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Treatment Options for Iron Deficiency Anemia in Children in Saudi Arabia

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Abstract: **Methods: To assess the diagnostic criteria and therapeutic modalities for pediatric IDA employed by physicians in a major public healthcare facility in Riyadh, a validated questionnaire including demographic data and patient case scenarios related to diagnosis and treatment of IDA was employed. Robust regression analysis was used to identify factors associated with overall score of participants. Wide variability was observed in IDA diagnosis and therapy practices. For nutritional IDA, only 15.6% recommended no other laboratory tests in addition to CBC. The majority preferred treatment with ferrous sulfate (77.6%) divided into two doses (57.1%), but the total daily elemental iron doses varied widely from 2 to 6 mg/kg. Of all assessed factors, median score was significantly highest in pediatric hematologists compared with pediatricians, family medicine specialists and GPs; p = 0.007, and those work in tertiary care compared with those in primary care; p = 0.043. However, in multivariate robust regression analysis, overall score was only significantly associated with professional qualification [pediatric hematologist β = 13.71,95%CI 2.48–24.95, p = 0.017; pediatrician β = 1.77,95%C (− 6.05–9.59, p = 0.66; family medicine β = 2.66,95%CI-4.30-9.58, p = 0.45 compared with general practitioner]. Conclusion: Wide variations exist among physicians in diagnosis and treatment of pediatric IDA.**

Keywords: **Iron deficiency anemia, Treatment, Diagnosis, Assessment, Pediatric.**

I. INTRODUCTION

Iron deficiency anemia (IDA) accounts approximately for 50% of all anemia cases in the world [1]. Pregnant women, infants aged 4 months to 2 years, young female, vegetarian people, and school-aged children particularly are at increased risk of IDA [4]. IDA is a consequence of loss of iron, which plays a significant role in normal RBCs synthesis [5]. Iron is specifically important for the central nervous system development, particularly at the first 2 years of life. Approximately 80% of the amount of iron in newborns, up to 1 year of age, is accreted during the last 3 months of pregnancy. A study conducted in the United States found that 9% of infants aged 1–2 years, and 9–10% of teenagers had IDA [7]. In some Arabic countries, the prevalence of IDA among infants was above 70% [8]. A cross-sectional study conducted in Jeddah estimated an IDA prevalence of 20. 5% among school children [10].Another study conducted in a northwestern region of

KSA found that 49% of infants aged 6 months to 2 years suffered from IDA [11]. A study conducted among school girls aged between 7 and 14 years in Riyadh reported an IDA prevalence of 26% [12]. Many studies examining the relationship between IDA and neurological/behavioral developments in children found significant associations between IDA and neurological/ behavioral consequences [12–14]. The American Academy of Pediatrics (APP) recommends that children at 1 year of age should undergo comprehensive screening for anemia. This includes determining Hb concentration and assessing IDA risk factors. If the IDA risk factors are noticed in children between one and 3 years, prompt screening should be conducted [15, 16]. Some reports emphasized use of hematological parameters such as serum transferrin, serum ferritin (SF), transferrin receptor 1 (TfR1), morphology and number of RBCs and Hb concentration. SF is considered a sensitive test for Iron stores. Therefore, it has been recommended that tests not affected by these health conditions, such as C-reactive protein (CRP), Reticulocyte Hemoglobin Content (CHr) or TfR1 must be added as a diagnostic test when the patient is diagnosed with any of these conditions [20].Although CHr has been shown to represents a strong biomarker for pediatric ID [21], however, it has been argued that the CHr test cannot differentiate between IDA and thalassemia, and TfR1 cannot differentiate between IDA and hemolytic anemia. In addition, the TfR1 test is not yet widely available in many countries [21]. An increased Hb of 1 gram per dl after 30 days of medication is considered a proper response to therapy and confirms IDA diagnosis. Current available medical literature suggests that 3–6 mg/kg/day of iron is an efficient IDA treatment [24, 25]. However, despite being the overwhelming preference for pediatric hematology/oncology specialists, no evidence is available yet to support the choice of iron dosage of 6 mg/kg/day in children. Many studies have shown success with low dosages and that higher dose might result in increased adverse events (AEs) and poor adherence [26]. Typically, treatment is taken orally, but treatment through parenteral route might be used in IDA patients who cannot tolerate oral route; for instance, those diagnosed with gastrectomy, bariatric surgery, and small intestine surgery [27]. This is because diagnosis of IDA often is challenging, and a highly sensitive and specific diagnostic test currently is not available. In addition, despite the fact that IDA treatment consists initially of oral iron supplement, there is no consensus on the schedule of dosage and the total period of therapy [22].

