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ORIGINAL ARTICLE

C Reactive Protein Response in Severe Acute Malnutrition with Infection

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Abstract

Background: *Nearly half of all deaths in children under-five are attributable to malnutrition, translating into the loss of about 3 million young lives a year. The interaction between malnutrition and infection can create a potentially lethal cycle of worsening illness and deteriorating nutritional status. They have altered defense mechanisms during an early infections process, with an increased synthesis of some acute phase proteins including CRP.*

Objectives: *Objective of the study was to identify whether CRP response is helpful in early detection of infection in severe SAM. It may also help to reduce childhood mortality associated with SAM.*

Methods: *This cross-sectional study was conducted with total 50 SAM patients who were admitted in the Gastroenterology Hepatology and Nutrition unit of Dhaka Shishu (Children) Hospital from October 2010 to March 2011. Immediately after admission, clinical evaluation and management was started after sending several investigations along with serum CRP. Re-evaluation of serum CRP was done approximately after 7 days. Data were analyzed by using SPSS version 24.*

Results*: Among the 50 SAM patients, 29 patients were presented with oedema(group-A) and 21 patients were without oedema (group-B). Majority (40) were below 2 years of age with male predominance. Thirty-five patients were partially immunized [69% in group-A and 71.4% in group-B]. During initial assessment, 46% children were hypothermic and 76% were hypoglycemic. Nutritional status (z score) weight-for-age, height/length-for-age, weight for height/length in group-A were -4.56±1.00, -4.27±1.97, -2.71±0.97 and in group-B were -4.65±0.78, -5.06±2.34, -2.58±1.00 respectively. Pneumonia (42%) and diarrhoea (36%) were more common. Increased WBC count was found in 80% patients; and only 10% had low hemoglobin level (<5 gm/dl). Majority (44%) of them had pulmonary infection which was found in their chest X-rays. Immediately after admission serum CRP were high [mean CRP 39.44(±16.04)] in all most all patients, irrespective of their types of malnutrition. After 7 days of management, their CRP became normal [07.24 (± 2.75)], p=<0.001. Mean CRP was less [34.90 (±16.60)] in group-A than in group-B [45.72 (±13.16)] on admission and the finding was statistically significant, p=<0.001.*

Conclusion: *Plasma level of CRP constitute a good screening test for the presence of infection in malnourished children and act as a sensitive indicator of recovery from infection and malnutrition.*

Keywords: *Severe acute malnutrition (SAM), C reactive protein (CRP).*

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Introduction

At least 1 in 3 children under five years of age is not getting the proper nutrition they need to grow well, and 1 in 2 suffers from hidden hunger; particularly in crucial first 1,000 days from conception to child's second birthday and often beyond. An increasing number of children and young people are surviving, but far too few are thriving because of malnutrition, undermining the capacity of millions of children to grow and develop to their full potential.[1] Severe acute malnutrition limits the development potential of a country, and is strongly associated with increased mortality, morbidity, reduced cognitive performance and compromised productivity among its population.[2]

Over the years undernutrition rates remain still alarming; stunting is declining too slowly while wasting still impacts the lives off far too many young children.[3] Even in the year 2020, WHO estimated that globally 47 million children under 5 years of age are wasted, 14.3 million are severely wasted and 144 million are stunted. Around 45% of deaths among children under-5 years of age are linked to undernutrition. These mostly occur in low and middle-income countries.[4] Malnutrition puts children at a greater risk of dying from common infections, increases the frequency and severity of infections, and delays recovery. This interaction creates a potentially deadly cycle of deteriorating health and worsening nutritional status.[3]

The vast majority of malnourished children live in developing regions, mainly in Asia and Africa.[4,5] WHO estimates in 2019 in South-East Asia about 4.7 million under-5 children were moderately and severely wasted (<-2SD) and about 2 million were severely (<-3SD) wasted. About 13.9 million children were moderately and severely stunted (<-2SD) (according to median weight-for-height and height-for-age of the WHO Child Growth Standards).[6] National Guidelines for the Management of Severe Acute Malnourished Children in Bangladesh (July 2017) defined severe acute malnutrition (SAM) by the presence of severe wasting and/or bipedal oedema. A child aged 06-59 months is classified as severe acute malnourished if she/he has one or more of the following: (a) Mid-upper arm circumference (MUAC) <115 mm, (b) Weight-for-length Z score (WLZ) <-3, or Weight-for-height z-score (WHZ) <-3, (d)Bipedal oedema (Kwashiorkor, Marasmic-kwashiorkor, Marasmus). A child less than 6 months old is classified as SAM when one or more of the following: (a) WLZ <-3 (b) Bipedal oedema (c) visible wasting is present.[7]

