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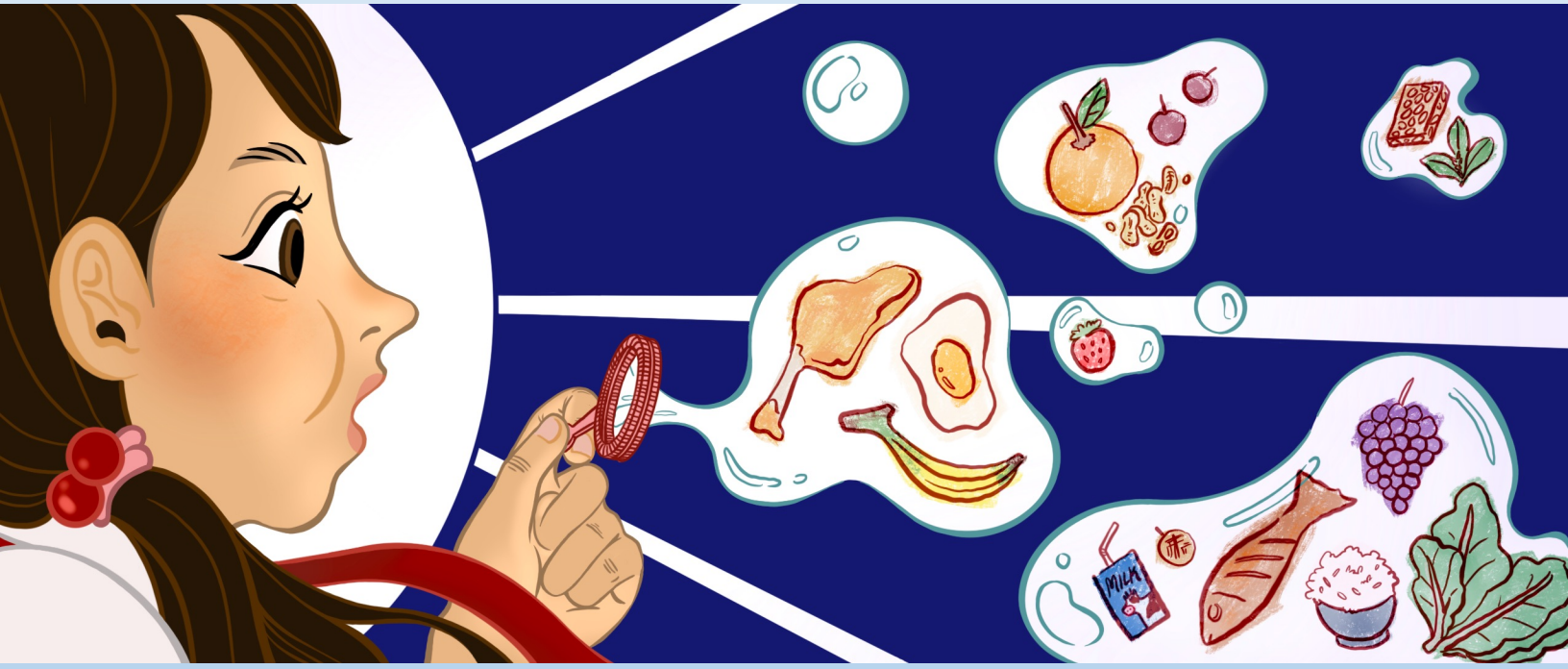

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

Is the Ketogenic Diet Effective and Safe in Children with Intractable Epilepsy? A Systematic Review

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Abstract:

Background: The ketogenic diet (KD) has long been prescribed to children with recurrent epilepsy due to its minimal neurotoxic effects. The side effects caused this diet to be abandoned. New diets are emerging as options such as modified Atkins diet (MAD), low glycemic index therapy (LGIT) and medium-chain triglyceride (MCT). This study compared the safety and effectiveness of the KD and these new methods.

***Method*:** Systematic review was conducted by searching databases such as PubMed, ScienceDirect, SpringerOpen, Cochrane, Proquest and Scopus based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.

Result: : A total of 439 pediatric patients aged 0 - 18 years who were intervened with a ketogenic diet compared with other dietary options. A total of five studies reported a higher mean reduction in seizure incidence >90% in children who were intervened with a ketogenic diet compared to other diets, one of which reported KD > MAD (53.3% KD vs. 26.6% MAD).

***Conclusion*:** Although KD remains effective, MAD, LGIT, MCT and Polyunsaturated Fatty Acids KD (PUFAKD) diets provide comparable benefits with potential for better adherence. The classic KD group showed a higher morbidity rate; however, it demonstrated significant effectiveness in lowering the incidence of recurrent seizures in children.

Keywords: children, intractable epilepsy, ketogenic diet

Introduction

Epilepsy is a chronic neurological condition that affects over 50 million people of all ages and sexes worldwide. The prevalence of epilepsy is disproportionately concentrated in low and middle-income countries (LMICs).[1] Epilepsy contributes to a significant disease burden in children and adolescents worldwide. Globally, more than 11 million children aged less than 15 years have active epilepsy.[2] In 2017, more than 291 million children aged less than 20 had epilepsy and intellectual disabilities, of which 95% lived in low- and middle-income countries.[3]

The main goals of epilepsy treatment include three basic issues: achieving the best possible seizure control, avoiding the undesired effects of treatment, and maintaining/improving the quality of patients' lives. Therefore, numerous attempts are made to offer alternative treatments for drug-resistant seizures, an example of which is the ketogenic diet.[1]

The classic ketogenic diet (KD) is a high-fat, low-carbohydrate diet, in which fat, instead of glucose, acts as a major energy source through the production of ketone bodies. The KD was formally introduced in 1921 to mimic the biochemical changes associated with fasting and gained recognition as a potent treatment for pediatric epilepsy in the mid-1990s.[4]

Although its efficacy is proven, KD is not an easy and convenient method of treatment to both patients and caregivers. Maintaining a high-fat diet can be unpalatable and result in various adverse effects. Preparing each meal with calculation and measurement of food composition and ingredients can be impossible to some patients and caregivers. Therefore, alternatives to the classic KD have been developed and studied.

Currently, four main KDs are used in clinical practice: KD, the medium-chain triglyceride (MCT) diet, the modified Atkins diet (MAD), and the low glycemic index treatment (LGIT). The efficacy of the three KD alternatives MCT, MAD, and LGIT has been compared to that of classic KD in various studies, including randomized controlled trials. When KDs must be maintained for several years because of seizure recurrence or clinical course of the disease, it is reasonable to consider switching to alternatives to the classic that have been developed and studied. MAD or LGIT were developed as less restrictive and more palatable options to the classic KD when considering the risks of long-term complications.[1]

In this systematic review we want to find out a comparison efficacy and safety of the alternative models of MCT diet, MAD, and LGIT compared to the classic KD in reducing seizures.

Method

Literature Search

We explored PubMed, ScienceDirect, ProQuest Dialog (PQD), Cochrane and Springer Open from articles published in the recent 10 years November, 2009 to November, 2024 using the following keywords (MesH Term) of "child", "pediatric", "ketogenic diet", "keto diet", "intractable epilepsy", "refractory epilepsy", "safety", "adverse effects", "efficacy", "effectiveness", "seizure reduction", "morbidity outcome".

Online scientific articles were first screened by title and abstract based on the following inclusion criteria: publication in English, cohort and randomized-controlled trial study design focusing on Ketogenic Diet (KD) versus other dietary option with outcomes of seizure reduction incidence and adverse effects of diet; the study subject age <18 years and diagnosed with intractable epilepsy. The exclusion criteria were unavailable online full-text publication; systematic-reviews; meta-analyses; informal literature review. The results were presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline (**Figure 1**).

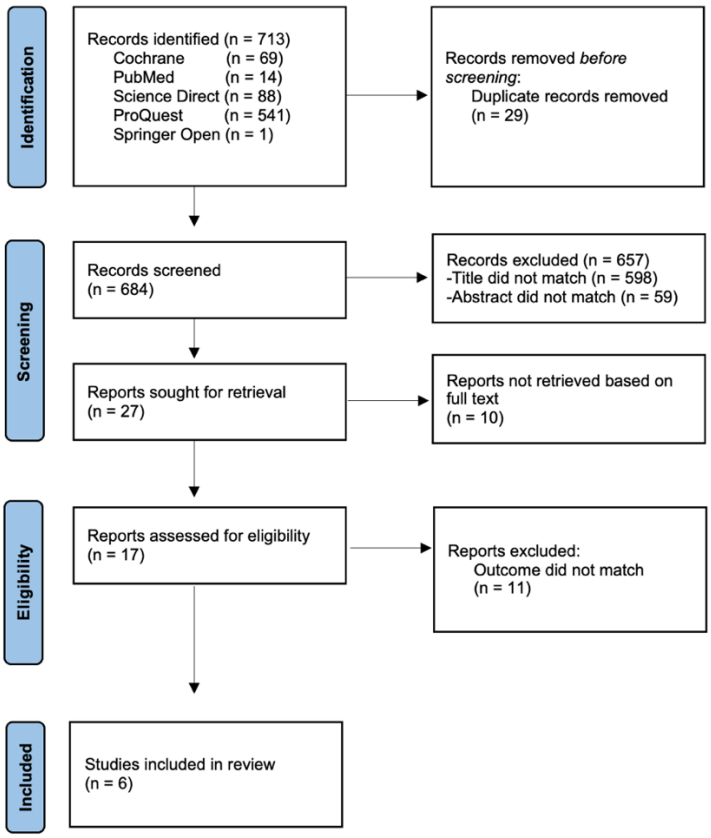

Figure 1. PRISMA flowchart on study screening and selection process.

Ketogenic Diet

The classic KD has been used worldwide as a well-established treatment for intractable epilepsy with expanding indications, especially in the neuro-metabolic field. KD is a high-fat, low-carbohydrate, and adequate-protein diet designed to induce ketosis; a state that has been shown to reduce seizure frequency in many patients. It consists of the ratio of 70-80% fat, 10-20% protein, and less than 10% carbohydrate.[5] The KD has several types, including the classical KD, MCT, Polyunsaturated Fatty Acids KD (PUFAKD), MAD, and LGIT.[6-8]

The classical KD is the original form of the ketogenic diet, developed in the 1920s primarily to treat drug-resistant epilepsy, particularly in children. KD uses a 4:1 ratio of fat to combined with LCT and carbohydrates. The MCT is a variation of the ketogenic diet that incorporates medium-chain triglycerides (MCTs) as the primary fat source. MCTs promotes faster ketosis due to quicker liver absorption. PUFAKD is another variation of ketogenic diet which emphasizes the inclusion of polyunsaturated fatty acids (PUFAs) as the primary fat source. PUFAs incorporates omega-3-rich fats for anti-inflammatory benefits in seizure control. Moreover, MAD is less restrictive variation of ketogenic diet, allowing more protein and easier adherence. MAD focuses on limiting carbohydrates to induce ketosis while allowing for greater flexibility in protein and fat intake. It was developed as an alternative for individuals, particularly those with epilepsy, who find the classical ketogenic diet too rigid or challenging to follow.[6-8]

Another dietary approach used to manage epilepsy is LGIT. While both KD and LGIT aim to reduce seizures by altering the brain's energy metabolism, LGIT focuses on limiting high-glycemic foods to stabilize glucose, minimizing spikes in insulin.[6-8]

Data Extraction

Titles and abstracts retrieved from the database were independently screened by five reviewers to identify relevant studies that met the selection criteria outlined above, who also independently assessed eligibility by further reviewing the full text. Disagreements were resolved through consultation with a sixth reviewer. Data from the articles then were extracted, including lead author, year of publication, type of study, country, age of subject, age of seizure onset, number of subjects, type of intervention, follow-up period, frequency of daily seizure, record method of seizure, incidence of seizure reduction, and adverse effect of diet. The reviewers extracted data independently and discrepancies were identified and resolved in consultation with other reviewers. The selection process is shown in the PRISMA 2020 flow diagram (**Figure 1**).

Result

There were 713 articles found based on the literature search, of which 6 identified as relevant to the topic and met the inclusion criteria. The articles included were Randomized controlled trials published from November 2009 - November 2024. A total of 564 pediatric patients aged 0 - 18 years who were intervened with a ketogenic diet compared with other dietary options such as PUFAKD, MAD, LGIT and KD 2,5:1 was studied. The subject characteristics are shown in **Table 1.**

Cases of seizure free children were reported in two study where the classic ketogenic diet reported a higher number of seizure free cases compared to the modified atkins diet (53.3% vs 26.6% and 60% vs 46.67%) as shown in **Table 2** and **Table 3**, while other study reported a higher number of seizure free cases in polyunsaturated fatty acids ketogenic diet compared to the classic ketogenic diet (37% vs 32%) as shown in **Table 3**. During the 2 follow up periods month 3 and 6 (**Table 2** and **Table 3**), a total of three studies reported a higher mean reduction in seizure incidence >90% in children who were intervened with a ketogenic diet compared to other diets, three of which reported KD > MAD (37% KD vs. 32% MAD; 6.6% KD vs. 0% MAD; 37% KD vs. 30% MAD)[16,17,18,21,22]. Four studies also reported a higher mean reduction in seizure incidence 50-90% in children who were intervened with a ketogenic diet, four of which reported KD > MAD (43% KD vs. 42% MAD; 45.8% KD vs. 45.5% MAD; 44.2% KD vs. 25.0% MAD; 39% KD vs. 36% MAD)[17,18,21,22].

A higher percentage of gastrointestinal adverse events such as vomiting, diarrhea, and constipation was reported in all studies of KD compared to MAD. Incidence of kidney stones was reported higher in KD compared to MAD group (4 % vs. 0%; 8.3% vs. 0%)[17,21]. During the 6-month follow-up period, ketogenic hypercholesterolaemia was also shown to be higher in the KD group than the MAD group (14 % vs. 11 %; 8.3% vs. 0%) as shown in **Table 4**[17,21].

Discussion

Classic KD is a low-carbohydrate and high-fat diet, that is considered wildly successful in treating children with recurrent epilepsy and seizure.[9-11] Throughout the history of neurological medication, KD was deemed efficient due to its minimal neurotoxic effects. The main features of a KD treatment are the production of ketone bodies, mainly β-hydroxybutyrate, acetoacetate, and acetone formed during the breakdown of fatty acids in the liver, along with a reduction in blood glucose levels. Ketone bodies serve as an alternative energy source to glucose and are also important for the development of the brain, providing essential materials for building cell membranes and lipids.[12] To improve dietary based treatment efficacy and flexibility, several variants of the KD have been developed as opposing factors to minimize side effects

that are commonly recorded in short-to-medium term benefits of neurological symptoms.[13]

The classic KD is effective for managing intractable epilepsy in children but can be difficult to maintain. This has led to alternative diets like the MAD, LGIT, and MCT diet, which aim to provide similar benefits with potentially easier adherence. MAD is a high-fat, low-carb diet with greater protein flexibility, without strict calorie counting. Studies show MAD can reduce seizure frequency similarly to KD and may be easier to follow for some families.[14] LGIT emphasizes low-glycemic carbs to stabilize blood sugar. Research suggests LGIT can significantly reduce seizures and may be easier to adhere to than KD.1 Medium-chain triglyceride diet uses to induce ketosis with a higher carbohydrate allowance, potentially making it more palatable. Studies show it to be as effective as KD in seizure reduction, with fewer side effects for some patients.[15]

In this study, we conducted a systematic review of studies focusing on effectiveness and safety of classic KD compared to MAD, LGIT, MCT and KD 3:1 and KD 2.5:1. We focused on seizure recurrence and diet-related side effects, assessing outcome reductions after 3 and 6 months.

In the 3 months follow up, the efficacy percentage of the control group (KD) showed higher results in >90% outcome reduction in recurrent seizures compared to other methods (6.67% vs 0%; 21% vs 27%; 32% vs 37%; 26.6% vs 53.33%), respectively written "case" vs "control".[16-18] This result was also in line with a RCT study that stated efficacy of KD during the 4 months follow up was evidently effective in reducing recurrent seizure.[19] Although this outcome was regarded as comparable in efficacy by a study conducted in 2021, other studies have shown that using modified KD 2.5:1 granted more efficacy in seizure control due to fewer adverse events, with no significant difference in the biochemical parameters as compared to other modified KD ratio.[16,20]

To further verify the efficacy and safety of KD, results from other methods have showed that >50%-≤90% seizure reduction were more significant compared to KD in 3 months follow up, with reports of MCT and modified KD in the intervention group presented higher results (63% vs 58%).[16] However, one study conducted by Kim et al. presented a different result, where the control group using KD was proven more effective in >50%-≤90% reduction of recurrent seizure as compared to modified KD (42% vs 43%).[17]

Table 1. The Characteristics of Subjects

No	Author (year)	Type of Study	Study Location	Mean age, month (SD)		Type of Intervention				Follow-up Period (month)	Mean age at onset of seizure, month (SD)		Mean daily seizure frequency, n (SD)	
				Case	Control	Case	Sample (n)	Control	Sample (n)		Case	Control	Case	Control
1	Raju et al, 2011[16]	RCT	India	2.8 (1.1)		KD 2,5:1	19	KD	19	3	NR		47.8 (38.5)	
2	El-Shafie et al, 2023[18]	RCT	Egypt	48-85a		MAD	15	KD	15	3, 6	21.5-55a		10	
3	Poorshiri et al, 2021[21]	RCT	Iran	4.5 (1.5)		MAD	15	KD	30	6	NR		NR	
4	Sondhi et al, 2020[23]	RCT	India	5.2 (3.2)		MAD	58	KD	55	6	0.7 (1.4)		20.1 (31)	
						LGIT	57							
5	Kim et al, 2016[17]	RCT	Korea	4.9 (4)		MAD	53	KD	51	3, 6	2.3 (2.8)		4.6 (NR)	
6	Ray et al, 2024[22]	RCT	India	55.2 (27.6)	49.2 (15.6)	PUFA KD	27	KD	25	6	57 (27.47)	50 (26.03)	75.62 (17.7)	62.6 (16.4)

RCT = Randomized Controlled Trial, a = Interquartile range is reported, KD = Classic Ketogenic Diet, MAD = Modified Atkins Diet, LGIT = Low Glycemic Index Therapy, PUFAKD = Polyunsaturated Fatty Acids Ketogenic Diet, NR = Not Reported

