complications present, exacerbation of prior co-morbid disease or transient organ dysfunction lasting less than 48 hours present.	
Grade 3: Severe symptoms including pain that is severe, vomiting. Medical intervention is needed.	Severe AP: Meets definition for AP per INSPPIRE definition[34] with prolonged organ dysfunction lasting over 48 hours present.	
Grade 4: Severe complications which may be life threatening. Urgent intervention is needed.		
Grade 5 - Death		

ULN: Upper limit of normal, AP: Acute pancreatitis, INSPPIRE: International Study group of Pediatric Pancreatitis: In search for a cure, NASPGHAN: North American Society of Pediatric Gastroenterology, Hepatology and Nutrition classification

5. Future Directions

Large cohort prospective studies are needed to identify more risks and validate already identified risks. There appears to be genetic risks particularly in known pancreatitis risk genes, but further work is needed to understand more complex gene and environment interactions. In addition to data derived from large cohort studies, the use of machine learning may offer more accurate risk stratification in AAP. Randomized controlled trials of low cost, low toxicity prophylactic medications such as vitamin A warrant further exploration. Given the need for large observational cohort studies, we have established an anonymous registry. If possible, please add a few comments about any case of AAP, you manage here: https://redcap.peds.uab.edu/redcap/surveys/?s=34WFNDKLT7CJW7J3

6. Conclusion

Survival of ALL has significantly improved with asparaginase administration. AAP is associated with significant morbidity and mortality. Therefore, timely and accurate risk identification and proactive risk mitigation strategies are desperately needed.

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