The scenario of Bangladesh is much frightening as it possesses a major bulk of malnourished children of the developing countries though the situation is slowly improving here from ninties.[8] Severe acute malnutrition affects 450,000 children, while close to 2 million children have moderate acute malnutrition.[9] A great deal has been achieved to improve children's lives; moderate and severe underweight prevalence became 22.6% and moderate and severe stunting became 28% in recent year (2019).[10] In recent (2018-1019) database from National Institute of Population Research and Training (NIPORT) and ICF reported in WHO-UNICEF showing severe wasting 1.5 million, moderate and severe wasting 8.4 million, stunting 30.8millions, 219 million underweight among the 14516.61 million under 5 children of Bangladesh.[11] But still in 2019, child mortality rate for Bangladesh was 30.8 deaths per 1,000 live births; majority reason behind is malnutrition.[12]

In majority cases deaths of malnourished children are associated with infection like pneumonia, septicemia, diarrhoea, particularly mismanagement of diarrhoea with dehydration, sepsis and hypovolumic shock, severe anemia, electrolytes imbalance, vitamin-A deficiency, hypoglycemia, hypothermia etc.[13-15] Among them diarrhoea and pneumonia are very much prone to develop and their incidence of severity, duration of illness, complications are higher in malnourished children.[16-19] Immunodeficiency is common in malnourished children and breaks down the host resistance in large segments. The most existent abnormality detected in various studies has been (1) Impairment in cell mediated immunity (2) Children with SAM are difficult to sensitize by repeated antigens (3) Even delayed hypersensitivity reactions that recall previous sensitization are also delayed. The underlying mechanism include lymphopenia, reduce number of T-lymphocytes in peripheral blood, impaired response to mitogen and antigen, decreases lymphokine production and serum inhibition.[13]

It is well established that nearly every aspect of the body's defense system is damaged by severe malnutrition.[20] But it is not clear whether malnourished infants can mount a comprehensive acute phase protein (APP) response. The characteristic response to an infective stress includes increased plasma concentrations of APP, which play important role in host defense.[21]

Acute-phase protein is defined as a protein whose plasma concentrations increase during certain inflammatory disorders.[22] They are C-reactive protein (CRP), serum amyloid-A, fibrinogen and alpha-1-acid glycoprotein.[23] Perhaps the best known of them is CRP[22], a plasma protein that is produced from liver and its level rises in response to inflammation.[23,24] It is primarily induced by the IL-6 action on the gene responsible for transcription of CRP during the acute phase of an inflammatory/ infectious process.[23] These plasma proteins have role in combating infections, including modulating T-lymphocyte function and the complement system, scavenging haemoglobin and protecting the integrity of healthy tissues against the effect of proteases produced by the pathogens or release from damaged cells.[21,24]

In a study of marasmic children with infection showed that the kinetic mechanism used in mounting an APP response included alterations in both the rate of synthesis and catabolism of protein.[25] Children with kwashiorkor however differ from those with marasmus is having slower rates in whole body protein breakdown, which may reduce the availability of endogenous amino acids for APP synthesis.[26] Manary et al[27] found increased CRP in both oedematous and non-oedematous malnutrition with no significant difference but Amnesty et al[28] found high CRP levels in children with marasmus.

The present study is carried out to determine CRP response in SAM children with infection to see whether they can mount a general APP response and to compare the response between oedematous and non-oedematous SAM. However published evidences in favor of our observation are scanty and we believe it may help in early accurate detection of infection and reduce childhood mortality associated with SAM.