II. PATIENTS AND METHODS

An anonymous cross-sectional survey was conducted at health facilities affiliated with the National Guard Ministry of Health in the central region of Saudi Arabia between April 16 and October 19. 2017. These medical facilities include primary care [Iskan Clinic, Healthcare Specialty Center (HCSC).), National Guard Comprehensive Specialty Clinic (NGCSC), Dirab Clinic, and Price Bader Primary Care Clinic (PBRCC)] and tertiary (KASCH). All general practitioners (GPs), family physicians, physicians, pediatricians and pediatric hematologists working at these facilities were invited to participate in the study. The purpose of the study was explained in detail and those interested in participating signed a formal consent form. A validated questionnaire in the English version was used to assess the diagnostic criteria and treatment modalities of IDA in children used by each respondent [22].The questionnaire consists of two parts. The first part included demographic data and the second part of the questionnaire included two scenarios. Case scenarios were presented and respondents were asked to identify appropriate diagnostic tools and optimal therapeutic interventions according to their preferences. Responses were assessed against published evidence on the diagnosis and treatment of IDA.22, 24, 28-30. An overall score (for diagnosis and treatment) was calculated for each participant based on their responses to all items on the list. quiz.The total score of is 19.

III. STATISTICAL ANALYSIS

Data are presented as proportions (%) or medians (interquartile range) and compared using the $\chi 2$ test, Mann-Whitney test, or Kruskal-Wallis test, as appropriate. Robust regression analysis was used to identify variables associated with scores. These variables include sociodemographics, professional qualifications, professional rank, type of current work environment, years of employment since fellowship, number of pediatrician colleagues and availability of workplace scholarships. variables found to be significant in robust univariate analyzes were included in the final multivariate model. All tests were two-sided and p values < 0.05 is considered significant. The statistical software packages IBMSPSS (version 20) and Stata (StataCorp, Texas, USA, version 15) were used for data management and analysis.

IV. RESULTS

3% of participants reported their current work setting was a primary care center and 51. 7% a tertiary care center. Approximately 50% of the participants reported that more than 10 pediatricians' practice at their centers and 60. 5% reported that there was a pediatric fellowship associated with their centers; Table 1. In case 1, there were wide variations in the diagnostic procedures recommended by participants (Table 2). The majority of respondents recommended additional