Table 2. Outcome of Seizure Reduction in 3 Months

Author , year	Type of Intervention, Sample Size		Seizure free, n (%)		>90% Seizure Reduction, n (%)		90-50% Seizure Reduction, n (%)		<50% Seizure Reduction, n (%)	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
El-Shafie et al, 2023[18]	MAD, 15	KD, 15	4 (26.6)	8 (53.3)	1 (6.67)	0 (0)	8 (53.3)	6 (39.9)	2 (13.3)	1 (6.67)
Kim et al, 2016[17]	MAD, 53	KD, 51	NR	NR	17 (32)	19 (37)	22 (42)	22 (43)	NR	NR
Raju *et al*, 2011[16]	KD 2,5:1, 19	KD, 19	NR	NR	4 (21)	5 (27)	12 (63)	11 (58)	NR	NR

MAD = Modified Atkins Diet, KD = Classic Ketogenic Diet, LGIT = Low Glycemic Index Therapy, PUFAKD = Polyunsaturated Fatty Acids Ketogenic Diet, NR = Not Reported

Table 3. Outcome of Seizure Reduction in 6 Months

Author , year	Type of Intervention, Sample Size		Seizure free, n (%)		>90% Seizure Reduction, n (%)		90-50% Seizure Reduction, n (%)		<50% Seizure Reduction, n (%)	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
El-Shafie et al, 2023[18]	MAD, 15	KD, 15	7 (56.67)	9 (60)	0 (0)	0 (0))	7 (46.67)	5 (53.33)	1 (6.67)	1 (6.67)
Poorshiri et al, 2021[21]	MAD, 15	KD, 30	NR	NR	0 (0)	2 (6.6)	5 (45.5)	11 (45.8)	NR	NR
Sondhi et al, 2020[23]	MAD, 58	KD, 55	NR	NR	6 (11.5)	6 (11.5)	13 (25)	23 (44.2)	14 (26.9)	13 (25)
	LGIT, 57		NR	NR	8 (14.8)	-	15 (27.8)	-	15 (27.8)	-
Kim et al, 2016[17]	MAD, 53	KD, 51	NR	NR	16 (30)	19 (37)	19 (36)	20 (39)	NR	NR
Ray *et al*, 2024[22]	PUFAKD, 27	KD, 25	10 (37)	8 (32)	0 (0)	3 (12)	9 (33.3)	9 (36)	8 (29.6)	5 (20)

KD = Classic Ketogenic Diet, MAD = Modified Atkins Diet, NR = Not Reported

Table 4. Outcome of Adverse Effect

Author, year	Follow-up period, month	Type of Intervention, Sample Size (n)		Vomiting, n (%)		Diarrhoea, n (%)		Constipation, n (%)		Lack of Energy, n (%)		Severe Infection, n (%)		Renal Stone, n (%)		Hyper-cholesterolemia, n (%)	
		Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Kim et al, 2016[17]	3	MAD, 53	KD, 51	8 (15.0)	9 (18.0)	3 (6.0)	5 (10.0)	12 (23.0)	14 (27.0)	10 (19.0)	13 (25.0)	0 (0.0)	3 (6.0)	0 (0.0)	0 (0.0)	10 (19.0)	7 (14.0)
	6			2 (4.0)	2 (4.0)	0 (0.0)	1 (2.0)	10 (20.0)	9 (17.0)	1 (2.0)	2 (4.0)	2 (4.0)	0 (0.0)	0 (0.0)	2 (4.0)	6 (11.0)	7 (14.0)
Raju et al, 2011[16]	3	KD 2,5:1, 19	KD, 19	NR	NR	NR	NR	3 (15.7)	5 (26.3)	NR	NR	1 (5.2)	2 (10.5)	NR	NR	NR	NR
Poorshiri et al, 2021[21]	6	MAD, 15	KD, 30	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0 (0.0)	2 (8.3)	0 (0.0)	2 (8.3)
Ray et al, 2024[22]	6	KD, 25	PUFAKD, 27	4 (16)	13 (48.0)	1 (4.0)	5 (18.5)	7 (28.0)	7 (25.9)	1 (4.0)	-	NR	NR	NR	NR	NR	NR

MAD = Modified Atkins Diet, KD= Ketogenic Diet, PUFAKD= Polyunsaturated Fatty Acids Ketogenic Diet, NR= Not Reported

In a longer observation period of 6 months, classic KD was shown to achieve consistent results with a highly coherent in >90% or percentage in reducing the incidence of recurrent seizures >90% (30% vs. 37%; 46.7% vs. 60%; 0% vs. 6.6%; 0% vs 12%)[17-18,21- 22], compared to other diets. In contrast to the 3 months results, the classic KD group showed a higher percentage in reducing the incidence of recurrent seizures 50%-≤90% (36% vs. 39%;33.3% vs 36%;26.4% vs. 44.2%)[17,22-23], compared to the alternative diet. This proves that the classic KD has promising efficacy in the longer term. This outcome is in accordance with a study conducted in 2024, showing significant efficacy in 32% seizure free with classic KD in a 6 month study course.[22] To strengthen the previous scientific studies, a recent study in 2020 and 2024 showed the percentage reduction in recurrent seizure <50% higher in the alternative diet group.[22-23]

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In terms of diet safety at 3 months of observation, two studies reported no significant difference in classic KD compared to other diets for gastrointestinal disorders such as vomiting (15% vs. 18%)[17], diarrhea (6% vs. 10%)[17] and constipation (15.7% vs. 26.3%; 23% vs. 27%).[16-17] Studies conducted in 2019 and 2021 also stated, in a 3-month study follow up, results showed no significance in gastrointestinal adverse events, deeming classic KD to be safe have no basis for discontinuation.[28-29] Two studies reported adverse events of severe infection in classic KD and other dietary methods, both of which proved to be safe, characterized by an incidence rate of ≤10%.[16-17]

Gastrointestinal disorders were followed until 6 months of age, the incidence of vomiting showed inconsistent results with one study reporting a greater percentage in the control group than other diets, the rest showing similar percentages (4% vs. 4%; 16% vs. 48%), respectively.[17,22] Similarly, the incidence of diarrhea and constipation showed inconsistent results (0% vs. 2%, 4% vs. 18.5%) and (20% vs. 17%; 28% vs.

25.9%), respectively.[17,22] This finding is in line with a study in conducted in 2016 which stated similar outcomes regarding safety and efficacy of classic KD, that although classic KD remains significant in seizure reduction, along the study course of more than 3 months, emergence of gastrointestinal disorders would be apparent but insignificant.[30] Children who experienced a lack of energy showed that the alternative diet have a higher percentage (19% vs. 25%) than the classic KD in 3 month observation.[17] The incidence of serious infections dropped to 0% in the classic KD group after 6 months, this suggests that classic KD is not associated with these side effects.[11] This finding is consistent with that of a study in China, that adverse events of infections were deemed insignificant, and therefore regarded as unrelated to KD.31

One study conducted a long-term follow-up until 12 months of age, found that the percentage of gastrointestinal disorders in the form of vomiting and constipation was greater in the classic KD group (39% vs. 45%), respectively.[2] These results were in line with that of a recent study in 2023, in a 15-month study course, classic KD group showed a significant correlation with lower microbial diversity, therefore regarding KD's long term use as an underlying factor in emergence of gastrointestinal disorders such as vomiting, constipation, along with diarrhea.[32-33] This finding cohered with several studies in long term classic KD usage as key reasoning for gastrointestinal disorders. A recent systematic review in 2024 stated that gastrointestinal disorders were found more frequent in classic KD as compared to other methods although still deemed insignificant, therefore concluding that further observation is needed when diet in intractable epilepsy children is given.[34]

Nutritional therapy is not enough to treat intractable epilepsy. Recently, the American Academy of Pediatrics (AAP) strongly recommended the comprehensive therapy of both pharmacology and dietary intervention such as classic KD for intractable epilepsy, along with primary preventions of infections occurrences as well as trauma. Efficacy results in seizure reduction with KD were found in 3, 6 and 12 months, with reports of seizure free 3%, 3% and 11%, respectively.[35] Seizure reduction of 90-99% in 3, 6 and 12 months was also found significant by 31%, 29% and 20%, respectively[35], deeming KD as the dietary treatment of choice for the years heretofore. Routine observation of results and monitoring of adequate dietary treatment should be done accordingly in subsequent months to achieve optimal outcome and treatment compliance.

The principal strength of our study lies in its status as the first systematic review to evaluate the efficacy of classic ketogenic diets compared with alternative diets (MAD, LGIT, MCT, KD3:1, KD2.5:1, PUFAKD), focusing on seizure reduction and safety profile. We endeavored to conduct high-quality research in accordance with

established guidelines for such analyses, strictly adhering to the Cochrane Collaboration's recommendations on intervention studies.

Limitations include study heterogeneity, including a variety of countries where data were collected and a wide range of publication dates. There were also differences in the sample size of children, classic KD and other diets, duration of intervention, and dosage and compliance (information not available for all studies).

Conclusion

The classic KD remains highly effective in reducing recurrent seizures in children, despite its higher morbidity rate compared to alternative diets like MAD, LGIT, MCT, and PUFAKD. While these alternatives offer comparable benefits and may improve adherence, KD's proven efficacy makes it a valuable treatment option. Awareness of KD among pediatricians remains limited, partly due to its potential side effects, including gastrointestinal issues and adherence challenges. Professional guidance and further research are essential to optimize KD use and address its limitations.

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Conflict of Interest

None declared

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References

1. Borowicz-Reutt K, Krawczyk M, Czernia J. Ketogenic diet in the treatment of epilepsy. Nutrients. 2024;16(9). https://doi.org/ 10.3390/nu16091258
2. Rabie F, Al Asmari A, Al-Barak S, Al-Rashed F, Marei N. Prevalence and determinants of epilepsy among school children in aseer region- KSA. J Educ Pract. 2016;7(21):149–53
3. Olusanya BO, Wright SM, Nair MKC, Boo NY, Halpern R, Kuper H, et al. Global burden of childhood epilepsy, intellectual disability, and sensory impairments. Pediatrics. 2020;146(1). https://doi.org/10.1542/peds.2019-2623
4. Ko A, Kwon HE, Kim HD. Updates on the ketogenic diet therapy for pediatric epilepsy. Biomed J. 2022;45(1):19-26. https://doi.org/10.1016/j.bj.2021.11.003

5. D'Andrea Meira I, Romao TT, Pires do Prado HJ, Kruger LT, Pires MEP, da Conceicao PO. Ketogenic Diet and Epilepsy: What We Know So Far. Front Neurosci. 2019;13:5. https://doi.org/10.3389/fnins.2019.000 05
6. Barzegar M, Afghan M, Tarmahi V, Behtari M, Rahimi Khamaneh S, Raeisi S. Ketogenic diet: overview, types, and possible anti-seizure mechanisms. Nutr Neurosci. 2021;24(4):307-16. https://doi.org/10.1080/1028415x.2019.1627769
7. Ashtary-Larky D, Bagheri R, Bavi H, Baker JS, Moro T, Mancin L, Paoli A. Ketogenic diets, physical activity and body composition: a review. Br J Nutr. 2022;127(12):1898-920. https://doi.org/10.1017/s0007114521002609
8. DeGiorgio CM, Miller PR, Harper R, Gornbein J, Schrader L, Soss J, Meymandi S. Fish oil (n-3 fatty acids) in drug resistant epilepsy: a randomised placebo-controlled crossover study. J Neurol Neurosurg Psychiatry. 2015;86(1):65-70. https://doi.org/10.1136/jnnp-2014-307749
9. Masood W, Annamaraju P, Khan Suheb M, Uppaluri K. Ketogenic diet. Treasure Island (FL): StatPearls Publishing [Internet]. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499830/.
10. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7(6):500-6. https://doi.org/10.1016/s1474-4422(08)70092-9
11. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia. 2009;50(5):1109-17. https://doi.org/10.1111/j.1528-1167.2008.01870.x
12. Masino SA, Rho JM. Mechanisms of ketogenic diet action. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jasper's basic mechanisms of the epilepsies [Internet]. 4th ed. Bethesda (MD): National Center for Biotechnology Information (US); 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK98219/pdf/Bookshelf_NBK98219.pdf
13. Sharma S, Tripathi M. Ketogenic diet in epileptic encephalopathies. Epilepsy Res Treat. 2013;2013:652052. https://doi.org/10.1155/2013/652052
14. Sharma S, Jain P. The ketogenic diet and other dietary treatments for refractory epilepsy in children. Ann Indian Acad Neurol. 2014;17(3):253-8. https://doi.org/10.4103/0972-2327.138471
15. Sourbron J, Klinkenberg S, van Kuijk SMJ, Lagae L, Lambrechts D, Braakman HMH, Majoie M. Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis. Childs Nerv Syst. 2020;36(6):1099-109. https://doi.org/10.1007/s00381-020-04578-7
16. Raju KN, Gulati S, Kabra M, Agarwala A, Sharma S, Pandey RM, Kalra V. Efficacy of 4:1 (classic) versus 2.5:1 ketogenic ratio diets in refractory epilepsy in young children: a randomized open labeled study. Epilepsy Res. 2011;96(1-2):96-100. https://doi.org/10.1016/j.eplepsyres.2011.05.005
17. Kim JA, Yoon JR, Lee EJ, Lee JS, Kim JT, Kim HD, Kang HC. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. Epilepsia. 2016;57(1):51-8. https://doi.org/10.1111/epi.13256
18. El-Shafie AM, Bahbah WA, Abd El Naby SA, Omar ZA, Basma EM, Hegazy AAA, El Zefzaf HMS. Impact of two ketogenic diet types in refractory childhood epilepsy. Pediatr Res. 2023;94(6):1978-89. https://doi.org/10.1038/s41390-023-02554-w
19. Lambrechts DA, de Kinderen RJ, Vles JS, de Louw AJ, Aldenkamp AP, Majoie HJ. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. Acta Neurol Scand. 2017;135(2):231-9. https://doi.org/10.1111/ane.12592
20. Lakshminarayanan K, Agarawal A, Panda PK, Sinha R, Tripathi M, Pandey RM, Gulati S. Efficacy of low glycemic index diet therapy (LGIT) in children aged 2-8 years with drug-resistant epilepsy: A randomized controlled trial. Epilepsy Res. 2021;171:106574. https://doi.org/10.1016/j.eplepsyres.2021.106574
21. Poorshiri B, Barzegar M, Tahmasebi S, Shiva S, Raeisi S, Ebadi Z. The efficacy comparison of classic ketogenic diet and modified Atkins diet in children with refractory epilepsy: a clinical trial. Acta Neurol Belg. 2021;121(2):483-7. https://doi.org/10.1007/s13760-019-01225-0
22. Ray S, Nathan J, Godhia M. Efficacy and tolerability of classical and polyunsaturated fatty acids ketogenic diet in controlling paediatric refractory epilepsy - A randomized study. Epilepsy Res. 2024;204:107395. https://doi.org/10.1016/j.eplepsyres.2024.107395
23. Sondhi V, Agarwala A, Pandey RM, Chakrabarty B, Jauhari P, Lodha R, et al. Efficacy of ketogenic diet, modified atkins diet, and low glycemic index therapy diet

among children with drug-resistant epilepsy: a randomized clinical trial. JAMA Pediatr. 2020;174(10):944-51. https://doi.org/10.1001/ jamapediatrics.2020.2282

24. Rafli A, Handryastuti S, Karyanti MR, Devaera Y, Hafifah CN, Mangunatmadja I, et al. The effectiveness of modified atkins ketogenic diet on children with intractable epilepsy: a pilot study from indonesia. J Nutr Metab. 2023;2023:9222632. https://doi.org/10.1155/2023/9222632
25. Baghdadi LR, Alhomaidi RA, Alhelal FS, Alqahtani AA, Aldosary SA, Almohammedi SM, et al. Effect of a ketogenic diet on decrease of seizures in refractory epilepsy among children (infancy to 14 years old) in Saudi Arabia: a cross-sectional study. Transl Pediatr. 2023;12(9):1676-89. https://doi.org/10.21037/tp-23-211
26. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3(2):175-92. https://doi.org/10.1002/epi4.12225
27. Muthaffar OY, Alyazidi AS, Alsowat D, Alasiri AA, Albaradie R, Jad LA, et al. Short-term effectiveness and side effects of ketogenic diet for drug-resistant epilepsy in children with genetic epilepsy syndromes. Front Neurol. 2024;15:1484752. https://doi.org/10.3389/fneur.2024.1484752
28. Gerges M, Selim L, Girgis M, El Ghannam A, Abdelghaffar H, El-Ayadi A. Implementation of ketogenic diet in children with drug-resistant epilepsy in a medium resources setting: Egyptian experience. Epilepsy Behav Case Rep. 2019;11:35-8. https://doi.org /10.1016/j.ebcr.2018.11.001
29. Armeno M, Verini A, Caballero E, Cresta A, Valenzuela GR, Caraballo R. Long-term effectiveness and adverse effects of ketogenic diet therapy in infants with drug-resistant epilepsy treated at a single center in Argentina. Epilepsy Res. 2021;178:106793. https://doi.org/10.1016/j.eplepsyres.2021.106793
30. Ashrafi MR, Hosseini SA, Zamani GR, Mohammadi M, Tavassoli A, Badv RS, et al. The efficacy of the ketogenic diet in infants and young children with refractory epilepsies using a formula-based powder. Acta Neurol Belg. 2017;117(1):175-82. https://doi.org/10.1007/s13760-016-0732-0
31. Tong X, Deng Y, Liu L, Tang X, Yu T, Gan J, et al. Clinical implementation of ketogenic diet in children with drug-resistant epilepsy: Advantages, disadvantages, and difficulties. Seizure. 2022;99:75-81. https://doi.org/10.1016/j.seizure.2022.04.015
32. Menzies J, Sundararaj A, Cardamone M, McHarg A, Leach S, Krishnan U. Ketogenic diets in children with intractable epilepsy and its effects on gastrointestinal function, gut microbiome, inflammation, and quality of life. J Pediatr Gastroenterol Nutr. 2023;77(5):679-85. https://doi.org/10.1097/MPG.0000000000003928
33. Lum GR, Ha SM, Olson CA, Blencowe M, Paramo J, Reyes B, et al. Ketogenic diet therapy for pediatric epilepsy is associated with alterations in the human gut microbiome that confer seizure resistance in mice. Cell Rep. 2023;42(12):113521. https://doi.org/10.1016/j.celrep.2023.113521
34. Parveen D, Jain V, Kannan D, Mandava P, Urazbayeva M, Marie C, et al. Advances in Ketogenic Diet Therapies in Pediatric Epilepsy: A Systematic Review. Prim Care Companion CNS Disord. 2024;26(3). https:// doi.org /10.4088/PCC.23r03661
35. Freeman JM, Kossoff EH, Hartman AL. The ketogenic diet: one decade later. Pediatrics. 2007;119(3):535-43. https://doi.org/10.1542/peds.2006-2447

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Original Article

Effect of Exclusive Breastfeeding on Neurodevelopmental of Children 6-24 Months: A Case-Control Study

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Abstract:

Background: A positive correlation between breastfeeding and a child's neurodevelopmental has been established. However, the specific impact of exclusive versus non-exclusive on neurodevelopmental outcomes has not been extensively studied. This study aims to compare neurodevelopmental outcomes between exclusively and non-exclusively breastfed children.