Materials and Methods

This cross sectional study was conducted with severe acute malnlurished patients who were admitted in Gastroenterology Hepatology and Nutrition unit of Dhaka Shishu (Children) Hospital from October 2010 to March 2011. Total 50 patients who fulfilled the following inclusion and exclusion criteria were enrolled in the study. Inclusion criteria were: a) Age: 6 months-59 months b)Irrespective of sex c) Anthropometric measurement fulfill WHO classification when the child present a ratio of - i) W/H <-3 SD with oedema ii) W/H <-3 SD without oedema d) Presence of evidence of infection [Diagnosis of infection required one or more of the following on admission - 1) WBC count >11X10^9/L, 2) Hyperthermia/Hypothermia (body temperature >37°C or <35.5°C) and Hypoglycemia(<3mmol/L or 54 mg/dl), 3) Suggestive Chest X-ray, 4) Positive growth in blood and urine culture, 5) Diagnosis of specific type of infection based on symptoms and signs. Exclusion criteria: a) Patient with secondary malnutrition due to other causes like DM, hyperthyroidism, congenital anomalies or cerebral palsy and b) patient with oedema due to other diseases like CCF, NS, cirrhosis of liver, protein loosing enteropathy.

For each child a semi-structured questionnaire was prepared which included age, sex, nutritional status, birth history, immunization status, previous illness, socio demographic, maternal education, nutrition, psychosocial history like monthly family income of parents. Anthropometric assessments were done immediately after admission. Weight was confirmed by two observers to avoid interpersonal variation. Weight was measured by standard weighing scale, MISAKI (made in Japan), capacity 12 kg (26 Ibs), GRAD = 0-10kg, precision - 50 gm, Accuracy- 5gm. Length/height was measured with locally constructed WHO recommended wooden board (infantometer) in bear leg. Patients <85 cm in length, or children too weak to stand, their length were measured while lying down. If the child was d"85 cm but could not be measured standing, 0.5 cm was subtracted from the supine length. Reference standard was taken as 50th centile of National Centre for Health Statistics (NCHS). Weight for height and height for age was converted into Z score after standardizing with NCHS reference data. Clinical varieties were noted according to WHO classification. Accuracy was carefully maintained and inter-observational error was minimized by involving trained personnel's.

In all children clinical evaluation was done immediately after admission by physical examination then investigation were sent like CBC, RBS, chest X-ray, parasitological examination of smear blood for malaria, serum electrolytes, serum total protein, serum albumin, routine analysis of stool and urine. Blood, urine, stool samples were sent for culture as per need to diagnose infection. Then serum CRP measurement had done to whom infection was suspected on the basis of clinical, biochemical and

radiological criteria before starting nutritional therapy and medical treatment.

Approximately 7 days after admission a new blood sample for CRP was collected. One ml of venous blood was required to determine serum CRP by using CRP reagent. This synthetic particle coated with antibody to CRP, aggregate in presence of CRP in the sample. The increase in turbidity which accompanies aggregation is proportional to the CRP concentration. Accurate result had collected by spectophotometric reading using automatic analyzer machine (Dimension RX max) in clinical biochemistry laboratory in Dhaka Shishu (children) Hospital. A measurement of serum CRP >10 mg/l was considered as infection marker.

For every child after immediate evaluation and collecting blood sample, management has been given according to National Guideline for the severely malnourished children in Bangladesh. For nutrition F-75 formula were started containing 75 Kcal/100 ml,and were treated with antibiotics (Ampicillin ±Gentamycin). All these investigations were done in the pathology, microbiology and radiology department of Dhaka Shishu (Children) Hospital. Informed written consent was taken from parents. Reassurance was given to parents regarding study and all investigations were done at free of cost. Clearance was taken from the ethical review committee and permission of the hospital authority to use the machine. Data entry and analysis was done by using SPSS version-24.

Results

All the 50 severe acute malnourished patients were divided in group-A (n=29) who were severely malnourished with oedema and group-B (n=21) who were severely malnourished without oedema. Majority of study population were below 2 years of age, 25(50%) population from group-A and 15(30%) from group-B and their mean age was11.96 (± 8.93) month in group-A and 16.14(±14.29) month in group-B. Male were predominant in both groups (group-A 58.6% and group-B 71.4%). Most of the children came from slum area and belong to poor family (£5000taka) in both group-A(72.4%) and group-B (66.7%). Majority of children were partially immunized (69% in group-A and 71.4% in group-B) (Table I).