laboratory tests to the CBC test; SF and TIBC were the most frequent (70. 7, 51%, respectively) recommended additional tests. Moreover, 2% of respondents suggested blood film as another additional lab test not include in the list. Amongst the listed oral iron preparation, most (77. 6%) of the respondents preferred treatment with ferrous sulfate; previous successful experience was the most (51%) cited reason. In terms of total daily iron dose, the respondents' recommendations were equally distributed across the three listed choices. Respondents were asked about total daily elemental iron dose they will recommend based on the degree of anemia severity. The majority (47. 6%) of the respondents recommended a 6 mg/kg dose, whereas 5. 4% would choose a 2–3 mg/dl dose. In case of patient's Hb was 10. 1 g/dl (rather than 8. 1 g/dl), 19% indicated they would not change the dosage, whereas the majority (34%) would choose a 2–3 mg/dl dose and 24. 5% of the respondents would choose a 4–5 mg/dl dose. As a continuation of this case scenario, participants were asked whether they will continue oral therapy at the 12th weeks visit if the patient's hemoglobin is 12. 2 g/ dL, MCV 78 fL and ferritin 25 ng/mL and his whole cow milk intake is limited. In case scenario 2, majority of respondents recommended treatment with ferrous sulfate (76.2%) divided into two daily doses (62. 6%). While 50. 3% of respondents reported that patient's daily dose should be based on weight, 49. 7% recommended that dose should be based on number of tablets. For participants who reported that the daily dose will be based on the number of tablets, approximately 42. 5% reported that they will choose 1 iron tablet daily, 53. 4% reported that they will choose 2– 3 iron tablets daily, and 4. 1% reported other numbers of tablets. In terms of those who recommended daily dose should be based on the weight, 32. 4% recommended a 2–3 mg/kg dose, 58. 1% recommended a 4–5 mg/kg dose and 6. 7% indicated other doses; Table 3. In continuation to the case scenario 2, respondents were asked regarding parenteral iron treatment they would recommend in case there is no response to oral iron. Correct responses on different questions related to diagnosis and management of IDA are represented in Table 4. Majority of the respondents recognized the appropriate oral iron preparation (87. 8%) and related factors that should guide their recommendations of the optimum oral iron preparation; 95%. While the vast majority of participants (99. 3%) could properly divide the total daily iron dose, 68% were able to identify the total daily elemental iron dose. Percentages of the correct answers related to which total daily elemental iron dose they would choose if the Hb was 6. 1 g/dl or 10. 1 g/dl (rather than 8.1 g/dl) were 78. 9, 61. 9%, respectively. However, they were less likely to know the Hb value below which they would recommend blood transfusion (33. 3%). Approximately 64% of the participants identified the correct answer associated with continued iron therapy when the patient improved and lab result showed normal Hb, MCV, and ferritin values. For case scenario 2, a high proportion identified the correct oral iron preparation (85%), and only half of them were able to indicate the correct daily dose. While 99. 3% of participants could know the correct division of the total daily iron dose, only 32. 7% of them identified the optimum parenteral iron treatment. Differences in overall median scores of correct answers by demographic and professional characteristics are represented in Table 3. Overall scores differed significantly by professional qualification (P = 0. 007) and type of current work setting (P = 0. 043). Robust regression analysis for factors associated with overall score is represented in Table 4. In univariate analysis, professional qualification and type of current work setting were the only two variables statistically significantly associated with overall score. overall scores was professional qualification (P = 0. 017). Based on findings of the above detailed regression analysis, further analyses were carried out to fully describe differences in scores both in the diagnostic and therapeutic domains questions by professional qualifications and type of current work setting. Consistently, the proportion of those achieved highest score of correct answers were pediatric hematologists, compared with respondents with other professional qualifications. Moreover, participants who work in tertiary care had significantly higher proportion of those achieved highest score of correct answers compared with those who work in primary care.

Table 1: Socio-demographic and professional characteristics of the participants

Characteristic		*N*	%
Age, Median (Q1-Q3)		39.0	[28–46]
Gender	F	73.0	49.7
	M	74.0	50.3
Professional Qualification	GP	50.0	34.0
	Family medicine	12.0	8.2
	Pediatrician	77.0	52.4
	Pediatric Hematologist	8.0	5.4
Professional Rank	Assistant Consultant	22.0	15.0
	Associate Consultant	6.0	4.1
	Consultant	36.0	24.5

	staff physician	48.0	32.7
	Resident	33.0	22.4
Type of current work setting	Primary Care	71.0	48.3
	Tertiary Care	76.0	51.7
Years in practice since fellowship	0–5 years	58.0	39.5
	6–10 years	29.0	19.7
	11–15 years	16.0	10.9
	> 15 years	27.0	18.4
No. of co-worker pediatricians	1–2 physicians	47.0	32.0
	3–5 physicians	19.0	12.9
	6–10 physicians	7.0	4.8
	> 10 physicians	74.0	50.3
Availability of fellowship program at work place	No	55.0	37.4
	Yes	89.0	60.5

Table 2: Responses of participants to case 1

Case #1 A previously healthy 18-month-old male is referred to your clinic for evaluation of anemia. He was exclusively breastfed for 8 months, and since then has been receiving 1–1 ½ liter whole cow milk daily and limited iron-rich foods. The physical examination is normal except for pallor. His hemoglobin is 8.1 g/dL, RBC count 4 million/mm3, RDW 20%, and MCV 58 fL. No other laboratory tests were previously performed by the PCP.