Method: A case-control study was conducted on children aged 6-24 months at the Pediatric Neurology Clinic, Department of Child Health, FKUI-RSCM (Cipto Mangunkusumo National Central General Hospital) Jakarta and Anakku Clinic Pondok Pinang Center South Jakarta, from March 2021 to May 2021. Data were collected through parent interviews and subject observations. Statistical analysis was performed using SPSS Statistics for Windows.

Results: The study included 140 subjects equally divided into two groups: 70 children with exclusive breastfeeding history and 70 children with non-exclusive breastfeeding (breast milk and formula). Although neurodevelopmental delays were observed to be lower in the exclusive breastfeeding group compared to the non-exclusive group, statistical analysis across all four domains showed no significant differences (gross motor $p = 0.087$; fine motor $p = 0.207$; social-emotional $p = 0.441$; language $p=0.727$).

Conclusion: Exclusive breastfeeding showed a trend towards reduced risk of neurodevelopmental delays in children aged 6-24 months, although not statistically significant. Infant formula can be a safe alternative to complement breast milk, especially when breast milk production decreases, while maintaining optimal nutritional status.

Keywords: children aged 6-24 months, exclusive breastfeeding, neurodevelopment

Introduction

Based on the 2018 Indonesian Health Research, 17.7% of children under five years old are undernourished and malnourished, 8% are overweight, and 10.2% are wasted and severely wasted.[1] Breastmilk feeding is closely related to a child's nutritional status, as it is the primary source of nutrition and energy for children under 6 months old.[2] Exclusive breastfeeding before birth is highly beneficial for a baby's health, as they receive colostrum, which is rich in protein and antibodies and boosts the child's immune system.[3] Those who exclusively breastfeed for six months are less likely to develop future health problems, probable reductions in overweight, and increases in intelligence.[4] Breastfeeding benefits the neurodevelopmental progress of both full-term and preterm infants. This is due to the nutritional differences between breast milk and formula, as well as the unique bond formed between mother and child during breastfeeding.[5]

Although a positive correlation between breastfeeding and a child's neurodevelopmental progress has been established, the neurodevelopmental differences between exclusively breastfed and non-exclusively breastfed children aged 6 to 24 months has not been extensively studied.[5] Therefore, this study aims to investigate the differences in neurodevelopment between exclusively breastfed and non-exclusively breastfed children aged 6 to 24 months in both a tertiary referral hospital and a private clinic in South Jakarta.

Method

Study Design

A case-control study was conducted among children aged 6 to 24 months who visited the Neurology Outpatient Clinic at Cipto Mangunkusumo Hospital in Jakarta and Anakku Pondok Pinang Center from March until May 2021. Inclusion criteria for the study were children aged 6 to 24 months who were either exclusively breastfed or non-exclusively breastfed (breastmilk combined with formula milk), with either normal or impaired neurodevelopmental status. Exclusion criteria included children with chronic diseases, congenital diseases, and conditions that could hinder motor development.

Data Collection

Data was gathered through both parent interviews using questionnaires and direct observation of the subjects. The questionnaires assessed family history, nutritional status, and neurodevelopment stages based on age-appropriate milestones, which is divided into four domains: gross motor skills, fine motor skills, social-emotional, and language.

Data Analysis

Data analysis was conducted using SPSS version 20. Bivariate analysis, employing the chi-square test, was used to analyze the data. Statistical significance was determined by

a p-value of less than 0.05, and results were presented in terms of odds ratios and confidence intervals 95%.

Ethical Approval

Ethical approval for this study was obtained from the Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital's ethics committee (No. 235/UN.F1/ETIK/PPM.00.02.2021). Informed consent was obtained from participants' parents prior their inclusion in the study. The consent process ensured that the guardians understood the study's objectives and the voluntary nature of their participation.

Result

A total of 140 children who met the inclusion criteria were included as subjects in this study. Of these, 70 children were exclusively breastfed, while the remaining 70 received a combination of breastmilk and formula. The majority of the respondents were male (n=91, 65.0%), aged 21 – 24 months (n=65, 46.4%), with a gestational age of more than 37 weeks (n=129, 92.1%), and a birth weight of more than 2500 grams (n=130, 92.9%). The characteristics of the subjects are presented in **Table 1**.

Table 1. Characteristics of subjects.

Characteristics	Total (n=140) n (%)
Gender	
Male	91 (65.0%)
Female	49 (35.0%)
Age	
6 – 10 months	24 (17.1%)
11 – 15 months	27 (19.3%)
16 – 20 months	24 (17.2%)
21 – 24 months	65 (46.4%)
Gestational Age	
<37 weeks	11 (7.9%)
≥ 37 weeks	129 (92.1%)
Birth weight	
<2500 gram	10 (7.1%)
≥2500 gram	130 (92.9%)

In the domains of gross motor skills, fine motor skills, and language, a higher proportion of non-exclusively breastfed infants had developmental delays compared to exclusively breastfed infants (25.7% vs. 12.9%, 17.1% vs. 8.6%, and 40.0% vs. 35.7%, respectively). However, bivariate analysis indicated that exclusive breastfeeding was not statistically significantly correlated with neurodevelopment in all domains.

This is evidenced by p-values greater than 0.05 in all domains and wide confidence intervals (gross motor p = 0.087; fine motor p = 0.207; social-emotional p = 0.441; language p=0.727) **(Table 2).**

Table 2. Bivariate analysis comparing the neurodevelopment status of exclusively and non-exclusively breastfed infants.

Neurodevelopment Domains	Exclusively Breastfed (n = 70)	Non-exclusively Breastfed (n = 70)	p-value	OR	95% Confidence Interval
Gross Motor					
Appropriate	61 (87.1%)	52 (74.3%)	0.087	2.346	0.972 – 5.665
Delayed	9 (12.9%)	18 (25.7%)			
Fine Motor					
Appropriate	64 (91.4%)	58 (82.9%)	0.207	2.207	0.778 – 6.259
Delayed	6 (8.6.%)	12 (17.1%)			
Social-emotional					
Appropriate	65 (92.9%)	68 (97.1%)	0.441	0.382	0.072 – 2.041
Delayed	5 (7.1%)	2 (2.9%)			
Language					
Appropriate	45 (64.3%)	42 (60.0%)	0.727	1.200	0.394 – 7.483
Delayed	25 (35.7%)	28 (40.0%)			

Additionally, an analysis of nutritional status revealed a higher prevalence of undernourishment or malnutrition among non-exclusively breastfed infants compared to exclusively breastfed infants (7.1% vs. 4.3%), although this difference was not statistically significant **(Table 3).**

Table 3. Bivariate analysis comparing the nutritional status of exclusively and non-exclusively breastfed infants.

Nutritional Status	Exclusively Breastfed (n = 70)	Non-exclusively Breastfed (n = 70)	p-value	OR	95% Confidence Interval
Normal	67 (95.7%)	65 (92.9%)	0.718	1.718	0.394 – 7.483
Undernourished /Malnourished	3 (4.3%)	5 (7.1%)			

Discussion

Child development can be assessed into four key domains: gross motor skills, fine motor skills, speech and language, and social-emotional development. These domains

are interconnected and influenced by the maturation of the central nervous system.[6] This study revealed an interesting finding between exclusive breastfeeding and neurodevelopment in children aged 6 – 24 months. Exclusively breastfed children exhibited a lower incidence of neurodevelopment delays compared to non-exclusively breastfed children, with the exception in social-emotional development. However, these differences were not statistically significant. Similarly, a study conducted by Enambere et al., revealed no significant neurodevelopmental differences between exclusive breastfeeding, formula feeding, and non-exclusive breastfeeding.[7] In contrast, a study by Nurlaila et al., reported a significant correlation between exclusive breastfeeding and motoric development.[8]

Exclusive breastfeeding provides numerous benefits for children development. Breastmilk contains a complex nutrient, such as lactose, calcium, vitamin B16, zinc, and long-chain fatty acids, specifically docosahexaenoic acid (DHA) and arachidonic acid (ARA). These nutrients are important for the child's gross motor skills, which are an essential domain to children growth and development.[8] Breastmilk also important for promoting brain and retinal development.[9-11] Exclusive breastfeeding supports children in reaching their optimal growth potential.[12]

Several factors can impede exclusive breastfeeding practice, such as, mother experience breast pain, inverted nipples, and inadequate milk production. Children who are not exclusively breastfed face a higher risk of developmental delay.[9]

The majority of the study participants were 21-24 months old (46.4%). At this age, breastmilk is no longer the primary source of nutrient, complementary feeding becomes the predominant source of nutrition, surpassing the role of breast milk.[13] This dietary transition aligns with WHO recommendations, which promote continued breastfeeding beyond the age of two, although with decrease proportions.[14] These circumstances may influence the result of the study, as evaluating the long-term benefits of exclusive breastfeeding become increasingly complex due to the presence of various confounding factors that can influence the outcomes during this nutritional transition.[15]

A good nutritional status indicates that the child's nutritional needs, including for brain development, has been adequately met. No significant difference in nutritional status was observed between exclusively and non-exclusively breastfed children in this study, with 95.7% and 92.9% of children, respectively, has good nutritional status. We concluded that complementary feeding may have effects on improving nutritional status regardless of previous breastfeeding practices, resulting in no significant incidence of developmental delay between two groups. This also highlights the importance of maintaining optimal nutritional status during the critical growth period for neurodevelopment.[16]

Formula milk can also be a suitable alternative to breast milk, as long as it provides adequate nutrition.[17] Although there are ongoing debates about the formula milk, it remains a primary choice for children who cannot be breastfed. There are two types of formula milk: complete starting formula, designed for healthy infants without any particular requirements, and adapted starting formula, formulated for infants with specific physiological needs and often requiring a lower mineral content. Additionally, specialized milk formula also can be administered to children with lactose intolerance, such as lactose-free formulas. Furthermore, hydrolysed protein formulas with simple fats can prescribed for infants with acute or chronic diarrhea, and preterm infant formular are designed for premature to gain more energy.[18]

There is an ongoing pursuit to make infant formulas as similar to breast milk as possible. However, some nutritional component cannot be perfectly replicated and certain combination can result in undesirable interactions. For example, supplementing eicosapentaenoic acid without adequate DHA or adding excessive amounts of polyunsaturated fatty acids and iron without sufficient antioxidant protection can have detrimental effects. Another challenge in formulating infant formula is ensuring optimal bioavailability. While the goal is to mimic the complex composition of breastmilk, differences in the relative proportion of nutrients can impact their bioavailability. For instance, in situation where there is competition for enzymes (between n-3 and n-6 polyunsaturated fatty acids) or receptor binding sites in the intestine (zinc, iron, and copper) relative proportions may have significant implications.[19]

Several factors influence the breastfeeding practice, including maternal education level. In Indonesia, study has shown a significant correlation between maternal education and exclusive breastfeeding practice. Higher level of education is associated with increased self-efficacy, leading to more positive exclusive breastfeeding practice. Another factor is the mother's employment status. Working mothers often encounter difficulties in practicing exclusive breastfeeding due to time constraints and limited opportunities for pumping and feeding their child.[20-22]

Urban children are more likely to received exclusive breastfeeding compared to rural children. This may be attributed to increased exposure for mothers to information regarding the benefit of exclusive breastfeeding. In contrast, rural areas often have limited access to accurate health information. Socioeconomic factors also play a significant role in the practice of exclusive breastfeeding.[20, 21, 23]

This study highlights the impact of exclusive breastfeeding in neurodevelopment. However, further research is needed to identify potential confounding factors that may influence the neurodevelopment, such as environmental stimulation. Environmental factors and lifestyle habits, including excessive screen time, can

significantly impact child development.[24-27] Therefore, a more comprehensive approach that addresses both nutritional and environmental factors is needed.

Conclusion

Exclusive breastfeeding has been associated with a lower incidence of neurodevelopmental delay in children aged 6-24 months, although not statistically significant. Formula milk can be suitable alternative for children who cannot be breastfed, provided that adequate nutritional intake is maintained.

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Conflict of Interest

None declared.

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References

1. Kementerian Kesehatan Republik Indonesia. Profil kesehatan Indonesia tahun 2021; 2021. Available from: https://www.kemkes.go.id/app_asset/file_content_download/Profil-Kesehatan-Indonesia-2021.pdf.
2. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. Cochrane Database Syst Rev. 2012;2012(8):Cd003517. https://doi.org/10.1002/14651858.CD003517.pub2
3. Tomaszewska A, Jeleniewska A, Porębska K, Królikowska K, Rustecka A, Lipińska-Opałka A, et al. Immunomodulatory effect of infectious disease of a breastfed child on the cellular composition of breast milk. nutrients. 2023;15(17). https://doi.org/10.3390/nu15173844
4. Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387(10017):475-90. https://doi.org/10.1016/s0140-6736(15)01024-7
5. Brown Belfort M. The science of breastfeeding and brain development. Breastfeed Med. 2017;12(8):459-61. https://doi.org/10.1089/bfm.2017.0122
6. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010;20(4):327-48. https://doi.org/10.1007/s11065-010-9148-4
7. Enambere RR, Kurniasari MD, Dary, Putra KP. Pemberian ASI eksklusif, susu formula dan kombinasi keduanya terhadap pertumbuhan dan perkembangan anak usia 6-11 bulan di puskesmas cebongan salatiga. Jurnal Ilmu Keperawatan dan Kebidanan. 2020;11(1):13-26
8. Nurlaila N, Riyatun K, Iswati N. Hubungan pemberian asi eksklusif dengan perkembangan motorik pada bayi. Jurnal Ilmiah Kesehatan Keperawatan. 2017;13. https://doi.org/10.26753/jikk.v13i2.213
9. Intani T, Syafrita Y, Chundrayetti E. Hubungan pemberian asi eksklusif dan stimulasi psikososial dengan perkembangan bayi berumur 6-12 bulan. Jurnal Kesehatan Andalas. 2019;8:7. https://doi.org/10.25077/jka.v8i1S.920

10. Deoni SC, Dean DC, 3rd, Piryatinsky I, O'Muircheartaigh J, Waskiewicz N, Lehman K, et al. Breastfeeding and early white matter development: A cross-sectional study. Neuroimage. 2013;82:77-86. https://doi.org/10.1016/j.neuroimage.2013.05.090
11. Kar P, Reynolds JE, Grohs MN, Bell RC, Jarman M, Dewey D, Lebel C. Association between breastfeeding during infancy and white matter microstructure in early childhood. Neuroimage. 2021;236:118084. https://doi.org/10.1016/j.neuroimage.2021.118084
12. Anggraeni T. Hubungan pemberian asi eksklusif dengan perkembangan motorik halus anak usia 7-24 bulan di desa jembungan. Indonesian Journal on Medical Science. 2016;3(2)
13. UNICEF. Improving young children's diets during the complementary feeding period. UNICEF Programming Guidance. New York: UNICEF; 2020. Available from: https://www.unicef.org/media/93981/file/Complementary-Feeding-Guidance-2020.pdf.
14. World Health Organization. Infant and young child feeding2023 28 November 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/infant-and-young-child-feeding.
15. Sağlam N, Bülbül L, Kazancı SY, Hatipoğlu SS. Factors affecting breastfeeding and complementary feeding choices for children aged 24 to 48 months. Sisli Etfal Hastan Tip Bul. 2019;53(2):165-71. https://doi.org/10.14744/semb.2018.91328
16. Cohen Kadosh K, Muhardi L, Parikh P, Basso M, Jan Mohamed HJ, Prawitasari T, et al. Nutritional support of neurodevelopment and cognitive function in infants and young children-an update and novel insights. Nutrients. 2021;13(1). https://doi.org/10.3390/nu13010 199
17. Martin CR, Ling PR, Blackburn GL. Review of infant feedin key features of breast milk and infant formula. Nutrients. 2016;8(5). https://doi.org/10.3390/nu8050279
18. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin North Am. 2013;60(1):49-74. https://doi.org/10.1016/j.pcl.2012.10.002
19. Institute of Medicine Committee on the Evaluation of the Addition of Ingredients New to Infant F. Infant formula: evaluating the safety of new ingredients. Washington (DC): National Academies Press (US) Copyright 2004 by the National Academy of Sciences. All rights reserved.; 2004.
20. Laksono AD, Wulandari RD, Ibad M, Kusrini I. The effects of mother's education on achieving exclusive breastfeeding in Indonesia. BMC Public Health. 2021;21(1):14. https://doi.org/10.1186/s12889-020-10018-7
21. Kartika L, Tanggulungan FF, Sinurat RPF, Tambunan AT, Aiba S. Relationship between mothers' knowledge and exclusive breastfeeding behavior in one private hospital in West Indonesia. International Journal of Nursing and Health Services. 2021;4(1):1-8. https://doi.org/https://doi.org/10.35654/ijnhs.v4i1.359
22. Maftuchah M, Afriani A, Maulida A. Faktor yang mempengaruhi penggunaan susu formula sebagai pengganti asi eksklusif. Jurnal SMART Kebidanan. 2018;4:67. https://doi.org/10.34310/sjkb.v4i2.135
23. Widiyanto S, Aviyanti D, A MT. Hubungan pendidikan dan pengetahuan ibu tentang asi eksklusif dengan sikap terhadap pemberian ASI eksklusif. Jurnal Kedokteran Muhammadiyah. 2012;1(1):25-9
24. Calorina L, Pawito P, Prasetya H. The effect of gadget use on child development: a path analysis evidence from melawi, west kalimantan. Journal of Maternal and Child Health. 2020;5(1):110-9
25. Anggraheny HD, Sugiarto D, Hapsari S. ASI Eksklusif meningkatkan perkembangan motorik anak 2-3 tahun. Jurnal Kedokteran Muhammadiyah. 2014;3(2)
26. Heni, Mujahid AJ. Pengaruh penggunaan smartphone terhadap perkembangan personal sosial anak usia pra-sekolah. Jurnal Keperawatan Silampari. 2018;2(1). https://doi.org/10.31539/jks.v2i1.341
27. Suhana, M. Influence of gadget usage on children's social-emotional development. Proceedings of the International Conference of Early Childhood Education (ICECE 2017); 2017: Atlantis Press.