Table I

Socio-economic and socio-demographic characteristic of study population (N=50)

Characteristics	Group-A (Oedematous SAM)	Group-B (Non oedematous SAM)
Age		
6-23 months	25 (50%)	15(30%)
24-59 months	4(8%)	6(12%)
Mean age group (age in month)	11.96 (± 8.93)	16.14 (±14.29)
Gender		
Male	17(58.6%)	15(71.4%)
Female	12(41.4%)	06(28.6%)
Socio-economic status		
Poor (£5000)	21(72.4%)	14(66.7%)
Lower Middle (5000-10000)	05(17.2%)	03(14.3%)
Middle (10000-15000)	03(10.3%)	04(19.0%)
Residence		
Rural	7 (14%)	7(14%)
Urban	8(16%)	4(8%)
Slum	14 (28%)	10(20%)
Immunization		
No immunization	02(6.9%)	03(14.3%)
Partially Immunized	20(69)%	15(71.4%)
Completely Immunized	07(24.1%)	03(14.3%)

During initial assessment of the study population total 23(46%) children were hypothermic; 14(48.3%) from group-A and 9(42.8%) from group-B. Whereas total 10(20%) children of which 4(13.8%) from group-A and 6(28.6%) from group-B were hyperthermic by rectal thermometer (Fig. 1) and similar result were found by axillary thermometer. At admission in group-A hypoglycemia was present in 38(76%) cases, in group-B hypoglycemia was present in 22(76%) cases. Majority of study population were hypoglycaemic in both groups (Fig. 2).

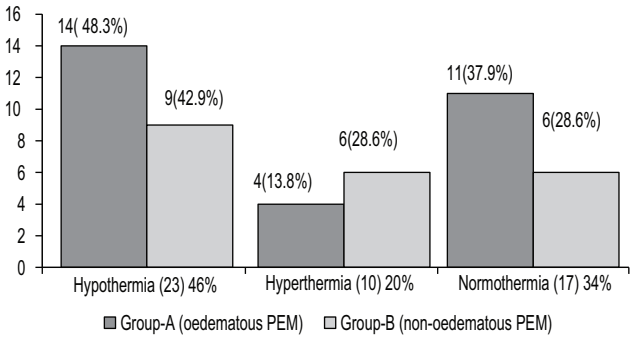

Fig 1 *Distribution of SAM patients by their thermal status (Rectal)*

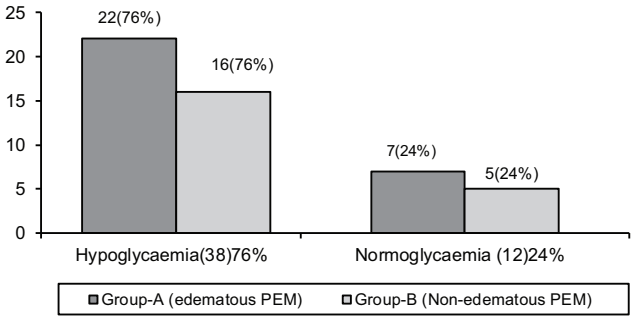

Fig 2 *Distribution of study population by glycaemic status*

In Group-A Z score (weight for age, height/length for age, weight for height/length) were -4.56±1.00, -4.27±1.97, -2.71±0.97 and in group-B were -4.65±0.78, -5.06±2.34, -2.58±1.00 respectively (Table II). Complete blood picture showed that 40 out of 50 study population had WBC count >11000/cu mm; but only 10% had hemoglobin level <5 gm/dl. Majority (44%) of them had pulmonary infection in their chest X-rays (Table III).

Table II

Mean values with standard deviation of anthropometric assessment of study population (N=50)

Study population		Wt for Age %	Wt for Age Z score	Ht for Age %	Ht for Age Z score	Wt for Ht / length%	Wt for Ht /length Z score
Group-A	Mean	59.41	-4.56	84.48	-4.27	73.25	-2.71
(Oedematous SAM)	±SD	±10.96	±1.00	±8.21	±1.97	±20.53	±0.97
Group-B	Mean	51.28	-4.65	83.57	-5.06	84.00	-2.58
(Non-oedematous SAM)	±SD	±9.86	±0.78	±10.59	±2.34	±21.23	±1.00