	Respondent answers	%
2	2–3 mg/kg	34.0
3	4–5 mg/kg	24.5
4	6 mg/kg	17.7
5	other (please specify)	4.1
6	Missing	0.7
How would you divide the total daily iron dose (Select one)?		
1	Once daily (QDay)	34.0
2	Divided into 2 doses (BID)	57.1
3	Divided into 3 doses (TID)	7.5
4	Other (please specify)	0.7
5	Missing	0.7
What is the hemoglobin value below which you would definitely recommend a blood transfusion (assuming the child looks "well compensated" with no co-morbidities) (Select one)?		
1	There is no hemoglobin below which I would definitely recommend a blood transfusion	21.8
2	3 g/dL	7.5
3	4 g/dL	2.0
4	5 g/dL	14.3
5	6 g/dL	40.1
6	Other (please specify)	11.6
7	Missing	2.7

Case #1 (continued) At a follow-up visit at 12 weeks, the patient's hemoglobin is 12.2 g/dL, MCV 78 fL and ferritin 25 ng/mL, and his whole cow milkintake is limited.

Would you recommend continued oral iron therapy (Select one)?

1	No	31.3
2	Yes, 1–2 additional month of iron therapy	36.1
3	Yes, 3 or more additional months of iron therapy	25.9
4	Other (please specify)	4.1
5	Missing	2.6

Table 3: Differences in overall scores by demographic and professional characteristics

Characteristics		Overall Score		
		Median	(Q1,Q3)	*p*
Gender	Female	68	(63–74)	0.217*
	Male	68	(63–79)	
Professional qualification	GP	63	(63–74)	0.007†
	Family medicine	68	(61–76)	
	Pediatrician	68	(63–79)	
	Pediatric Hematologist	84	(71–89)	
Professional rank	Assistant consultant	74	(63–79)	0.413†
	Associated consultant	68	(63–74)	
	consultant	68	(63–76)	
	Staff physician	63	(63–74)	
	Resident	68	(58–74)	
Type of current work setting	primary care	63	(63–74)	0.043*
	Tertiary care	68	(63–79)	
Years in practice since fellowship	0–5 years	68	(58–74)	0.848†
	6–10 years	68	(63–79)	
	11–15 years	68	(61–76)	
	> 15 years	68	(63–79)	
No. of co-worker pediatricians	1–2 physicians	63	(58–74)	0.188†
	3–5 physicians	68	(63–68)	
	6–10 physicians	74	(68–79)	
	> 10 physicians	68	(63–79)	
Availability of Fellowship program at work place	No	68	(63–74)	0.813*
	Yes	68	(63–79)	

* Mann-Whitney Test †Kruskal-Wallis Test Q1-Q3: first and third quartiles

Table 4: Factors associated with overall score

Factor	*N* (%)	Univariate analysis		Multivariate analysis	
		β (95% CI)	*p*	β (95% CI)	*p*
Professional qualification					
Pediatric hematologist	8(5.4)	14.98(6.81,23.15)	< 0.0001	13.71(2.48,24.95)	0.017
Pediatrician	77(52.4)	2.87(−1.02,6.77)	0.15	1.77(−6.05,9.59)	0.66
Family medicine	12(8.2)	2.69(−4.20,9.58)	0.44	2.66(−4.30,9.58)	0.45
General practitioner	50(34)	1		1	
Type of current work setting					
Tertiary	76(51.7)	3.63(−0.03,7.28)	0.05	1.26(−6.40,8.92)	0.75
Primary	71(48.3)	1		1	