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Case Report

Diagnostic and Management Approach of Pancreatic Pseudocyst in Children

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Abstract:

Background: Pancreatic pseudocyst is a fluid-filled sac within the pancreas encapsulated by fibrous tissue. Blunt-abdominal trauma is the leading risk factor in children. Due to varied and non-specific clinical manifestations, diagnosis can be challenging. Thus, this study aimed to explain the diagnostic and management approach of pediatric pancreatic pseudocyst.

***Case*:** An 8-year-old boy presented with a 3-month history of progressive abdominal mass accompanied by abdominal pain, bilious vomiting, constipation, and weight loss. Physical examination revealed a skin-colored mass located in the epigastric region. A CT-scan confirmed a cystic lesion with well-defined borders in the pancreas. Laboratory tests indicated elevated levels of plasma amylase and lipase enzymes. The patient underwent endoscopic ultrasound (EUS), followed by cyst drainage. Analysis of the pseudocyst fluid revealed increased amylase and lipase enzymes, and carbohydrate antigen 19-9 (CA 19-9) levels.

***Discussion*:** A thorough patient history and physical examination are essential in diagnosing pancreatic pseudocyst. While CT-scan provides valuable information, EUS has higher sensitivity and specificity for diagnosis. Amylase and lipase enzymes levels are frequently elevated, and CA-19-9 can be useful, however, should be complemented with other biomarkers. Drainage is indicated for cysts that do not resolve spontaneously. Adequate nutrition is also crucial for successful patient management.

Conclusion: Pancreatic pseudocysts should be considered in children with an abdominal mass following blunt-abdominal trauma. Endoscopic ultrasound (EUS) is a valuable tool for both diagnosing and assisting the management of pancreatic pseudocysts.

Keywords: blunt abdominal trauma, endoscopic ultrasound, pancreatic pseudocysts

Introduction

Pancreatic pseudocyst is defined as a fluid-filled sac within the pancreas that contains pancreatic enzymes and necrotic tissues. It is surrounded by a non-epithelial fibrous tissue.[1, 2] The incidence of pancreatic pseudocyst is low, accounting for 1.6 to 4.5% per year. Currently, comprehensive data on pancreatic pseudocyst in pediatric is still limited due to its rare occurrence in children.[3]

Blunt abdominal trauma is the most common risk factor of pediatric pancreatic pseudocyst.[3-6] Pancreatic pseudocyst is more common in boys with an average age of onset around 7.5 years old.[1] Clinical presentations are often varied and typically exhibited as non-specific gastrointestinal symptoms such as abdominal pain, vomiting, abdominal mass, and fever. Endoscopic ultrasound (EUS) accompanied with drainage is the current first-line treatment for pancreatic pseudocyst.[3, 7]

Despite being rare in children, pancreatic pseudocyst has high morbidity if left untreated.[5] Previous studies have reported that 30 – 50% of persistent, untreated pseudocyst could lead to complications, such as abscess formation, fistula, spontaneous rupture, and massive bleeding, which may result in death.[8] Pancreatic pseudocyst larger than 6 centimeters that shows no improvement after 6 weeks generally requires medical intervention. This establishes the importance of early identification and treatment to prevent unwanted complications. Thus, this study aims to explain the diagnostic and management approach for pancreatic pseudocyst in children due to blunt abdominal trauma.

Case

An 8-year-old boy was referred to the tertiary, national-referral hospital with a chief complaint of abdominal mass that had been present for three-months prior to admission. Four months prior to admission, he and his mother had a motorcycle accident. During the accident, he fell from the motorcycle and got hit in the stomach by the motorcycle handle. Subsequently, the patient experienced intermittent abdominal pain in the upper left quadrant and the epigastric region, with a 3-4 on a Visual Acuity Score (VAS). The pain was subsided with analgesic.

Three months prior to the admission, the patient had another abdominal trauma as he was punched on the left side of his stomach during a playfight with his friend. After the incident, he started to experience nausea and vomiting 2-4 times per day, consisting of food. Then, he went to a primary healthcare center and was given anti-nausea medication. However, the symptom only mildly decreased and continued to appear intermittently. He also started to notice a growing, skin-colored lump in the abdomen at the size of a chicken egg, with no redness and no bruising. He experienced intermittent abdominal pain, with an intensity of VAS 4-5, localized in the same area

as the initial injury. The pain was unaffected by position or food intake and did not radiate to the back or chest. There was no fever, breathing difficulty, icterus, jaundice, or changes in urination or defecation. Despite maintaining a good appetite, he experienced an unintended weight loss of 4 kg over the past three months.

Three weeks prior to hospital admission, he experienced a recurrence of nausea and vomiting. The vomit was bilious, occurring 2-4 times per day. Furthermore, the lump has reportedly grown progressively over the past month. He also suffered more frequent, severe abdominal pain. In addition, he was constipated for three days. Due to these worsening symptoms, he was admitted to the regional public hospital and underwent an abdominal CT-scan with contrast for further evaluation. The scan revealed a 13.5 x 11.36 x 17.03 cm cystic lesion with well-defined borders and a lobulated margin in the corpus pancreas, suggestive of a pancreas pseudocyst (Figure 1). No abnormalities were found in other organs. The patient was prescribed anti-nausea and laxative for 5 days, after which the symptoms subsided. The patient was then referred to Dr. Cipto Mangunkusumo General Hospital (RSCM) for further evaluation of the suspected pancreas pseudocyst.

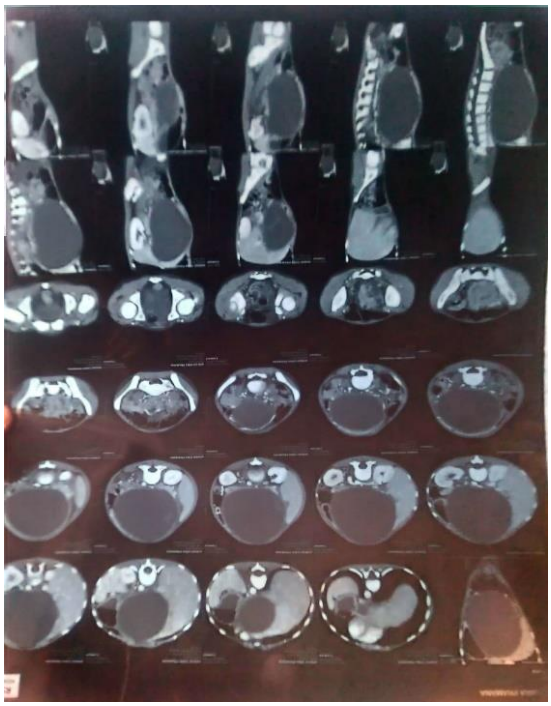

Figure 1. Abdominal CT-scan with contrast

The day before admission to RSCM, he experienced three episodes of non-bilious vomit in 24 hours and new episode of abdominal pain with a VAS of 2-3. There was no fever, constipation, dyspnea, cough, or coryza. Upon admission to RSCM, he was no longer experiencing nausea, and his oral intake was sufficient.

On physical examination, he looked weighed 17.6 kg, was 123 cm tall, and had an upper arm circumference of 12 cm. This indicates malnutrition (based on upper arm circumference) with severely underweight, but normal stature. His vital sign was within normal limits. Abdominal physical examination revealed a distended abdomen with normal bowel sounds (Figure 2). A 21 cm x 15 cm well-defined, skin-colored mass was palpated in the epigastric region. The liver was difficult to assess, and the spleen was not palpable. No other abnormalities were found during the physical examination.

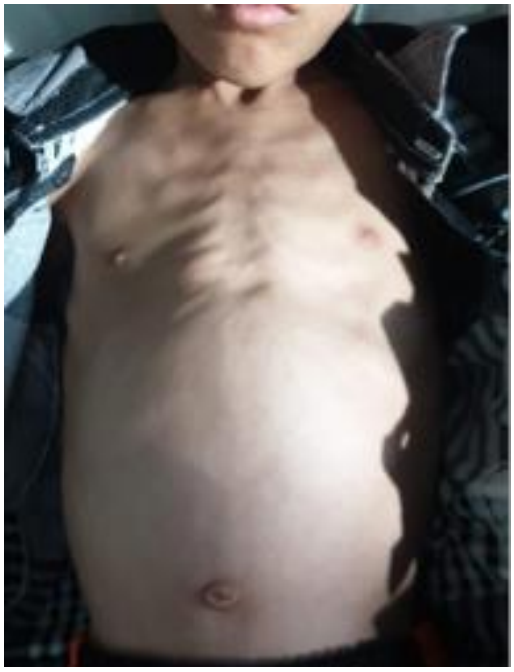

Figure 2. Patient clinical appearance

Laboratory tests indicated normocytic normochromic anaemia (Hb 10.8 g/dL, MCV 79.9 fL, MCH 26.2 pg, MCHC 32.8 g/dL), with normal leucocyte and thrombocyte counts. Additionally, the patient exhibited a mild hypokalaemia, hypophosphatemia, and increased of amylase and lipase enzymes levels (3.2 mEq/L, 3.6 mg/dL, 160 U/L and 343 U/L, respectively). Plasma albumin (3,8 g/dL), AST/ALT (14 U/L / 26 U/L), ureum (30 mg/dL), creatinine (0,4 mg/dL), and PT/APTT (1x/1.3x) levels remained within normal range.

On the sixth day of hospitalization, the patient was scheduled to underwent endoscopic ultrasound (EUS) and esophagogastroduodenoscopy (EGD). The EUS revealed a well-defined, 11 cm x 10 cm anechoic cyst pressing against the anterior wall of the stomach. The EGD examination showed a grade B esophagitis accompanied by gastritis, delayed gastric emptying, and a Forrest class III ulcer in the corpus, as well as laryngopharyngeal reflux. The EUS examination was then followed by the drainage of the pancreatic pseudocyst using a double pigtail plastic stent.

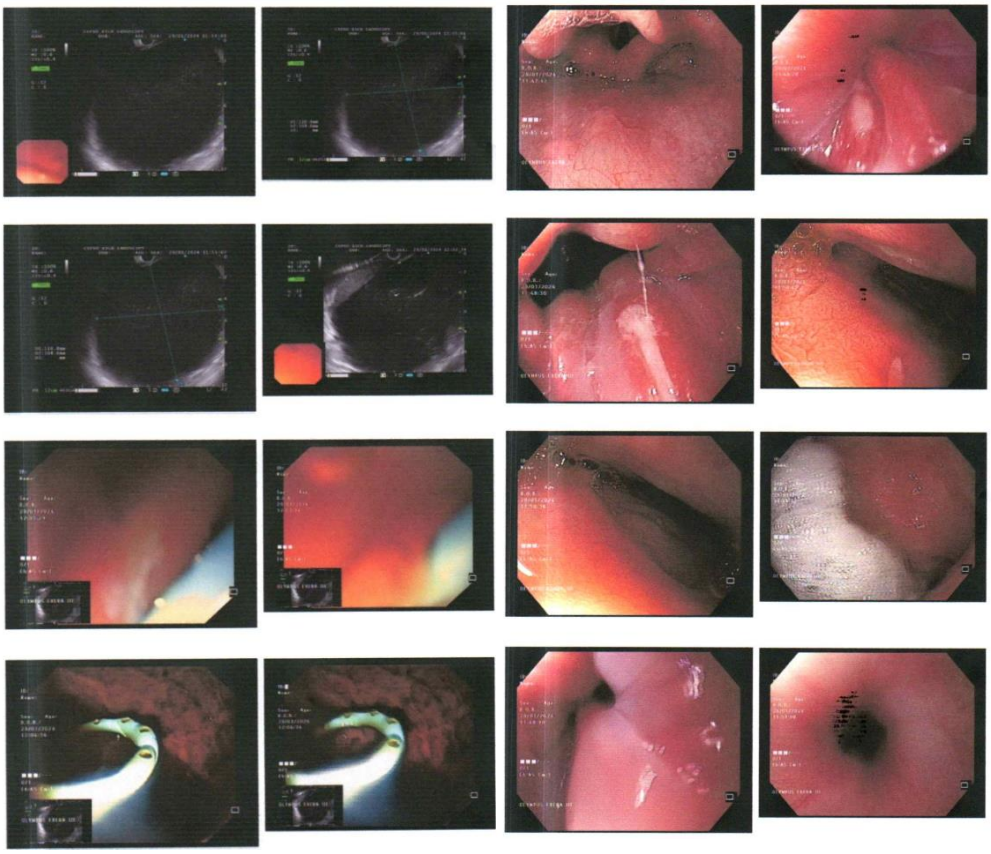

Figure 3. Endoscopic Ultrasound (EUS) and Esofagogastroduodenoskopi (EGD)

After drainage, the patient received total parental nutrition with a total fluid intake of 1300 ml/24 hours and an initial glucose infusion rate of 6 mg/kg/min. Gradually, he was transitioned to oral intake, starting with of 5 x 250 ml of specialized formula and one regular meal per day (lunch, 300 kcal). Patient received intravenous protein pump inhibitor (PPI) esomeprazole 20 mg every 12 hours for 3 days, then continued with intravenous omeprazole 20 mg twice a day. The administration of omeprazole 20 mg every 12 hours is planned to be continued orally before meals for 4 weeks, and then, will be reduced to 20 mg every 24 hours orally for 8 weeks.

The result of pseudocyst fluid analysis showed elevated levels of amylase, lipase, as well as carbohydrate antigen 19-9 (CA 19-9) (8583 U/L, 271270 U/L, and 2711.9 U/mL, respectively). Conversely, a carcinoembryonic antigen (CEA) result remained low (CEA < 0.5 ng/mL). On the seventh day of treatment, the plasma amylase enzyme level (60 U/L) remained elevated above the normal range (<31 U/L) but showed improvement compared to previous results. Meanwhile, the lipase enzyme level (62 U/L) had decreased to within the normal range. The patient was subsequently discharged after becoming symptom-free. Monthly follow-ups showed he was no longer exhibited any complaints and had improved nutritional status.

Discussion

This case report describes an 8-year boy who presented with a three-month history of abdominal mass. This mass was developed after two episodes of blunt abdominal trauma, four months prior and the other three month prior to hospitalization. The patient also experienced recurrent abdominal pain, nausea, bilious vomiting, weight loss, and constipation.

Several differential diagnoses could be considered in this case. Due to the absence of splenomegaly on physical examination, the possibility of a mass in the spleen can be ruled out. Additionally, the absence of urinary disturbances or high blood pressure made kidney malignancy or hydronephrosis unlikely. These differential diagnoses were further confirmed by normal findings of spleen and kidney in abdominal CT scan.

Furthermore, several potential diagnoses for this patient's abdominal pain could be considered, including functional gastrointestinal disorder (FGID), such as gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), or functional dyspepsia. However, based on the characteristics of the pain, which were not affected by food or drink intake, and the presence of an abdominal mass preceded by a clear history of trauma in the patient made FGID an unlikely primary cause for the patient's complaints. The patient's symptoms of constipation and bilious vomiting suggest an obstruction in the gastrointestinal tract. This is similar to a case report of an 8-year-old patient with a pancreatic pseudocyst reported by Suleman et al.[9] Common symptoms that are found in patients with pancreatic pseudocyst include abdominal pain (76-90%), nausea and vomiting (50%), and weight loss (20-51%)10, all of which is shown in this patient.

The blunt abdominal trauma in this patient is likely caused an injury to the pancreatic duct, leading to the extravasation of pancreatic fluid. Subsequently, this fluid formed a localized sac surrounded by the walls of adjacent organs, such as the pancreas, omentum, and colon. Furthermore, pseudocysts generally take 4-6 weeks to develop.[4] This timeframe aligns with the onset of the patient's abdominal mass symptoms. Imaging studies are the most important diagnostic modality for establishing the diagnosis of pancreatic cystic lesions, such as pancreatic pseudocyst. Abdominal ultrasound is often used to evaluate suspected pseudocysts, typically showing an anechoic round or oval structure with distal acoustic enhancement. CT scans can also evaluate pseudocysts and identify other surrounding pathologies, but may have difficulty to differentiate pseudocysts from neoplasms. On CT scans, pancreatic pseudocyst appears as well-defined, low-attenuation, and homogeneous. Magnetic Resonance Imaging (MRI) is the most sensitive and accurate method for diagnosing pancreatic pseudocyst, but it is not routinely used in clinical practice as CT scans usually already provide sufficient diagnostic information.

Endoscopic ultrasound (EUS) is another diagnostic tool for pancreatic pseudocyst, which has high sensitivity and specificity (93-100% and 92-98%, respectively). This makes it more superior than CT scans, which only have a sensitivity of 90-100%.[11] EUS also avoids radiation exposure and can differentiate pseudocyst and other pancreatic cyst.[3,7] While endoscopic retrograde cholangio-pancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) can also contribute to the diagnosis of pancreatic pseudocyst, their availability is significantly limited in developing countries.[3] In this patient, a CT scan initially identified a pancreatic pseudocyst and for further evaluation, the patient underwent EUS.

Several laboratory markers are useful in diagnosing pancreatic pseudocyst. CA 19-9, a polymer glycoprotein used as a biomarker for pancreatic malignancy, is not specific for detecting malignancy since it can also be elevated in various conditions, such as pancreatitis, pancreatic cysts, diabetes mellitus, liver fibrosis, and cholestasis.[12, 13] CA 19-9 levels below 37 U/mL suggest pseudocyst or serous cystadenoma over other types of pancreatic cystic lesions. CA 19-9 shows high specificity (98%) but low sensitivity (19%).[12, 14] Therefore, CA 19-9 should be combined with other biomarkers, particularly amylase and lipase. A meta-analysis found that an amylase concentration of <250 U/L in cyst fluid has excellent specificity (98%) for ruling out the diagnosis of pseudocyst.[15] Another study revealed that amylase levels >8500 U/L were observed in 91% of pseudocyst cases.[16] Another study showed that amylase levels >5000 U/L were found in 94% of cases, and lipase levels >2000 U/L were found in all cases of pseudocyst.17

In other diagnoses, such as mucinous cystic neoplasm and mucinous cystadenocarcinoma, amylase and lipase levels are typically low, while other tumor markers, such as CEA and CA 125, may be elevated.[3] In this case, the patient had elevated blood amylase and lipase levels, as well as elevated amylase, lipase, and CA 19-9, levels from the cyst fluid analysis. However, CEA levels remained low. These findings support the diagnosis of a pancreatic pseudocyst.