Table III

Distribution of SAM patients by laboratory findings on admission

Laboratory findings	No of patients	Percentages
Hb (gm/dl)		
<5	5	10
5-10	45	90
WBC(/cumm)		
<12000	10	20
12000-20000	16	32
21000-30000	04	08
>30000	20	40
Chest X-ray findings		
Normal	10	20
Pulmonary infection	22	44
Not done	18	36

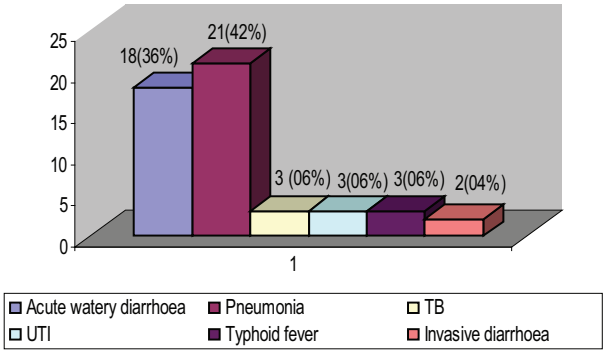

Fig 3 Distribution of SAM patients by types of infection (N=50)

Fig 3 *Distribution of SAM patients by types of infection*

Pneumonia (42%) and diarrhoea (36%) were more common among the study population (Fig 3).

Table IV
Distribution of study population by CRP values on admission and after 7 days (N=50)

CRP value (mg/L)	On admission		After 7 days	
	Group-A (Oedematous SAM) n=29	Group-B (Non-oedematous SAM) n=21	Group-A (Oedematous SAM) n=29	Group-B (Non-oedematous SAM) n=21
0-5	00(00%)	00(00%)	09(31.04%)	11(52.38%)
6-9	01(3.49%)	00(00%)	20(68.96%)	10(47.62%)
10-29	16(55.17%)	00(00%)	00(00%)	00(00%)
30-49	06(20.69%)	06(28.57%)	00(00%)	00(00%)
50-70	06(20.69%)	15(71.43%)	00(00%)	00(00%)

Table V
Mean CRP value of the study population on admission and after 7 days (N=50)

	CRP on admission	CRP after 7 days	p value
Mean (±SD)	39.44 (± 16.04)	07.24 (± 2.75)	<0.001

Table VI
Mean CRP value in two groups of study population on admission (N=50)

CRP	Group-A (Oedematous SAM) Mean (±SD)	Group-B (Non-oedematous SAM) Mean (±SD)	p value
	34.90 (± 16.60)	45.72 (± 13.16)	0.01

During admission out of 29 patients in group-A, 28 had CRP value >10 mg/L and in group-B out of 21 patients all had CRP value >10 mg/L. That is majority of malnourished children had high CRP value on admission irrespective of their type of malnutrition. After 7 days of given management, follow up CRP level done and revealed all patients in both groups had normal CRP value (<10mg/L) (Table IV). Mean CRP value were assessed; on admission it was 39.44(±16.04) and after 7 days (while infection controlled) was 07.24(± 2.75). CRP value was high in severe malnourished child on admission when associated with infection but significantly low on recovery (p <0.001) (Table V). Mean CRP value of group-A was less [34.90 (±16.60)] than in group-B [45.72 (±13.16)] on admission and finding was statistically significant (p=<0.01) (Table VI).

Discussion

Malnutrition is an important public health problem; it is a world health crisis. Millions of people are suffering from different forms of malnutrition. Nutrition is the main cause of death and disease in the world. The developmental, economic, social and medical impacts of malnutrition are serious and lasting.[29]

Globally nearly 47 million children of under-five suffer from severe acute malnutrition and about 45% of under-five death in the world is associated with malnutrition.[4] Nearly half of all deaths in children under 5 are attributable to undernutrition; undernutrition puts children at greater risk of dying from common infections, increases the frequency and severity of such infections, and delays recovery which contributes to an estimated 3 million deaths/year.[3] The prevalence of childhood malnutrition in Bangladesh is among the highest in the world. Even

though we have achieved significant progress in reducing the proportion, the magnitude of the problem still is of great concern.[30,31]

The characteristic response to an infective stress includes increased plasma concentration of CRP, a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory process in body.[23] This study was unique in its kind which attempted to reveal CRP response in severe acute malnurished children associated with infection to determine whether oedematous SAM child can mount a general acute phase protein (APP) response and also to compare the response in children with oedematous SAM and with non oedematous SAM.