V. DISCUSSION

To the best of our knowledge, this is the first study conducted in the Arabian Gulf region to assess the diagnostic and therapeutic modalities employed by physicians for the management of pediatric IDA. The study findings show wide variations in practices and recommendations regarding the proper diagnosis and treatment of pediatric IDA in KSA by physicians involved in management and care. This reflects lack of local guidelines for management of this widely prevalent medical condition. National guidelines are urgently needed. Further, the study identifies some healthcare practitioners who might benefit from further training to improve their pediatric IDA management skills. Namely, physicians working in primary care setting, GPs, family medicine practitioners and pediatricians. Research work on diagnostic criteria and therapeutic modalities employed by physicians for pediatric IDA is sparse. While previous studies focused on IDA epidemiology 1, 7, 8, 12, 29, diagnosis 24, 2931, treatment 24, 32, or prevention 28, 29, 33, findings of our study and

another study conducted in U. S by Powers et al. 17 were the only two studies to demonstrate a wide variation among physicians in IDA diagnosis and treatment. However, compared with Powers et al. study, the present study adopted a unique approach. The total score we calculated in this study, based on participants responses to different questions, allowed us to identify various sub-optimal practices regarding diagnosis and treatment of pediatric IDA. The documented wide variations in this study regarding the diagnostic criteria for IDA worth consideration. Many of the patients managed at primary care facilities or referred to tertiary hospitals undergo unnecessary tests in addition to the CBC 31. The study finding that only 15. 6 of participants in the present study recommended that no additional laboratory tests necessary beyond the CBC concur with findings of a study conducted in the U. S. by Powers J et al. 17They also found a similar percentage of 15. AAP guidelines recommend that patient found anemic on initial screening should undergo confirmative testing for dubious IDA that include measuring TfR1 concentration, CHr or Ret-He, and or SF with CRP 29. However, the AAP does not indicate that neither CHr cannot differentiate between IDA and thalassemia nor TfR1 cannot differentiate between IDA and hemolytic anemia 34. Further, these tests are not readily available in all healthcare centers, particularly in resource-limited countries. Therefore, making a clinical decision based on such tests might not be viable. In this study, most participants do not use a specific guidelines to confirm diagnosis of IDA. In the aforementioned U. S. study which surveyed pediatric hematology oncology physicians, most participants did not employ the AAPs approach 17. Powers et al. recommended that CBC, peripheral blood smear and reticulocyte count along with serum iron, SF and TIBC usually can be used to establish the diagnosis of IDA 23. While such tests were chosen by over 50 of Powers et al. study participants, SF and TIBC were selected by approximately half of our participants. In regard IDA treatment, elicited responses indicate that over half of our study participants base their therapeutic decision on their previous experience than on evidence. Almost all published literature recommends a dose of 36 mg/kg/day of iron as an efficient IDA treatment 24, 30. However despite using 6 mg/kg/day being the overwhelming preference for pediatric hematology oncology specialists, there is no evidence base for such choice. Many studies have shown treatment success with low dosages. A randomized trial in Ghana compared patients to 40 mg of iron, or almost 3 mg/kg/day either as a single dosage or in three divided dosages, found similar success in both groups 32. Another study including 90 elderly patients compared three daily doses of iron 15 mg, 50 mg, and 150 mg. After 60 days, in all three groups, the increases in Hb concentration and SF were similar. This suggests that low oral dosage of iron treatment could be as effective as high dosage. Furthermore, in the lowest dose groups, the rates of dropout and adverse effects were lower 35.

VI. CONCLUSION

There are many differences in the diagnostic and treatment approaches used by physicians for pediatric IDA in Saudi Arabia. This situation is further exacerbated by the lack of evidence-based guidelines for the optimal management of this widely diagnosed condition. These instructions are essential. Large-scale clinical trials and prospective studies are needed to better inform these guidelines and programs. The study identifies certain healthcare professionals who may benefit from intervention programs aimed at maximizing optimal care for IDA patients.

Abbreviations AEs: Adverse events; APP: American Academy of Pediatrics; CBC: Complete blood count; CHr: Reticulocyte Hemoglobin Content; CRP: C-reactive protein; FDA: Food and Drug Administration; GP: General practitioner; Hb: hemoglobin; ID: Iron Deficiency; IDA: Iron deficiency anemia; IV: Intra venous; KSA: Kingdom of Saudi Arabia; MCV: Mean Corpuscular Volume; QDay: Once daily dose; RBC: Red blood cells count; SF: serum ferritin; TfR1: Transferrin receptor 1

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