Drainage was indicated in this case as the pseudocyst had persisted for over 6 weeks and exceeded 6 cm in size, making spontaneous resolution unlikely.[18] Ultrasound and endoscopy were used to guide the drainage procedure, allowing identification of vascular structures around the cyst. Studies show EUS-guided drainage has a success rate of 78-89% and a complication rate of 4-7%, making it a safer option than conventional drainage.[4] In addition to EUS-guided drainage, surgical drainage may be indicated for pancreatic pseudocysts with complications, such as infection, necrosis, duct strictures, biliary stenosis, or compression of adjacent structures.[2]

Fully-covered self-expanding metal stents (FCSEMS) are an alternative to plastic stent, offering a lower risk of occlusion and potentially reducing the need for repeat procedures. While there is still ongoing debate regarding the pros and cons of FCEMS versus plastic stents in pseudocyst drainage, a study by Sharaiha et al. reported that plastic stents have a 2.5 times higher risk of complication.[19] However, a meta-analysis by Saunders, which included 698 patients, revealed no significant differences in success rates, complications, and recurrence rates between FCSEMS and plastic stents.[20] In this case, a double pigtail plastic stent was used, and the clinical outcome was favourable.

Adequate nutrition is crucial in managing pancreatic cystic lesions. The optimal timing for initiating enteral nutrition in patients with pancreatic pseudocysts remains a subject of ongoing debate. However, an early initiation of enteral feeding within 48 hours in patients with severe acute pancreatitis is associated with lower incidence of infection, shorter hospital stays, and decreased mortality rates compared to delayed enteral feeding or total parenteral nutrition.[21] In this case, the patient received enteral nutrition prior to the procedural intervention, followed by total parenteral nutrition post-procedure, and gradually transitioned to enteral nutrition. The patient showed a weight gain of 3.85 kg, increasing from 16.9 kg to 20.75 kg in one month. Notably, the enteral nutrition provided to the patient included a formula comprising 50% medium-chain triglycerides (MCT). To date, there are no randomized controlled trials assessing the efficacy of different nutritional formulas, including both standard and MCT-enriched formulas.[22] Nevertheless, using a predigested enteral formula containing a combination of long-chain fatty acids and MCTs, as used in this case, may be beneficial. MCTs require less reliance on lipase activity for their absorption, thereby facilitating easier digestion.[23]

The prognosis for the patient is generally good, as clinical improvement has already been observed following treatment. The definitive therapy by endoscopic-assisted drainage has an almost 100% success rate in managing pseudocysts.[24]

Conclusion

Pancreatic pseudocyst should be considered in children presenting with abdominal mass and a history of blunt abdominal trauma. While CT imaging provides valuable diagnostic information, EUS offers the highest sensitivity and specificity for confirming the diagnosis. Fluid analysis from the cyst gives more accurate diagnostic data compared to serum analysis. The management of guidance drainage as well as adequate nutritional support, has been associated with favorable outcomes.

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Conflict of Interest

None declared

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References

1. Jaiswal V, Naz S, Ishak A, Batra N, Quinonez J, Mukherjee D, Pokhrel NB. A rare case of pediatric pancreatic pseudocyst. Clin Case Rep. 2022;10(5):e05879. https://doi.org/10.1002/ccr3.5879
2. Aghdassi AA, Mayerle J, Kraft M, Sielenkämper AW, Heidecke CD, Lerch MM. Pancreatic pseudocysts--when and how to treat? HPB (Oxford). 2006;8(6):432-41. https://doi.org/10.1080/13651820600748012
3. Habashi S, Draganov PV. Pancreatic pseudocyst. World J Gastroenterol. 2009;15(1):38-47. https://doi.org/10.3748/wjg.15.38
4. Tyberg A, Karia K, Gabr M, Desai A, Doshi R, Gaidhane M, et al. Management of pancreatic fluid collections: A comprehensive review of the literature. World J Gastroenterol. 2016;22(7):2256-70. https://doi.org/10.3748/wjg.v22.i7.2256
5. Khalifa M, Gobran T, Shreef KS, Waly A. Pancreatic pseudocyst in children: a single-institute experience. Annals of Pediatric Surgery. 2015;11:127–31. https://doi.org/10.1097/01.XPS.0000462976.63254.c6
6. Vilas-Boas F, Macedo G. Pancreatic Cystic Lesions: New Endoscopic Trends in Diagnosis. J Clin Gastroenterol. 2018;52(1):13-9. https://doi.org/10.1097/mcg.0000000000000945
7. Rangwani S, Juakiem W, Krishna SG, El-Dika S. Role of Endoscopic Ultrasound in the Evaluation of Pancreatic Cystic Neoplasms: A Concise Review. Diagnostics (Basel). 2023;13(4). https://doi.org/10.3390/diagnostics13040705
8. Bhattacharya D, Ammori BJ. Minimally invasive approaches to the management of pancreatic pseudocysts: review of the literature. Surg Laparosc Endosc Percutan Tech. 2003;13(3):141-8. https://doi.org/10.1097/00129689-200306000-00001
9. Suleman M, Tadayo J, Tendwa I, Amsi P, Tsandiraki J, Lodhia J. Pancreatic pseudocyst as a cause for gastric outlet obstruction. Clin Case Rep. 2023;11(3):e7122. https://doi.org/10.1002/ccr3.7122
10. Rosso E, Alexakis N, Ghaneh P, Lombard M, Smart HL, Evans J, Neoptolemos JP. Pancreatic pseudocyst in chronic pancreatitis: endoscopic and surgical treatment. Dig Surg. 2003;20(5):397-406. https://doi.org/10.1159/000072706
11. Tan JH, Chin W, Shaikh AL, Zheng S. Pancreatic pseudocyst: Dilemma of its recent management (Review). Exp Ther Med. 2021;21(2):159. https://doi.org/ 10.3892/etm.2020.9590
12. Meira-Junior JD, Costa TN, Montagnini AL, Nahas SC, Jukemura J. Elevated CA 19-9 in an asymptomatic patient: what does it mean?. Arq Bras Cir Dig. 2022;35:e1687. https://doi.org/10.1590/0102-672020220002e168 7
13. Teng D, Wu K, Sun Y, Zhang M, Wang D, Wu J, et al. Significant increased CA199 levels in acute pancreatitis patients predicts the presence of pancreatic cancer. Oncotarget. 2018;9(16):12745-53. https://doi.org/10.18632/oncotarget.23993
14. van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005;62(3):383-9. https://doi.org/10.1016/s00165107(05)01581-6
15. Ngamruengphong S, Lennon AM. Analysis of Pancreatic Cyst Fluid. Surg Pathol Clin. 2016;9(4):677-84. https://doi.org/10.1016/j.path.2016.05.010

16. Snozek CL, Mascarenhas RC, O'Kane DJ. Use of cyst fluid CEA, CA19-9, and amylase for evaluation of pancreatic lesions. Clin Biochem. 2009;42(15):1585-8. https://doi.org/10.1016/j.clinbiochem.2009.06.02 0
17. Boot C. A review of pancreatic cyst fluid analysis in the differential diagnosis of pancreatic cyst lesions. Ann Clin Biochem. 2014;51(Pt 2):151-66. https://doi.org/10.1177/0004563213503819
18. Shehta A, Elghawalby A, Fouad A, Elshobary M, Abulazm I, Kassem A, et al. Surgical Management of Pancreatic Pseudocyst: A Single Center Experience. The Egyptian Journal of Surgery. 2020. https://doi.org/10.4103/ejs.ejs_169_20
19. Sharaiha RZ, DeFilippis EM, Kedia P, Gaidhane M, Boumitri C, Lim HW, et al. Metal versus plastic for pancreatic pseudocyst drainage: clinical outcomes and success. Gastrointest Endosc. 2015;82(5):822-7. https://doi.org/10.1016/j.gie.2015.02.035
20. Saunders R, Ramesh J, Cicconi S, Evans J, Yip VS, Raraty M, et al. A systematic review and meta-analysis of metal versus plastic stents for drainage of pancreatic fluid collections: metal stents are advantageous. Surg Endosc. 2019;33(5):1412-25. https://doi.org/10.1007/s00464-018-6416-5
21. Li JY, Yu T, Chen GC, Yuan YH, Zhong W, Zhao LN, Chen QK. Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: a meta-analysis. PLoS One. 2013;8(6):e64926. https://doi.org/10.1371/journal.pone.0064926
22. Arvanitakis M, Ockenga J, Bezmarevic M, Gianotti L, Krznarić Ž, Lobo DN, et al. ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. Clin Nutr. 2020;39(3):612-31. https://doi.org/10.1016/j.clnu.2020.01.004
23. Caliari S, Benini L, Sembenini C, Gregori B, Carnielli V, Vantini I. Medium-chain triglyceride absorption in patients with pancreatic insufficiency. Scand J Gastroenterol. 1996;31(1):90-4. https://doi.org/10.3109/00365529609031633
24. Agalianos C, Passas I, Sideris I, Davides D, Dervenis C. Review of management options for pancreatic pseudocysts. Transl Gastroenterol Hepatol. 2018;3:18. https://doi.org/10.21037/tgh.2018.03.03

APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Cholestasis as Primary Manifestation of Cytomegalovirus Infection: A Case Report

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Abstract:

Background: Jaundice, marked by yellow discoloration of the sclera, skin, and mucous membranes due to bilirubin accumulation, can be physiological in neonates but may also signal pathological conditions like cholestasis. Cholestasis is commonly associated with biliary atresia; however, it can arise from various causes such as cytomegalovirus (CMV) infection. Thus, this study aims to discuss the diagnostic approach on neonatal cholestasis as the main manifestation in CMV infection.

***Case*:** A 2-years-old boy referred to the hospital with chief complaint of jaundice in both eyes and skin since 4 days of age and persisted until the age of 40 days old. Abdominal ultrasound in prior hospital revealed obstruction of bile duct which indicative for biliary atresia. However, subsequent abdominal and ARFI ultrasound showed no showed results inconsistent with biliary atresia. Furthermore, other examinations indicating infection, which were confirmed as CMV infection through serological and PCR test. Patient was then treated using valganciclovir treatment.

***Discussion*:** The diagnostic approach for cholestasis includes comprehensive anamnesis and physical examination, laboratory tests including complete blood count, bilirubin levels, liver function analysis, and coagulation factors, as well as ultrasound. CMV infection should be considered a potential cause of neonatal cholestasis, even in the absence of specific manifestations beyond jaundice and gastrointestinal symptoms.

Conclusion: CMV infection can present solely with cholestasis and gastrointestinal symptoms, without other typical CMV manifestations. Thus, comprehensive evaluation, CMV screening, and careful assessment of the patient's condition are essential for accurate management.

Keywords: cholestasis, cytomegalovirus, diagnostic approach, infection

Introduction

Jaundice is a condition characterized by yellow discoloration of skin, sclera, and mucosal membrane, caused by the accumulation of bilirubin beyond normal level (hyperbilirubinemia).[1, 2] Jaundice commonly manifest during the first two weeks of life and is one of the most frequent causes of readmission for neonates after discharge from the hospital.[1] Around 60-80% of neonates, regardless of gestational age, experience jaundice during their first week of life, with most of them being mild, transient, and resolving spontaneously. This condition is referred as physiologic jaundice. However, in certain cases, jaundice may indicate an underlying pathological condition and is termed pathological jaundice. Physiological jaundice typically manifests 24 hours after birth and resolves before 14 days of age in term infant.).[1, 2] In contrast, pathological jaundice is defined as jaundice that appears before 24-hours of age, with total bilirubin exceed 95th percentile according to age, increase total bilirubin over 5 mg/dL/day or 0.2 mg/dL/hours, and persistent jaundice surpassing 14 days of age.[1] Evaluation of the underlying pathological cause of jaundice should be excluded first before establishing the diagnosis of physiological jaundice.

The primary cause of jaundice is cholestasis, which is defined as the stagnation or reduction in bile acid secretion and flow, due to obstruction or functional defect of the hepatocytes. The accumulation of bile duct, which contains bilirubin, may lead to the development of jaundice in cholestatic patient. In the neonatal period, the main cause of identified cholestasis is biliary atresia. Without proper management, 50% of patients with biliary atresia require a liver transplant before reaching the age of 2 years.[1, 3, 4] Other etiology of cholestasis in newly born infant is cytomegalovirus infection (CMV). Cytomegalovirus is a double-chain DNA virus from *Herpesviridae* family and transmitted from human to human without exhibiting any significant manifestation.[5] However, in vulnerable population such as immunodeficient patients, CMV infection caused high morbidity and mortality rates.[5, 6] In neonates, CMV infection is a congenital viral infection with highest prevalence and among the diseases with highest mortality and morbidity. The prevalence of CMV infection is slightly higher in the developing countries (0.6-6.1%) compared to the developed countries (0.2-6%).[5] Moreover, congenital CMV infection should be a concern as it is the main cause of sensorineural hearing loss not associated with genetic abnormalities and neurological developmental disabilities.[5, 6]

Biliary atresia and CMV infection are the main etiologies of cholestasis in neonates. However, the management and treatment approaches for these conditions differ significantly. Additionally, differentiating between the two conditions is quite challenging, as the result of physical examination, laboratory findings, and other supporting examinations often fail to establish the diagnosis. Thus, this study aims to

discuss the clinical approach of cholestasis in newly born infant with jaundice manifestation, particularly on the management of patient with CMV infection.

Case

A 2-years-old boy came to the hospital with a chief complain of yellow discoloration on both eyes, first noticed at 4 days old. The patient was born at term through caesarian section without any complications during and after birth. On the fourth days of age, patient's mother observed yellow discoloration of the sclera with normal skin color. She also noted a clay-colored stools without episodes of tea-colored urine. There is no complains of fever, vomiting, and lethargy. Patient was breastfeeding well and appeared active. Patient were then taken to a midwife, who recommended sunbathing in the morning. However, no improvement was observed.

At 40 days of age, patient's mother reported yellow discoloration on the skin with persistent prior manifestation. Patient were then taken to the hospital and ultrasound examination was performed, revealing a bile duct obstruction. Patient was referred to Cipto Mangunkusumo Hospital (RSCM), a tertiary, national referral, teaching hospital in Indonesia for further management. Prior to the arrival, patient was given amikacin 90 mg/24 hours IV for 5 days and ursodeoxycholic acid 50 mg per 3 hours (30 mg/kg/day), which was discontinued after the patient arrive in our hospital.

Patient is the fourth child of four siblings. Patient was born at a local hospital through caesarean section with birth weight of 3300 gram and a length of 51 cm. During pregnancy, patient's mother had no medical problem, never consumed any medication other than prenatal vitamins provided by the community health center, regularly attended check-ups with midwifes and had an ultrasound by obstetrician, which revealed normal pregnancy and fetus. Patient had no history of breastfeeding problem and had normal growth and development for his age. Patient only received one immunization in the right thigh after birth and never received further immunization due to jaundice.

Initial examination in our center demonstrated jaundice in the eyes and skin, with no complaint of fever, abdominal distention, lethargy, or seizures. Patient was given formula milk 90 ml per 3 hours to ensure adequate nutrient intake as the mother reported reduction of breast milk production. Patient was able to finish the milk provided, in addition to direct breastfeeding. During physical examination, the patient appeared moderately ill. Blood pressure was 81/40 mmHg (50th-90th percentile), pulse rate 130 beats/minute (regular, strong, and adequately filled), respiratory rate 32 breaths/minute, temperature 36.4°C, and oxygen saturation 98% on room air. The patient weighed 5.39 kg and measured 56.9 in height, with normal nutritional status based on the 2006 WHO Child Growth Standards curve. Eye examination revealed

pale conjunctiva and icteric sclera. Skin inspection revealed jaundice from the face to the arms and lower legs (Kramer scale IV). Other physical examinations were within normal limits.

Laboratory findings obtained six days prior admission to our hospital showed hemoglobin (Hb) 8.7 g/dL, hematocrit (Ht) 27%, leukocytes 16,700/µL, and platelets 548,000/µL. Total bilirubin was measured at 17.1 mg/dL, with direct bilirubin 12.8 mg/dL, and indirect bilirubin 4.2 mg/dL. Hepatitis B screening was reported as non-reactive. Upon admission to our center, the laboratory results revealed similar findings. Patient was anemic (Hb 8.7 g/dL) with a mean corpuscular volume (MCV) of 82.2 fl, mean corpuscular hemoglobin (MCH) of 29.2 pg, and mean corpuscular hemoglobin concentration (MCHC) of 35.5 g/dL, indicating a microcytic hypochromic anemia. Leukocytosis was identified, with leukocytes and thrombocytes counts of 20,620/µL and 594,000/µL, respectively. Electrolyte analysis showed sodium at 133 mEq/L, potassium at 5.6 mEq/L, and chloride at 106.3 mEq/L, indicating hyperkalemia. Bilirubin levels were reported as 17.91 mg/dL for total bilirubin, 12.15 mg/dL for direct bilirubin, and 5.76 mg/dL for indirect bilirubin. High level of liver function tests were also observed, with Serum Glutamic Oxaloacetic Transaminase (SGOT) at 534 U/L, Serum Glutamic Pyruvic Transaminase (SGPT) at 197 U/L, gamma-glutamyl transpeptidase (GGT) at 77 IU/L, and alkaline phosphatase at 405 IU/L. Coagulation profiles showed a prothrombin time (PT) and activated partial thromboplastin time (aPTT) of 1x and 1.4x, respectively. Urinalysis, random blood glucose were within normal limits. Overall, the findings indicated microcytic hypochromic anemia, leukocytosis, cholestasis, hyperkalemia, liver dysfunction, and bilirubinuria. Patient was then diagnosed with extrahepatic cholestasis suspected to be caused by biliary atresia and hyperkalemia, with differential diagnosis for cholestasis included CMV infection.