All severely malnourished children are at risk of hypoglycemia and hypothermia; which usually occur together and signs of infection are frequently associated with a high fatality.[32] Present study reflected that hypoglycemia found in majority cases (76%) in both groups of study population; similar to the findings of other authors.[33] Yokoyama et al[34] found 26% of severely malnourished children manifested hypothermia. Present study reflected that hypothermia was found in 48% cases in group-A and 43% cases in Group-B of study population.

This study reflected that diarrhea (36%) and pneumonia (44%) were more common type of infection and frequent association with severely malnourished children. Different study showed diarrhea and pneumonia were very much prone to developed in malnourished children.[16-19] On admission all the children had associated infection which was further supported by an elevated total count of WBC and X-ray findings. Here 32% cases had WBC count between >10,000-20,000)/cumm, and 40% had>30,000/cumm. Ninety percent cases were anemic and maintained Hb level between 5-10gm/dl. About 44% cases had pulmonary infection.

The synergistic malnutrition-infection complex has significant effects on child health.[35] This study revealed 97% cases of group-A and 100% cases of group-B had high CRP concentration on admission in association of infection, which suggests severely malnourished child are capable of mounting an APP response. As shown by Golden et al[35] and Tomkins et al[36] whole body protein synthesis rate is reduced in the infected malnourished children compared with both infected and uninfected well-nourished children, suggesting that the malnourished children may be mounting an APP response through mechanisms other than stimulation of synthesis rate.

Morlese et al[25] suggested that in severe malnutrition APPs increased due to changes in both rate of synthesis and catabolism of these proteins. This study finding of higher APP response of malnourished children is also reported by other authors.[25,37] In the present study after one week of dietary and anti-microbial treatment there was significant drop in the plasma levels of CRP in all cases when the infection had cleared but still malnourished, as like the finding that was previously reported by others.[38] We found mean CRP value was 39.44(±16.04) on admission and after one week 07.24(±2.75),this result was statistically significant (P=<0.001).

Reid et al[38] observed children with oedematous SAM can mount an APP response to infection that is similar with non-oedematous SAM, but the magnitude of the response is less in children with oedematous SAM. The weaker response in oedematous group is not surprising, because other aspect of host defense, relating to immune structure and function, are more compromised in children with oedematous SAM than those with non-oedematous SAM. The present study also reflected that mean CRP value in group-B (non-oedematous) cases were much higher 45.72(±13.16) than in group-A (oedematous) cases 34.90(±16.60) and the result was statistically significant (p <0.01).

Fifty percent of the cases from group-A and 30% cases from group-B were from 06 months to 23 months of age and mean age was 11.96(±8.3) months in group-A and 16.14(±14.29) months in group-B. Amin et al[39] showed majority (77%) of the malnourished children were below 2 years of age. Roy et al[17] showed, age was one of the significant determinants of childhood nutrition. The younger children (<2 years) had significantly higher level of severe malnutrition. As the age of these children grows up the proportion of children with malnutrition decreases. Among study population, male were predominant than female, as like other study.[39] It might be due to the fact that parents were more concerned about male children. Most of the children in this study belonged to poor socio-economic class. Majority of them from urban slum with monthly family income were below 5000 TK. This was in accordance with a similar report from Shakur et al[40] and Awal et al[41] showed that the relationship between malnutrition and poverty

exists in a vicious cycle. Poverty generates malnutrition and malnutrition generates poverty and diseases.

These children's immunization statuses were very poor, only 24% from group-A and 14% from group-B were completely immunized. Islam et al[42] found similar result. Their anthropometric assessment showed that mean nutritional status in Z score (weight for height/length) of group-A was SD-2.71±0.97 and in group-B was SD-2.58±1.00 which found similar like WHO references.[6] This study was a hospital base single centered study, it has chance of over representation which could not reflect general population and may not represent the similar situation in the whole population of the country. This study was a non-randomized cross-sectional study. A broad base longitudinal cohort study could be more meaningful.

Conclusion

In conclusion, plasma level of CRP constitutes a good screening test for the presence of infection in severely malnourished children and that APP is a sensitive indicator of recovery from infection and malnutrition.

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References

1. Malnutrition; The state of the world's children 2019. Available from: https://data.unicef.org/resources/state-of-the-worlds-children-2019/.
2. Akhter N, Haselow N. Using data from a nationally representative nutrition surveillance system to assess trends and influence nutrition programs and policy. *The journal of field actions* 2010;**4**(1). Available from: http://www.factsreports.revues.org/index395.html.
3. Malnutrition by UNICEF. Available at: https://data.unicef.org/topic/nutrition/malnutrition.
4. WHO Fact sheet on Malnutrition. Available from: https://www.who.int/news-room/fact-sheets/detail/malnutrition.
5. Onis MD, Blossner M, Borghi E, Frongillo EA, Morris R. Estimates of global prevalence of childhood underweight in 1990 and 2015. *JAMA* 2004;**291**: 2600-06.
6. UNICEF/WHO/World Bank joint child malnutrition estimates (global and regional) March 2020. Available from: https://data.unicef.org/ topic/nutrition/malnutrition/.
7. National Guidelines for the Facility-based Management of Children with Severe Acute Malnutrition in Bangladesh. By Institute of Public Health & Nutrition, Director General of Health Services, Ministry of Health and Family Welfare, Government of People's Republic of Bangladesh. July 2017.
8. UNICEF, Bangladesh Bureau of statistics planning division, Ministry of planning Government of the peoples Republic of Bangladesh. Summary of the situation of children & women in Bangladesh. Progotir Pathey 2003 on the road to progress. 2004;14-16.
9. Malnutrition; News & Events of ICDDRB. Available from: https://www.icddrb.org/news-and-events/press-corner/media-resources/malnutrition.
10. UNICEF Press release: Bangladesh sees sharp decline in child malnutrition, while violent disciplining of children rises, new survey reveals. Available from: https://www.unicef.org/bangladesh/en/press-releases/bangladesh-sees-sharp-decline-child-malnutrition-while-violent-disciplining-children.
11. UNICEF/WHO/World Bank joint child malnutrition estimates regional classification- March 2020. Available from: https://data.unicef.org/topic/nutrition/malnutrition/.
12. Key demographic indicators of Bangladesh-childhood mortality rate. Available from: https://data.unicef.org/country/bgd/.
13. Gupta S. Pediatric nutrition and nutritional deficiency states. The short Textbook of Pediatrics. 9th ed. New Delhi: Jaypee Brothers; 2001.p116-131.
14. Ghai OP. Nutrition & nutritional disorders. Essential Pediatrics. 3rd ed. New Delhi: Interprint 16-A; 1993.p 42-46.
15. Van den Broek JM, Roy SK, Khan WA, Ara G, Chakraborty B, Islam S, et al. Risk factors for mortality due to shigellosis: A case-control study among severely malnourished children in Bangladesh. *J Health Popul Nutr* 2005;**23**:259-65.
16. Baqui AH, Black RE, Arifeen SE, Hill K, Mirta SN, Sabir AA. Results of a nationwide verbal autopsy study. *Bulletin of the world health organization* 1998;**76**:161-71.

17. Roy NC. Use of mid upper arm circumference for evaluation of nutritional status of children and for identification of high-risk groups for malnutrition in rural Bangladesh. *J Health Popul Nutr* 2000;**18**:171-80.

18. Victora CG, Kirkwood BR, Asworth A, Black RE, Rogers S, Sazawal S, et al. Potential intervention for the prevention of childhood pneumonia in developing countries: Improving nutrition. *Am J clin Nutr* 1999;**70**:309-20.

19. Rica AL, Sacco L, Hyder A, Black RE. Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. *Bulletin of the World Health Organization* 2000;**78**:1207-21.

20. Chandra RK. Mccbillum Award Lecture, Nutrition and immunity. Lesions from the past and new insights the future. *Am J Clin Nutri* 1990;**53**:1087-107.

21. Downton SB, Colten HR. Acute phase reactants in inflammation and infection. *Semin Hematol* 1988;**25**:84-90.

22. William C. Shiel Jr. Medical definition of acute-phase protein. Available from: https://www.medicine net.com/acute-phase_protein/definition.htm.