Patient were then given extensively hydrolyzed protein formula containing medium-chain triglycerides (90 ml every 3 hours, equivalent to 480 kcal/day), empirical antibiotics (intravenous ceftriaxone 300 mg per 24 hours), ursodeoxycholic acid (80 mg per 8 hours, 50 mg/kgBW/day, per oral), management of hyperkalemia using salbutamol inhalation (2.5 mg every 8 hours), and supplementation of multivitamins, particularly fat-soluble vitamins. Patient was also referred to pediatric surgeon for further evaluation and management of suspected biliary atresia.

Subsequent examination and follow-up showed consistent clay-colored stools from three phase stool analysis. Abdominal and ARFI ultrasound showed results inconsistent with biliary atresia. Meanwhile, TORCH serology revealed reactive Cytomegalovirus (CMV) IgG and IgM, prompting quantitative blood CMV Polymerase Chain Reaction (PCR), which confirmed CMV infection (viral load:

$7.8x10^2$ IU/ml). Patient was then referred to ophthalmologist and otorhinolaryngology specialist for evaluation of chorioretinitis and hearing impairment due to CMV infection, which revealed normal results. A head ultrasound to check for CMV-related abnormalities revealed a right choroid plexus cyst, considered a normal variant.

Patient's final diagnosis were then established as intrahepatic cholestasis due to CMV infection and planned for valganciclovir treatment. During hospitalization, patient remained jaundice with no signs of progression. Stools remained clay-colored with normal bowel movement frequency and stool consistency. Repeat blood tests indicated decreased of leukocyte to 12,090/μL, leading to the discontinuation of antibiotics. On the ninth day of hospitalization, the patient was discharged for outpatient care due to clinical improvement and stable condition. Oral valganciclovir treatment was continued for six weeks.

Discussion

The diagnostic approach to jaundice in infants involves a comprehensive history taking, physical examination, and additional investigation. Detail information regarding the characteristic of the jaundice, including onset of the symptoms, progression, and associated symptoms, are crucial during the history taking.[7] The patient presented with jaundice at four days of age. Physiological jaundice remains a possible consideration, however, the presence of acholic stools and dark urine in this case suggest pathological jaundice, which required further investigation.

A comprehensive review of the maternal and neonatal history is essential to assess the possibility of congenital infections. This includes history of abortion, maternal liver dysfunction, infectious exposures indicated by fever or rash, and medication use during pregnancy. Additionally, it is important to evaluate neonatal screening result and the administration of vitamin K. This patient showed no significant maternal and neonatal history.[7]

Nutritional intake should also be investigated, including the type of milk, frequency of feeding, and volume consumed. Tolerance of enteral feeding, such as the timing of the first meconium passage, frequency of defecation, and stool's characteristic should also be assessed. In addition, it is important to inquire about any history of long-term parenteral nutrition.[7] In this case, breastfeeding jaundice was excluded, due to the adequate breastfeeding. There was no history of parenteral nutrition in this patient.

Apart from liver and biliary system dysfunction, hemolysis, congenital heart disease, and vascular abnormalities need to be considered as an etiology of cholestasis jaundice. In this case, the patient's condition from birth appears normal. The presence of

jaundice accompanied by acholic stools and dark urine and the absence of other abnormalities since birth is commonly seen in infants with biliary atresia.[7]

On physical examination, aside from inspection of the skin, sclera, and mucous membranes for jaundice, palpation of the liver and spleen should be performed. Hepatomegaly is a common finding in patients with biliary atresia, while splenomegaly is more likely to occur after the neonatal period. Splenomegaly in the 2-4 week of age is typically associated with hematological and storage disorders.[7] In this patients, hepatomegaly and splenomegaly were not present. However, their absence does not completely rule out biliary atresia. Other physical examination was unremarkable, which aligns with the potential diagnoses of biliary atresia or infection as the underlying cause of jaundice. Additional evaluations were then conducted, including laboratory test, imaging, histopathology, and an intraoperative cholangiogram.[7, 8]

Jaundice becomes apparent in infants only when serum total bilirubin levels exceed 2.5-3.0 mg/dL. While visual examination can be used to estimate bilirubin levels, the result is subjective and prone to error, even when performed by experienced clinicians. Therefore, laboratory measurement of serum total and conjugated bilirubin is essential for accurate diagnosis.[1, 8] Liver function test should also be evaluated to assess the severity of liver dysfunction. These tests include ALT, AST, alkaline phosphatase, gamma-glutamyl transferase (GGT), prothrombin time (PT), international normalized ratio (INR), and albumin. Elevated AST, with normal level of ALT and albumin levels, suggest a musculoskeletal or hematologic disorder than a hepatologic condition.[7, 8]

Laboratory findings in this patient revealed increased total bilirubin with direct bilirubin >1 mg/dL, accounting for more than 20% of the total bilirubin. These findings strongly support a diagnosis of cholestasis. This patient also exhibited elevated liver function test both AST and ALT suggesting a hepatocellular injury. The GGT level in this patient was at 77 IU/L, which is relatively low compared to the values typically observed in cases of biliary atresia, in which GGT levels usually exceed 250 IU/L.[7, 8] Therefore, the GGT findings in this patient were less consistent with a diagnosis of biliary atresia.

Imaging studies commonly used in the diagnosis of cholestasis include a 2-phase abdominal ultrasound, performed while the patient is fasting and after consumed fluids. This ultrasound can identify obstruction in biliary system and detect cyst. Moreover, this 2-phase abdominal ultrasound can assess parenchymal abnormalities, the hepatic vascular system, and spleen abnormalities. In this patient, the liver, spleen, and biliary system morphology appeared normal. There was no evidence of stenosis, and the gallbladder contraction was adequate. This ultrasound findings did not support the diagnosis of biliary atresia.[7, 8]

If infection is suspected, microbiological investigations, including blood and urine culture, as well as serological or PCR testing, should be performed. In this patient, TORCH serology result was reactive for both IgG and IgM CMV antibodies, prompting further CMV PCR testing to confirm the diagnosis of CMV infection.[7, 8] Cytomegalovirus (CMV) is the most common congenital viral infection. In infants with CMV infection, the infection can be either congenital or acquired after birth.4-6 [5, 6, 9]

To differentiate between congenital and acquired CMV infection, a PCR test on body fluids should be performed before the infant reaches 3 weeks of age. The detection of CMV DNA after 3 weeks of age could be due to either congenital or acquired infection, making it challenging to determine the precise source of infection.[9-11]

Viral DNA PCR testing is recommended using urine or saliva samples, as these specimens offer high sensitivity. A positive CMV PCR result on saliva should be confirmed with a PCR test on a urine sample, which has a sensitivity of 93-100%. While CMV serology can be used as a screening tool, it cannot be relied upon as the sole diagnostic test for CMV infection due to its limitations in sensitivity and specificity.[9-11]

In this 2-moths-3-week-old patient, a CMV PCR test using serum was chosen because PCR testing of saliva and urine samples had become less reliable at this stage. The positive CMV PCR result confirmed our diagnosis of CMV infection. However, as the patient was older than 3 weeks at the time of testing, it was not possible to determine whether the infection was congenital or acquired. Therefore, additional tests, such as liver function tests, hearing tests, and head ultrasound, are necessary to assess the severity of the infection and guide appropriate management.

Symptomatic congenital CMV infection typically presents with more severe manifestations and permanent abnormalities. In contrast, acquired CMV infection usually causes milder symptoms, although severe infections can occur, especially in premature infants.[9]

Previous study have stated that gastrointestinal symptoms had been frequently observed and indicative for CMV infection.[12] However, the occurrence of CMV infection commonly observed with other signs and symptoms. Congenital CMV infection is often associated with permanent sensorineural hearing loss, while acquired CMV infection is less likely to cause this type of hearing impairment. Furthermore, other potential manifestations of congenital CMV infection include petechiae, purpura, a blueberry muffin rash, hepatomegaly, splenomegaly, neurological

abnormalities (such as lethargy, hypotonia, seizures, and poor sucking reflex), ventriculomegaly, anemia, thrombocytopenia, leukopenia, elevated transaminase enzymes, direct hyperbilirubinemia, retinal hemorrhage, optic atrophy, strabismus, and cataracts.[5-7, 9]

Interestingly, this patient only presented with the manifestation of gastrointestinal problem. Based on the examination, there was no evidence of CMV chorioretinitis in both eyes. Hearing function tests, including OAE and BERA, also revealed no impairments. Head ultrasound also showed a normal variant, a right choroid plexus cyst, which is not a typical finding in CMV infection. This further emphasize the importance of CMV screening in patient with cholestasis.

The severity of CMV infection can be classified into mild, moderate, or severe. Mild CMV infection is characterized by subtle symptoms such as petechiae, mild hepatosplenomegaly, and slightly abnormal laboratory findings, including mild thrombocytopenia, anemia, leukopenia, elevated transaminases, and direct hyperbilirubinemia. Low birth weight may also be present, but without microcephaly or significant abnormalities on virologic tests. Furthermore, moderate CMV infection is associated with persistent laboratory abnormalities for more than two weeks and at least two persistent clinical manifestations.[9]

Severe CMV infection can be further categorized into three types: CMV disease, life-threatening CMV infection, and isolated hearing impairment. CMV disease is characterized by microcephaly, central nervous system calcifications, chorioretinitis, and white matter changes in the brain parenchyma. Life-threatening CMV infection involves severe involvement of one or more organs, but without significant central nervous system involvement.[9]

Generally, mild CMV infections do not require antiviral therapy. Antiviral therapy, such as ganciclovir or valganciclovir, is recommended for moderate and severe CMV infections. For moderate infections, therapy may be considered for 6 weeks to 6 months, in consultation with an infectious disease specialist. For severe and life-threatening infections, antiviral therapy should be initiated promptly and continued for approximately 6 months.[9, 11]

It is important to note that antiviral therapy is primarily recommended for infants younger than 4 weeks of age, as there is limited evidence from randomized controlled trials to support its use in older infants. However, therapy may still be considered for infants older than 4 weeks, depending on the individual patient's condition and in consultation with an infectious disease specialist.[9, 11]

In our case, after consultation with tropical disease and infectious disease specialists, antiviral therapy (valganciclovir) was initiated. The therapy is planned to last for 6 weeks, with close monitoring of the patient's clinical response and laboratory parameters, including for potential complications of CMV infection and side effects of the therapy.

Common short-term side effects of antiviral therapy include neutropenia and transient hepatotoxicity, which usually resolve upon discontinuation of the medication. While long-term side effects of ganciclovir and valganciclovir in humans have not been definitively established, animal studies have suggested potential carcinogenic and gonadotoxic effects. In addition to monitoring for side effects of therapy, it's important to monitor for symptoms of CMV infection. Hearing function tests should be performed every 3-6 months during the first year, every 6 months until the age of 3 years, and annually until the age of 6 years.[9]

The patient's outpatient follow-up showed improvement in symptoms, including stool color and weight gain. While the patient still exhibited jaundice, his clinical condition had improved. After four weeks of antiviral therapy, a serum PCR CMV test was performed to assess the treatment response. The negative result indicated a good therapeutic response, and therefore, antiviral therapy (valganciclovir) was discontinued.

Conclusion

Cholestasis is one of liver disease with clinical manifestation of yellow discoloration in the eyes and skin. Cholestasis occurs due to functional defect in hepatocytes or obstruction in bile duct which leads to the accumulation of bilirubin. CMV infection is one of the diseases which could cause cholestasis. Our study reported that CMV infection can present solely with cholestasis and gastrointestinal symptoms, without other typical CMV manifestations. Therefore, comprehensive evaluation, CMV screening, and careful assessment of the patient's condition are essential for accurate management.

Conflict of Interest

None declared

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References

1. Ansong-Assoku B, Shah S, Adnan M, Ankola P. Neonatal jaundice. Treasure Island (FL): StatPearls Publishing [Internet]. 2023 Feb [cited 2024 Apr 13]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532930/.
2. Pan D, Rivas Y. Jaundice. In: Adam H, Foy J, editors. Signs and symptoms in pediatrics. 1st ed. Illinois: American Academy of Pediatrics; 2015. p. 581-92.
3. Schreiber RA, Harpavat S, Hulscher JBF, Wildhaber BE. Biliary atresia in 2021: epidemiology, screening and public policy. J Clin Med. 2022;11(4):1-15. https://doi.org/10.3390/jcm11040999
4. Shah R, John S. Cholestatic jaundice. Treasure Island (FL): StatPearls Publishing [Internet]. 2023 Jul [cited 2024 Apr 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482279/.
5. Chiopris G, Veronese P, Cusenza F, Procaccianti M, Perrone S, Daccò V, et al. Congenital cytomegalovirus infection: update on diagnosis and treatment. Microorganisms. 2020;8(10):1516. https://doi.org/10.3390/microorganisms8101516
6. Gupta M, Shorman M. Cytomegalovirus. Treasure Island (FL): StatPearls Publishing [Internet]. 2023 Feb [cited 2024 Apr 13]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459185/
7. Fawaz R, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, et al. Guideline for the evaluation of ccholestatic jaundice in infants: joint recommendations of the north american society for pediatric gastroenterology, hepatology, and nutrition and the european society for pediatric gastroenterology, hepatology, and nutrition. J Pediatr Gastroenterol Nutr. 2017;64(1):154-68. https://doi.org/10.1097/MPG. 0000000000001334
8. Oswari H. Kuning pada bayi baru lahir. Jakarta: Badan Penerbit Ikatan Dokter Anak Indonesia; 2017.
9. Walston F, McDevitt K, Walter S, Luck S, Brown TH. Clinical guideline: diagnosis and management of congenital cytomegalovirus. United Kingdom: NHS East Engl Neonatal ODN; 2018. Available from: https://www.eoeneonatalpccsicnetwork.nhs.uk/wp-content/uploads/2022/02/cCMV-EoE-guideline.pdf.
10. Fowler KB, Boppana SB. Congenital cytomegalovirus infection. Semin Perinatol. 2018;42(3):149-54. https://doi.org/10.1053/j.semperi.2018.02.002
11. Marsico C, Kimberlin DW. Congenital cytomegalovirus infection: advances and challenges in diagnosis, prevention and treatment. Ital J Pediatr. 2017;43(1):38. https://doi.org/10.1186/s13052-017-0358-8
12. Abolurin OO, Senbanjo IO, Adekoya AO, Ajibola ED. Congenital cytomegalovirus infection as an important cause of infantile cholestatic jaundice: a case report. Pan Afr Med J. 2020;36:106. https://doi.org/10.11604/pamj.2020.36.106.20577

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Literature Review

Refeeding Syndrome in Malnutrition – Diagnosis and Management

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Abstract:

Background: Refeeding Syndrome (RS) is a one of the potentially life-threatening complications in malnourished children. The diagnosis of RS is often challenging due to its diverse clinical manifestations. A comprehensive understanding of the risk factors, sign, symptoms and the management of RS is important to reduce morbidity and mortality.

Discussion: The management of malnutrition consists of a ten-step process divided into three phases. Adherence to this protocol is important to mitigate the risk of RS. RS is a metabolic complication that occurs when malnourished children rapidly reintroduced to nutrition. This condition is characterized by a shift of electrolytes from the extracellular to the intracellular, leading to hypophosphatemia, hypokalemia, hypomagnesemia, and thiamine deficiency. Children with RS require aggressive electrolyte and vitamin supplementation, followed by a cautious nutritional re-initiation. A gradual approach to nutritional reintroduction and electrolyte supplementation, are a critical preventive measure of RS.

Conclusion: All malnourished children are at risk of RS. Recognizing its risk factors and watchful monitoring are essential for early detection and prevention of RS.

Keywords: malnutrition, refeeding syndrome

Introduction

Malnutrition remains a global challenge as it significantly increases morbidity and mortality.[1] This issue has been elevated to global health concern, included in Sustainable Development Goals (SDGs), specifically target two, with the theme "Zero Hunger," aiming to eradicate undernutrition by 2030 and eliminate stunting and wasting by 2025.[2]

In 2018, 17 million children worldwide experienced malnutrition, with more than three-quarters of these cases occur in low-income countries.[3] In Indonesia, data showed that 3.9% of toddlers suffer from malnutrition, and 13.8% face undernutrition. This condition indices that malnutrition in Indonesia remains a severe health problem.[4] In line with the high prevalence of malnutrition, 45% of child mortality is associated with malnutrition.[5] Study showed that malnutrition has a hazard ratio eight times higher compared to adequate nutrition.[6]

Refeeding syndrome (RS) is one of the complications from malnutrition that increases the risk of mortality. RS is defined by hypophosphatemia, hypokalemia, hypomagnesemia, and/or thiamine (vitamin B1) deficiency.[7] There is still limited data on the prevalence of RS, especially in Indonesia. Due to its wide and varied symptoms, practician often missed electrolyte examination, leading to underdiagnosed RS. Symptoms that may arise includes respiratory system disorders, heart failure, arrhythmia, coma, muscle weakness, and even death. Therefore, prevention, early detection, close monitoring during feeding, and a proper calorie regiment are key to the successful therapy for patients at risk of RS.[8]

This literature review will discuss the extent of the RS problem, risk factors, and outcome in Indonesia. By understanding these factors, it is hoped that the morbidity and mortality rates associated with RS incidents can be reduced.