23. Nehring SM, Goyal A, Bansal P. C Reactive Protein. [Updated 2020 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441843/.

24. Medline Plus. NIH-US national library of medicine: C-reactive protein. Available from: http://www.nlm.nih.gov/medlineplus/ency/artcle/ 003356.htm.

25. Morlese JF, Forrester T, Jahoor F. Acute-phase protein to infection in severe malnutrition. *Am J physiol* 1998;**275**:112-17.

26. Kushner I. The phenomenon of the acute phase response C-reactive protein and the plasma protein response to tissue injury. *Ann NY Acad Sci* 1982;**389**:39-48.

27. Manary MJ, Broadhead RL, Yarsheshki KE. Whole body protein kinetics in marasmus and kwarshiorkor during acute infection. *Am J clin Nutr* 1998;**67**:1205-09.

28. Amnesty -Valbuena A, Pereira N, Castillo J, Garcia D, Nuòez J,Cayama N, et al. Mdiadores de inflamación (proteina C reactiva) en el niòo con desautriciónproteico energética y enelniòoeutrófico. *Invest clin* 2004;**45**:53-62.

29. Branca F. Malnutrition is a world health crisis. Available from: https://www.who.int/news/item/26-09-2019-malnutrition-is-a-world-health-crisis&https://www.globalcause.co.uk/world-food-day/malnutrition-is-a-world-health-crisis-says-who-expert/.

30. IPHN, Severe malnutrition in Bangladesh. Available from: http://www.fao.org/ag/agn/nutrition/bgd_en.stm#:~:text=Rates%20of%20 malnutrition %20in%20Bangladesh,more%20than%2017%25% 20re%20wasted.&text=Malnutrition%20among%20women%20is%20also%20extremely%20prevalent%20in%20 Bangladesh.

31. NIPORT (National Institute of Population Research and Training) Dhaka, Bangladesh; Mitra and Associates, Dhaka, Bangladesh; Macro International, Calverton, Maryland USA; Bangladesh Demographic and Health Survey (BDHS)-2007, March 2009. Available from: https://dhsprogram.com/pubs/pdf/PR104/PR104.pdf.

32. Wharton B. Hypoglycaemia in children with Kwashiorkor. *Lancet* 1970;**1**:171-73.

33. Das BK, Ramesh J, Agarwal JK, Mishra OP, Bhatt RP. Blood sugar and serum insulin response in protein energy malnutrition. *Journal of Tropical Pediatrics* 1998;**44**:139-41.

34. Yokoyama M, Noto Y, Kida H. Hypothermia with acute renal failure in a patients suffering from diabetic nephropathy and malnutrition. *Diabetes Metab* 2000;**26**:145-47.

35. Golden M, Waterlow JC, Picou D. Protein turnover, synthesis and breakdown before and after recovery from protein energy malnutrition. *Clin Sci* 1977;**53**:473-77.

36. Tomkins AM, Garlick PJ, Schofield WN, Waterlow JC. The combined effects of infection and malnutrition on protein metabolism in children. *Clin Sci* 1983;**65**:313-424.

37. Dohery JF, Golden MHN, Raynes JG, Griffin CE, McAdam KPWJ. Acute-phase protein response is impaired in severely malnourished children. *Clin Sci* 1993;**84**:169-75.

38. Reid M, Badaloo A, Forrester T, Morlese JF, Heird WC, Jahoor F. The acute-phase protein response to infection in oedematous and nonoedematous protein-energy malnutrition. *Am J Clin Nutr* 2002;76:1409-15.

39. Amin MR, Begum KA, Banu N, Ehsan MA, Akbar MS. Socio-economic determinants and biochemical Status of severely malnourished children. *DS (Child) HJ* 1991;**7**:71-77.

40. Shakur MS, Banu N, Ehsan MA. Clinical, Biochemical & Socio-economic factors associated with severe degree malnutrition in children admitted in Dhaka Shishu (Children) Hospital. *DS (Child) HJ* 1991;**7**:5-12.

41. Awwal AMMA. The vicious cycle of malnutrition. Available from: http://nation.ittefaq.com/artman/publisher/printer 21403.html.

42. Islam MN. Changing clinical presentation of severe protein energy malnutrition (SAM) in infants (University of Dhaka). MD Thesis; 2001; 69-73.