Malnutrition

Diagnosis of Malnutrition

Malnutrition, a condition characterized by one or more of the following signs: a) weight-for-length/height (WHZ) less than -3 standard deviations (SD); b) clinically visible bilateral pitting edema; c) upper arm circumference (UAC) < 11.5 cm in children aged 6–59 months. Effective and appropriate management of malnutrition is crucial to prevent RS, a condition that significantly increases mortality rates in malnourished children.[3, 9-11]

Management of Malnutrition

The management of malnutrition typically requires approximately six months of treatment. Children with malnutrition need to be hospitalized until the complication subside, pitting edema decreases, and their appetite improved (regardless of nutritional

status based on anthropometry index). Treatment continues through outpatient care until WHZ > -2SD and/or UAC ≥12,5 and bilateral pitting edema completely resolved. Malnutrition management is divided into three phases: stabilization, transition, and rehabilitation. These phases are implemented through ten steps **(Table 1).** Not all malnourished children will undergo these three phases. The stabilization and transition phases are intended for malnourished children requiring inpatient care, while the outpatient malnourished children undergo only the rehabilitation phase.[10, 11]

Stabilization Phase

The goal of stabilization phase is to dealing with the life-threatening emergencies, such as hypoglycemia, hypothermia, and dehydration. The first three steps of the ten actions in malnutrition management are performed during this stabilization phase. This phase usually requires 1-2 days, but may extend to one week depending on the child's clinical condition. During this phase, children are provided with an F-75 formula, is a low protein, low lactose formula containing a mineral mix (potassium, magnesium, and zinc). This formula is administered at 50-75% of the Recommended Dietary Allowance (RDA), equivalent to 80–100 kcal/kg body weight per day. Immediate administration of a 100% RDA during this phase may increase mortality risk. Monitoring parameters in this phase include vital sign, danger signs, edema severity, formula intake, urine output, defecation frequency, stool consistency, and body weight.[10, 11]

Step 1: Prevention and Management of Hypoglycemia

Hypoglycemia in malnourished children is defined as a blood glucose level below 3 mmol/L or <54 mg/dL. In the healthcare facility without access to blood glucose testing, all malnourished children are considered hypoglycemic. The treatment for hypoglycemia involves oral administration of 50 mL of 10% glucose solution.[11]

Step 2: Prevention and Management of Hypothermia

Hypothermia is described as an axilla temperature below 36°C. If this condition is found with hypoglycemia, it may indicate the patient suffering from severe infections. In malnourished children, energy reserves are very limited, so they are unable to produce and maintain body temperature. To prevent hypothermia, children should be kept warm with clothing and blankets covering their entire body.[11]

Step 3: Prevention and Management of Dehydration

Assessing the degree of dehydration in malnourished children can be challenging. All malnourished children experiencing diarrhea and reduced urine output should be considered dehydrated. For malnourished children with mild/moderate dehydration, rehydration can be administered orally or through a nasogastric tube, until oral intake feasible. Rehydration Solution for Malnutrition (ReSoMal), a modified oral rehydration solution with reduced sodium and increased potassium, is recommended.

ReSoMal is made from diluted oral rehydration salts (ORS), sugar, electrolyte/mineral mix solution, and water. The electrolyte solution is given to address imbalance in electrolyte and mineral, including potassium, magnesium, copper, and zinc. For malnourished children with diarrhea, ReSoMal is administered at the following doses for each episode of diarrhea: 50–100 mL per diarrhea for children under 2 years old, or 100–200 mL per diarrhea for children aged 2 years and older.[10, 11]

Transition Phase

The transition phase marks the period when a patient progresses from a stable condition to the point that they qualify for outpatient care. Key characteristics of this phase include resolved complication, absence of hypoglycemia, regained appetite, and reduced of edema. During this phase, the recommended dietary intake is 100-150 kcal/kg body weight per day of F75/F100 or equivalent to 75-90% of RDA.[10, 11]

Rehabilitation Phase

The rehabilitation phase aims to reduce volume of the formula, maintain body weight, and continue breastfeeding. This phase typically lasts for 2-4 weeks and may be implemented in either inpatient or outpatient settings. In this phase, the recommended nutrition is 150-220 kcal/kg body weight per day of F100 and 4-6g/kg body weight per day of protein.[10, 11]

All malnourished children experience vitamin and mineral deficiency. Iron supplementation should only be administered after the child has regained a good appetite and weight gain, usually during the second week of rehabilitation phase. If administered too early, iron supplementation may worsen the infection. Monitoring in this phase includes recording formula intake and weight gain.[10, 11]

Refeeding Syndrome

Definition

Refeeding Syndrome (RS) is a potentially life-threatening condition that can occur in malnourished children caused by the rapid and sudden administration of nutrition. It is characterized by a shift of electrolyte from extracellular to the intracellular space resulting in fluid imbalance and complication such as arrhythmia, dyspnea, seizure, muscle weakness, heart failure and even death. Electrolyte imbalance that typically found in RS are hypophosphatemia, hypokalaemia, hypomagnesemia, and thiamine deficiency.[7, 12]

According to *American Society for Parenteral and Enteral Nutrition* (ASPEN), the diagnostic criteria of RS include a decrease in serum phosphate, potassium, and/or magnesium level by 10-20% for mild cases, 20-30% for moderate cases, and more than 30% or accompanied by organ dysfunction for severe cases. These criteria can

be observed within five days after food re-alimentation or increasing nutritional intake.[7]

Table 1. Ten Steps Management of Malnutrition[10]

No	Steps	Stabilization Phase Day 1-2	Transition Phase Day 3-7	Rehabilitation Phase Week 2-6	Follow Up Phase Week 7-26
1.	Treat/prevent hypoglycemia	→	→		
2.	Treat/prevent hypothermia	→	→		
3.	Treat/prevent dehydration	→	→		
4.	Correct electrolyte imbalance	→	→	→	
5.	Treat/prevent infection	→	→	→	→
6.	Correct micronutrient deficiencies	Without Fe →	→	With Fe →	→
7.	Start cautious feeding	→	↘		
8.	Achieve catch-up growth			→	→
9.	Provide sensory stimulation and emotional support	→	→	→	→
10.	Prepare for follow-up at home		→	→	

Prevalence

There is still limited data on the prevalence of RS. In France, 7.4% of 1,261 malnourished children experienced RS, while in Kenya, 21% of children suffer from RS.[13] Study showed that RS is associated with HIV infection. Children diagnosed with HIV positive have five times increased risk of developing RS compared to those who are HIV negative.[14] There are still few reports on the prevalence of RS in malnutrition with various comorbidities.

Mild symptoms of RS often go undetected, and electrolyte imbalance are frequently associated with other underlying medical conditions. Consequently, the true

prevalence of RS remains uncertain. Study in adult patients receiving total parenteral nutrition (TPN) showed that 30 – 43%% of those receiving phosphate supplementation still experienced hypophosphatemia.[7, 15, 16]

Pathophysiology

Pathophysiology of RS remains incompletely understood and has a multifactorial mechanism. During prolonged starvation, the human body adapts to a catabolic state, relying on glycogen and fat stores, and eventually protein, to meet energy demands. Re-alimentation initiate anabolic state, requiring increased energy and nutrient for tissue synthesis and repair. In chronic malnutrition, the body adapts by decreasing metabolic rate and nutrient consumption. Abrupt refeeding, especially with carbohydrate, stimulates insulin secretion leading to increased glucose uptake. This metabolism chain caused electrolyte shifting and fluid imbalance due to potassium, magnesium, and phosphate shift from extracellular to intracellular. Additionally, hormonal and metabolic changes can disrupt acid-base balance, leading to metabolic alkalosis.[7, 14, 17]

Under normal condition, glucose is the primary energy sources, making adequate carbohydrate intake essential. Two to three hours after carbohydrate consumption, glucose is produced and stored as glycogen. Glycogen stores in the body are limited, thus providing a short-term energy source during periods of fasting. Excess caloric intake is typically stored as fat, the body's primary energy reserve. The body conserves protein reserves, utilizing them primarily for structural and functional purposes. Following a short fasting period (approximately 24 hours), hepatic and muscle glycogenolysis occurs to compensate for the glucose deficit. Once glycogen stores are depleted, gluconeogenesis begins. [7, 18, 19]

Amino acid from muscle protein and fatty acid from adipose tissue are utilized in gluconeogenesis to generate glucose as the primary energy source for metabolic reconstruction. Pyruvate and lactate also contribute in gluconeogenesis. During prolonged fasting, protein breakdown increases. To conserve energy, body decreases its basal metabolic rate by 20-25%. In this condition, most organs and tissues rely on fatty acids as their primary energy source.[7, 18, 19]

The brain primarily utilizes glucose as its energy source and can only partially switch to ketones for energy. The body preserves protein and muscle mass by shifting to fat as an energy source. During this period, there is a decrease in proteolysis, an increase in fatty acid mobilization, and ketone body formation. Additionally, there is a decrease in intracellular micronutrient concentrations. While malnourished patients are primarily affected by these metabolic changes, RS can also occur in well-nourished or moderately nourished children after prolonged fasting.[7, 18, 19]

When carbohydrates are reintroduced, either orally, enterally, or parenterally, the body shift back to glucose as its energy source, leading to an increased demand for the production of phosphorylated intermediates of glycolysis, such as adenosine triphosphate (ATP) in red blood cells and 2,3-diphosphoglycerate (DPG), accompanied by the inhibition of fat metabolism. This condition leads to hypophosphatemia. Another mechanism contributing to hypophosphatemia is the depletion of body phosphate stores during starvation and increased cellular uptake of phosphate during the anabolic phase of refeeding.[7, 18, 19]

Phosphate is an essential mineral for metabolism, particularly in the ATP production and 2,3-DPG. Potassium and magnesium also shift to intracellular, caused by the anabolic phase and increased insulin production. Magnesium is a cofactor for NA-K+ ATP-ase pump, therefore uncorrected hypomagnesemia can disrupt potassium balance. Another metabolic disturbance includes fluid imbalance and vitamin deficiencies. Refeeding in malnourished children can lead to extracellular fluid expansion **(Figure 1).** Even though the exact mechanism of fluid imbalance remains uncertain, fluid and natrium retention could be caused by the effect of the hyperinsulinemia or the interplay between the homeostatic mechanisms regulating water, sodium, and carbohydrates.[7, 18, 19]

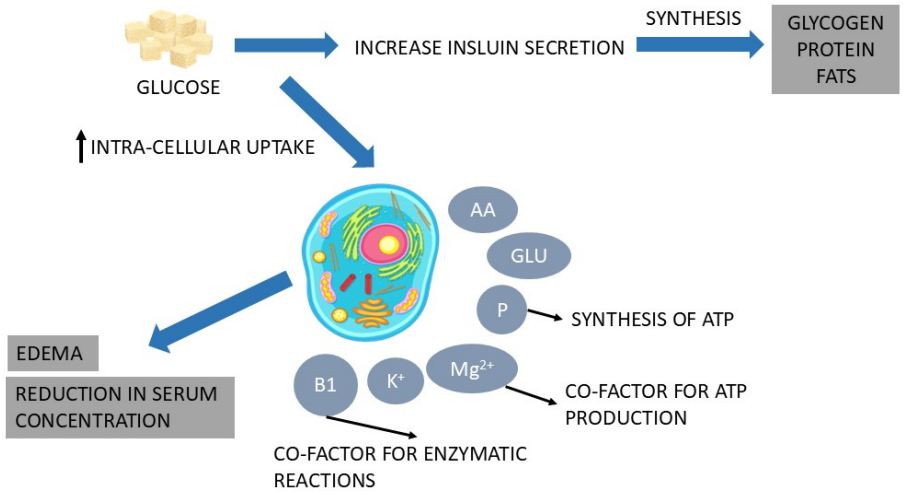

Figure 1. Pathophysiology of fluid and electrolyte imbalance in refeeding syndrome [7]

It is difficult to determine whether thiamine deficiency is caused by RS, or whether the deficiency pre-existed due to starvation. Thiamine, an important cofactor in carbohydrate metabolism, is involved in the conversion of phosphorylated glucose (Glucose-6-phosphate) to pyruvate. Pyruvate dehydrogenase, a thiamine-dependent enzyme, decarboxylates pyruvate to produce acetyl-coenzyme A, which enters the Krebs cycle to generate ATP – the cell's energy source **(Figure 2).** High-dose carbohydrate intake can increase thiamine requirements in malnourished children with low thiamine stores. This can lead to thiamine deficiency and its associated

complications. Therefore, thiamine supplementation is recommended both before and after carbohydrate consumption for patients at risk of refeeding syndrome.[8]

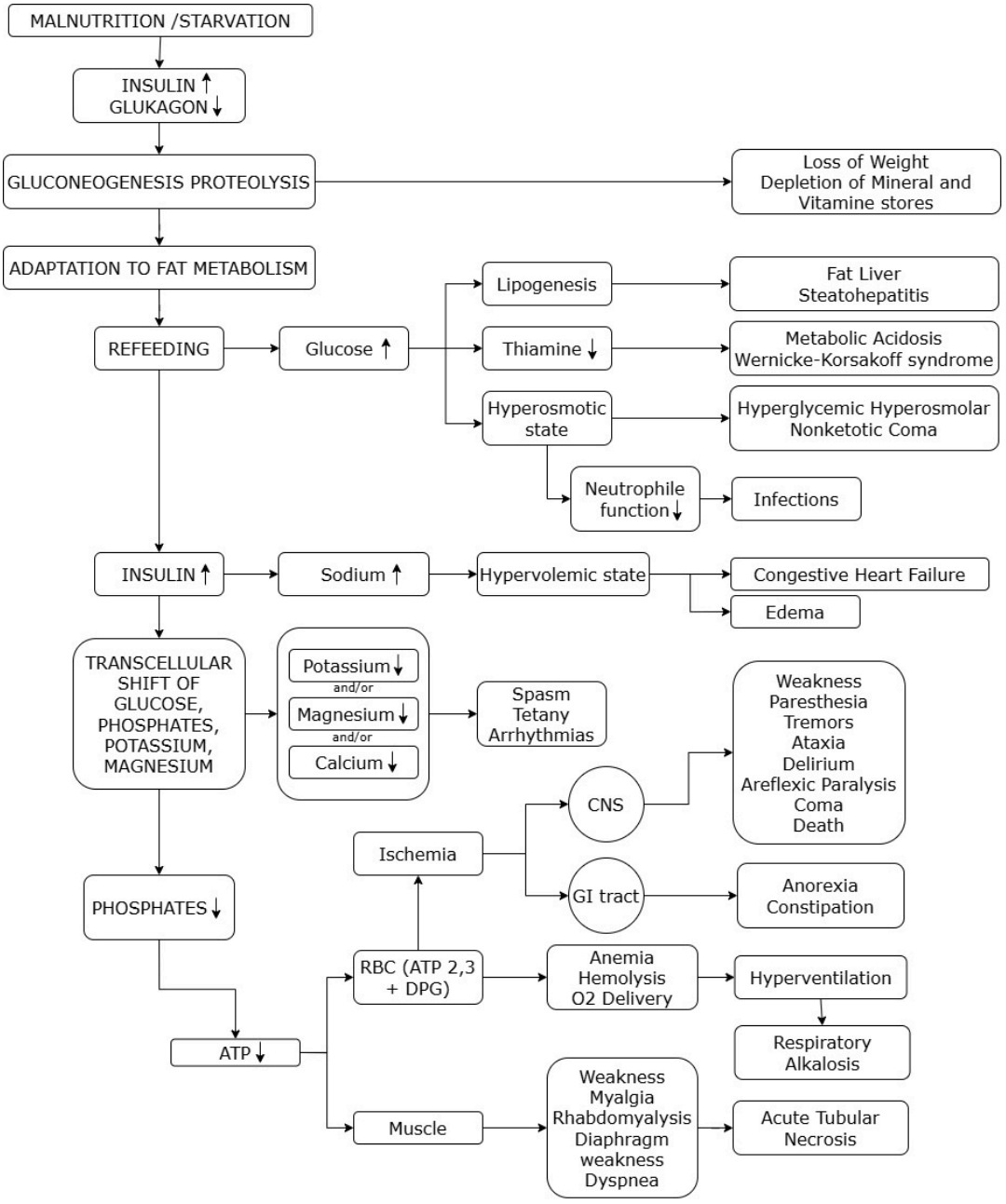

Figure 2. The consequences of major metabolic and biochemical changes in RS.[20]

Risk Factors

Previous nutritional status, history of weight loss, previous caloric intake, comorbidities, previous electrolyte imbalances (such as hypophosphatemia, hypomagnesemia, and hypokalemia) prior to nutritional therapy, muscle loss, and subcutaneous fat loss in malnourished children are risk factors for developing RS.[7]

RS risk factors that need careful attention include: 10% weight loss (or <80% of ideal body mass index) in the past 3 months, weight loss in the past consequent 5 days, low fluid intake for more than 7 days, chronic diseases causing malnutrition, such as cancer, inflammatory bowel disease, anorexia nervosa, marasmus, kwashiorkor, celiac disease, cystic fibrosis, chronic pancreatitis, cyclic vomiting syndrome, cerebral palsy, congenital heart disease, congenital pulmonary disease, post-operative conditions, prolonged fasting, low-energy diets, and hypoalbuminemia.[7] According to American Society for Parenteral and Enteral Nutrition, RS risk in children can be classified into 3 levels: low risk, moderate risk, and high risk **(Table 2).**[21]

Table 2. Criteria for children developing RS [21]

Criteria	Low risk (Minimal 3 of the following criteria)	Moderate risk (Minimal 2 of the following criteria)	High risk (Minimal 1 of the following criteria)
Weight-for-height z-score (1-24 months) or BMI-for-age z-score (2-20 years)	Weight-for-height z-score (1-24 months) or BMI-for-age z-score (2-20 years) between -1 and -1.9	Weight-for-height z-score (1-24 months) or BMI-for-age z-score (2-20 years) between -2 and -2.9	Weight-for-height z-score (1-24 months) or BMI-for-age z-score (2-20 years) ≥-3
Weight loss	Weight gain <75% of expected	Weight gain <50% of expected	Weight gain <25% of expected
Energy intake	Energy or protein intake <75% of needs for 3-5 consecutive days	Energy or protein intake <75% of needs for 5-7 consecutive days	Energy or protein intake <75% of needs for >7 consecutive days
Potassium, phosphate, or magnesium levels before nutritional therapy	Potassium, phosphate, or magnesium levels ≤25% below the lower limit of normal	Potassium, phosphate, or magnesium levels 25-50% below the lower limit of normal	Potassium, phosphate, or magnesium levels >50% below the lower limit of normal
Comorbidities	Mild diseases comorbidities	Moderate diseases comorbidities	Severe diseases comorbidities
Subcutaneous fat loss	Upper arm circumference z-score between -1 and -1.9 or mild subcutaneous fat loss	LILA z-score between -2 and -2.9 or moderate subcutaneous fat loss	LILA z-score >-3 or significant subcutaneous fat loss
Muscle mass loss		Mild loss of muscle mass	Significant loss of muscle mass

Clinical manifestations

Hypophosphatemia

Phosphate is an intracellular anion essential for metabolic processes involving ATP and 2,3-DPG. Severe hypophosphatemia (serum phosphate <1-1.5 mg/dL) can lead to severe disturbances in neurological, cardiac, respiratory, and hematological systems, increasing the risk of death. Several studies have linked hypophosphatemia to the initiation of nutritional support, either oral, enteral, or parenteral. Severe hypophosphatemia can cause neurological symptoms, such as paraesthesia, weakness, confusion, disorientation, encephalopathy, areflexia, paralysis, seizures, coma, and death.[22]

Hypophosphatemia can lead to decreased ATP and 2,3-DPG levels. This can result in impaired oxygen transport, including reduced oxygen delivery and disturbed glucose metabolism. Decreased 2,3-DPG levels increase hemoglobin's affinity for oxygen, shifting the oxygen dissociation curve to the left. Hypophosphatemia can also significantly decrease erythrocyte glucose-6-phosphate and fructose-6-phosphate levels, while increasing total triose phosphate levels (such as glyceraldehyde-3-phosphate and dihydroxyacetone phosphate). These changes can impair oxygenation and glucose metabolism, contributing to neurological and respiratory disturbances.[23]

Phosphate, an intracellular mineral, plays an important role in all intracellular processes and maintaining cellular membrane integrity. Many enzymes and second messengers are activated through phosphate binding. Phosphate is also essential for energy storage in the form of adenosine triphosphate (ATP). ATP can also influence hemoglobin's affinity for oxygen, regulating oxygen delivery to tissues. Additionally, ATP plays an important role in the kidney's acid-base buffering system.[24-27]

Chronic phosphate depletion occurs in refeeding syndrome. Increased insulin levels will increase cellular phosphate uptake and utilization. These changes result in both intracellular and extracellular phosphate deficits. Under these conditions, even a slight decrease in blood phosphate levels can disrupt cellular processes, that happen in every physiological system.[24-27]

Hypokalemia

Potassium is an important intracellular cation. Approximately 98% of the body's total potassium is intracellular, with the rest found in bones and cartilage. Potassium plays several crucial physiological roles, including regulating electrical activity in cell membranes, cellular metabolism, glycogen synthesis, and protein synthesis. Hypokalemia disrupts the electrical action potential across cell membranes, leading to membrane hyperpolarization and impaired muscle contraction. Mild to moderate hypokalemia (serum potassium concentration between 2.5 and 3.5 mEq/L) can cause nausea, vomiting, constipation, and fatigue. Untreated, severe hypokalemia (serum

potassium concentration <2.5 mEq/L) can result in paralysis, respiratory distress, rhabdomyolysis, muscle necrosis, myocardial contraction abnormalities, and impaired signal conduction.[7, 8]

Severe hypokalemia can lead to electrocardiogram abnormalities, such as ST-segment depression, T-wave flattening, T-wave inversion, or U-wave prominence. Patients with hypokalemia may experience arrhythmias, including atrial tachycardia, bradycardia, atrioventricular block, ventricular premature contractions, ventricular tachycardia, ventricular fibrillation, or sudden cardiac death.[7, 8]

Although blood potassium levels may appear normal in malnourished children, potassium depletion often occurs. With the anabolic shift in refeeding syndrome, insulin secretion increases, driving potassium into cells. This can lead to severe hypokalemia, disrupting cellular membrane electrochemistry, and potentially causing arrhythmias and cardiac arrest.[7, 8]

Hypomagnesemia

Magnesium is the second most common intracellular cation, primarily found in bones, muscles, and soft tissues. Approximately 1% of the body's magnesium is extracellular. Magnesium serves as an important cofactor for numerous enzymes involved in various biochemical reactions, including oxidative phosphorylation and ATP-dependent reactions.[21]

Hypomagnesemia (serum magnesium concentration <1.5 mg/dL) is frequently observed in critically ill patients and is associated with increased morbidity and mortality. Signs and symptoms of hypomagnesemia can be similar to those with hypokalemia or hypophosphatemia. Patients with mild to moderate hypomagnesemia may experience weakness, muscle twitching, tremors, altered mental status, anorexia, nausea, vomiting, and diarrhea. Severe hypomagnesemia (serum magnesium concentration <1.0 mg/dL) can manifest as electrocardiogram abnormalities, such as prolonged PR interval, widened QRS complex, prolonged QT interval, ST-segment depression, peaked T-waves, or T-wave flattening. Additionally, severe hypomagnesemia can lead to arrhythmias (atrial fibrillation, torsade de pointes, ventricular arrhythmias, ventricular tachycardia), tetany, seizures, coma, or even death.[21]

Untreated hypomagnesemia can lead to hypokalemia and hypocalcemia. Hypomagnesemia-induced hypokalemia results from disturbances in Na+/K+-ATPase activity. Hypomagnesemia-induced hypocalcemia is caused by impaired parathyroid hormone secretion or activity.[21]

Thiamine Deficiency

Thiamine, or vitamin B1, is an important cofactor in carbohydrate metabolism. As a water-soluble vitamin, thiamine is easily depleted during weight loss and malnutrition. Glucose administration following a starvation period suppresses gluconeogenesis through insulin secretion. Excessive glucose administration can lead to hyperglycemia, osmotic diuresis, dehydration, metabolic acidosis, and ketoacidosis. Additionally, excessive glucose can stimulate lipogenesis (due to insulin stimulation), resulting in fatty liver, increased carbon dioxide production, hypercapnia, and respiratory failure.[28]

With increased carbohydrate consumption, thiamine demand also increases as it is an important cofactor in glycolysis. Thiamine deficiency can lead to Wernicke encephalopathy (characterized by ocular abnormalities, ataxia, confusion, hypothermia, and coma) or Korsakoff syndrome (characterized by retrograde and anterograde amnesia, and confabulation). In anaerob metabolism, pyruvate is converted to lactate. Excessive lactate production can cause lactic acidosis, potentially leading to death. This has been reported in patients receiving parenteral nutrition without thiamine supplementation.[28]

While deficiencies in various vitamins can occur due to inadequate intake, thiamine deficiency is particularly important in refeeding syndrome complications, as it is an important coenzyme in carbohydrate metabolism.[28]

The summary of clinical manifestations of electrolyte imbalance in RS patients is depicted in **Figure 3**.[7]

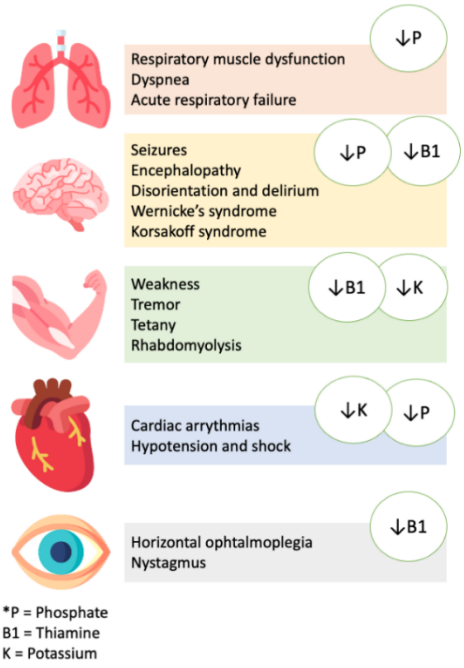

Figure 3. Summary of clinical manifestations of electrolyte imbalance in RS patients.[7]

Prevention

Preventing RS is our primary objective when starting nutritional support for malnourished children. Several steps can be taken to avoid RS and reduce its associated morbidity and mortality. Identifying patients at high risk for RS is very important before starting nutritional support, and overfeeding must be avoided.[28] The recommendation on RS prevention and management in children by ASPEN is summarized in **Table 3.**

When initiating nutritional support for patients at high risk for refeeding syndrome (RS), the primary rule is "start low, go slow." Nutritional support should be initiated carefully, starting at approximately 25-50% of recommended dietary allowance (RDA) targets on the first day and gradually increasing to the target intake by the third to fifth day. Hypophosphatemia, hypokalemia, and hypomagnesemia should be corrected before initiating nutritional support. Electrolyte supplementation (in patients with normal kidney function) is recommended before and during nutritional support. Increased caloric intake can lower serum phosphate concentrations, therefore phosphate supplementation of 10-15 mmol per 1000 kcal is recommended to maintain normal serum phosphate levels (in patients with normal kidney function). Patients with malnutrition, critical illness, trauma, or burns often experience phosphate depletion (despite normal serum phosphate levels), and their phosphate requirements are typically higher.[28]

That also applies to potassium and magnesium. After initiating and titrating nutritional support, electrolyte supplementation should be adjusted based on serum electrolyte concentrations and therapeutic response. As RS patients are at risk of impaired cardiac reserve and fluid overload, sodium and fluid intake should be minimized during the initial days of nutritional support (recommended sodium intake is ≤20 mEq/day with total fluid intake ≤1000 mL/day).[7, 28]

Thiamine requirements are increased in patients with cachexia. Thiamine supplementation at a dose of 50-100 mg/day intravenously or 100 mg orally for 5-7 days is recommended to prevent refeeding syndrome (RS). Patients should be closely monitored for signs and symptoms of RS, including vital signs (heart rate, blood pressure, respiratory rate, mental status, and neurological signs). These signs should be monitored for several days until target nutritional goals are achieved. Pulse oximetry can also be used. Electrocardiograms should be performed, especially for patients with hypokalemia. Additionally, patients should be monitored for neuromuscular signs and symptoms through physical examination. Fluid balance, edema, fluid overload, and weight measurements should also be closely calculated and monitored.[7, 28]

Table 3. ASPEN's recommendation on RS prevention and management in children.[21]

Aspect of Care	Recommendations
Initiation of Nutrition	• Start nutrition at a maximum target of 40-50%, but typically start glucose infusion at around 4-6 mg/kg/min and increase by 1-2 mg/kg/min daily, adjusting the glucose level to a maximum of 14-18 mg/kg/min (including enteral and parenteral glucose). • Calories from intravenous dextrose solutions and medications infused in dextrose should be considered within the above limits and/or started cautiously in patients with moderate to high risk. If the patient has received intravenous dextrose for several days and/or medications in dextrose and has not shown symptoms with stable electrolytes, calories from nutrition can be reintroduced at higher amounts than recommended above.
Fluid Restriction	No recommendation
Sodium Restriction	No recommendation
Protein Restriction	No recommendation
Electrolytes	• Check serum potassium, magnesium, and phosphate levels before initiating nutrition. • Monitor every 12 hours for the first 3 days in high-risk patients. Monitoring may be more frequent based on clinical presentation. • Replace electrolytes based on established standards of care. • No recommendation can be given on whether prophylactic electrolyte doses should be given if pre-feeding levels are normal. • If electrolytes are difficult to correct or decrease suddenly when starting nutrition, reduce calories/gram of dextrose by 50% and increase dextrose/calories by about 33% of the target every 1-2 days based on clinical presentation. Recommendations may change based on practitioner assessment and clinical presentation, and discontinuation of nutritional support may be considered when electrolyte levels are very low or decrease suddenly, posing a life-threatening risk.
Thiamine and Multivitamins	• Thiamine 2 mg/kg with a maximum limit of 100-200 mg/day before starting feeding or before starting intravenous fluids containing dextrose in high-risk patients. • Continue thiamine supplementation for 5-7 days or longer in patients with severe starvation, chronic alcoholism, or high

	risk of thiamine deficiency and/or signs of thiamine deficiency. Routine thiamine level checks may not be valuable. • Intravenous multivitamins are added to parenteral nutrition daily, unless contraindicated, as long as parenteral nutrition continues. For patients receiving oral/enteral nutrition, add oral/enteral multivitamins, complete once a day for 10 days or more based on clinical status and therapy mode. After the patient reaches adult weight, refer to adult multivitamin recommendations.
Monitoring and Long-Term Care	• Check vital signs every 4 hours for the first 24 hours after initiation in at-risk patients. • Cardiorespiratory monitoring is recommended for unstable patients or those with severe deficiencies, based on established standards of care. • Daily weight with intake and output monitoring. Estimate energy needs if necessary for patients receiving oral food. Evaluate short-term and long-term nutritional care goals daily for the first few days until the patient is considered stable (e.g., not requiring electrolyte supplementation for 2 days) and then based on institutional standards of care.

Conclusion

Refeeding syndrome is a life-threatening condition that can occur in malnourished children after the initiation of nutritional support. It is characterized by hypophosphatemia, hypomagnesemia, hypokalemia, and/or thiamine deficiency that develop after rapid re-alimentation within the initial 3-5 days of nutritional management. Children with signs and symptoms of refeeding syndrome require aggressive electrolyte and vitamin supplementation, supportive management (such as electrolyte correction and management of subsequent clinical manifestations), and the re-initiation of nutritional support with close monitoring

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Conflict of Interest

None declared.

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References

1. Anato A. Severe acute malnutrition and associated factors among children under-five years: A community based-cross sectional study in Ethiopia. Heliyon. 2022;8(10):e10791. https://doi.org/10.1016/j.heliyon.2022.e10791
2. United Nation. SDGS goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture 2024 [Available from: https://sdgs.un.org/goals/goal2.
3. World Health Organization. The world bank group joint child malnutrition estimates. levels and trends in child malnutrition. Geneva: World Health Organization; 2019.
4. Kementerian Kesehatan Republik Indonesia. Riset kesehatan dasar tahun 2018. Jakarta: Kementerian Kesehatan Republik Indonesia; 2019.
5. Ikobah JM, Uhegbu K, Akpan F, Muoneke L, Ekanem E. Predictors of In-Patient Mortality of Severe Acute Malnutrition of Hospitalised Children in a Tertiary Facility in Southern Nigeria. Cureus. 2022;14(4):e24195. https://doi.org/10.7759/cureus.24195
6. Schwinger C, Golden MH, Grellety E, Roberfroid D, Guesdon B. Severe acute malnutrition and mortality in children in the community: Comparison of indicators in a multi-country pooled analysis. PLoS One. 2019;14(8):e0219745. https://doi.org/10.1371/journal.pone.0219745
7. Corsello A, Trovato CM, Dipasquale V, Bolasco G, Labriola F, Gottrand F, et al. Refeeding Syndrome in pediatric age, an unknown disease: a narrative review. J Pediatr Gastroenterol Nutr. 2023;77(6):e75-e83. https://doi.org/10.1097/mpg.0000000000003945
8. Hother AL, Girma T, Rytter MJ, Abdissa A, Ritz C, Mølgaard C, et al. Serum phosphate and magnesium in children recovering from severe acute undernutrition in Ethiopia: an observational study. BMC Pediatr. 2016;16(1):178. https://doi.org/10.1186/s12887-016-0712-9
9. World Health Organization. Guideline updates on the management of severe acute malnutrition in infants and children. Geneva: World Health Organization; 2013.
10. Kementerian Kesehatan Republik Indonesia. Buku saku pencegahan dan tata laksana gizi buruk pada balita di layanan rawat jalan. Jakarta: Kementerian Kesehatan RI; 2020.
11. Tickell KD, Denno DM. Inpatient management of children with severe acute malnutrition: a review of WHO guidelines. Bull World Health Organ. 2016;94(9):642-51. https://doi.org/10.2471/blt.15.162867
12. Lenicek Krleza J, Misak Z, Jadresin O, Skaric I. Refeeding syndrome in children with different clinical aetiology. Eur J Clin Nutr. 2013;67(8):883-6. https://doi.org/10.1038/ejcn.2013.58
13. Blanc S, Vasileva T, Tume LN, Baudin F, Chessel Ford C, Chaparro Jotterand C, Valla FV. Incidence of Refeeding Syndrome in Critically Ill Children With Nutritional Support. Front Pediatr. 2022;10:932290. https://doi.org/10.3389/fped.2022.932290
14. Okinyi LK, editor The Prevalence of Refeeding Syndrome Among Children with Severe Acute Malnutrition: An Observational Study in Kenyatta National Hospital, Kenya. 2018.
15. Pantoja F, Fragkos KC, Patel PS, Keane N, Samaan MA, Barnova I, et al. Refeeding syndrome in adults receiving total parenteral nutrition: An audit of practice at a tertiary UK centre. Clin Nutr. 2019;38(3):1457-63. https://doi.org/10.1016/j.clnu.2018.06.967
16. de Vargas Cony K, de Magalhães Francesconi CF. An unexpectedly high incidence of refeeding syndrome in patients with total parenteral nutrition in a reference university hospital. Clin Nutr. 2021;40(6):3702-7. https://doi.org/10.1016/j.clnu.2021.04.016
17. Hearing SD. Refeeding syndrome. Bmj. 2004;328(7445):908-9. https://doi.org/10.1136/bmj.328.7445.908
18. Ormerod C, Farrer K, Harper L, Lal S. Refeeding syndrome: a clinical review. Br J Hosp Med (Lond). 2010;71(12):686-90. https://doi.org/10.12968/hmed.2010.71.12.686
19. Mehanna HM, Moledina J, Travis J. Refeeding syndrome: what it is, and how to prevent and treat it. Bmj. 2008;336(7659):1495-8. https://doi.org/10.1136/bmj.a301
20. Lenicek Krleza J, Mišak Z, Jadresin O, Grzunov A, Stepan Giljevic J. Refeeding Syndrome in Children: Risk Assessment, Diagnostics and Management. 2014. p. 109-36.
21. da Silva JSV, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, et al. ASPEN Consensus Recommendations for

Refeeding Syndrome. Nutr Clin Pract. 2020;35(2):178-95. https://doi.org/10.1002/ncp.10474
22. Yoshimatsu S, Chisti MJ, Hossain MI, Islam MM, Fukushima T, Wagatsuma Y, et al. Hypophosphataemia among severely-malnourished children: case series. J Health Popul Nutr. 2012;30(4):491-4. https://doi.org/10.3329/jhpn.v30i4.13419
23. Chanchal R, Gupta S, Kanta C, Singh K, Koonwar S. Hypophosphataemia in severe acute malnutrition: a prospective observational study. Br J Nutr. 2019;121(3):306-11. https://doi.org/10.1017/s0007114518003197
24. Kimutai D, Maleche-Obimbo E, Kamenwa R, Murila F. Hypo-phosphataemia in children under five years with kwashiorkor and marasmic kwashiorkor. East Afr Med J. 2009;86(7):330-6. https://doi.org/10.4314/eamj.v86i7.54147
25. Namusoke H, Hother AL, Rytter MJ, Kæstel P, Babirekere-Iriso E, Fabiansen C, et al. Changes in plasma phosphate during in-patient treatment of children with severe acute malnutrition: an observational study in Uganda. Am J Clin Nutr. 2016;103(2):551-8. https://doi.org/10.3945/ajcn.115.117374
26. Skipper A. Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases. Nutr Clin Pract. 2012;27(1):34-40. https://doi.org/10.1177/0884533611427916
27. Birmingham CL, Puddicombe D, Hlynsky J. Hypomagnesemia during refeeding in anorexia nervosa. Eat Weight Disord. 2004;9(3):236-7. https://doi.org/10.1007/bf03325074
28. Elwagei Suliman Ahmed S, Albougha S, Mahgoub I, Kadori M. Role of Thiamine in Refeeding Syndrome in Children. 2021.

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