Main Electrolytes Derangement in Re-feeding Syndrome in Malnourished Children Admitted to Nutritional Rehabilitation Center (NRC) in Basra

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Abstract: Background: Re-feeding syndrome is potentially lethal condition. It can be associated with significant mortality and morbidity. Fluid-balance abnormalities, abnormal glucose metabolism, hypophosphatemia, hypokalemia, hypomagnesemia and thiamin deficiency occur in the first 3-4 days of initiating nutritional support. (1) **Methods:** This is a prospective study; carried out to evaluate malnourished children underwent re-feeding with serious complications of fluid and electrolytes derangement assessed clinically and by laboratory investigations. The study was conducted on 71 infants and children aged 2-36 months (34 males and 37 females) attending Nutritional Rehabilitation Center in Basra General Hospital from (1st of February till the end of August) 2010.Measurement of weight and length by standard procedures was done and applied to appropriate charts for all patients recruited in the study. Serum electrolytes (phosphorus, potassium, and magnesium) and glucose were determined on first and fourth day of admission. **Results:** All studied children were underweight; 65(91.5%) werewasted. Young infants aged 2-6 months were significantly underweight and wasted (56.3%, 55.5%) respectively. Forty six (64.7%) of malnourished children were admitted with acute gastroenteritis and only 2(2.8%) with compliant of poor weight gain. Forty two(59%) of malnourished patients were considered as high risk group to develop re-feeding syndrome with decreased oral intake for 5-10 days being the most common risk factors in 38(90.4%) of patients. Only 12(16.9%) of patients developed clinical signs of re-feeding syndrome with abdominal distention being the most common sign. Serum Phosphorus and Potassium were significantly decreased with re-feeding in frequency of 31(43%), 28(39.4%) respectively. Hypophosphatemia was statistically significant in young infants 2-6 months (55%) followed by toddlers less than 18 months of age(54.6%),male patients(58.9%), those with acute gastroenteritis (60.9%) and with prolonged duration of hospitalization more than seven days (76.5%). Reduction in serum potassium was statistically significant in male patiens and those with acute gastroenteritis (55.9%, 54.4%) respectively. **Conclusion:** Severe wasting, underweight and high risk group were significantly associated with decreased serum Phosphorus with re-feeding on day four. While significant reduction of serum potassium was associated with severe wasting and high risk group. Serum glucose and magnesium level had no significant association to child related variables. There was a significant correlation of hypophosphatemia with age and initial diagnosis. While hypokalemia significantly associated with age, initial diagnosis and duration of hospitalization.

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1. Introduction

Malnutrition is the gravest single threat to the world's public health. Approximately 27% of children under five years in developing countries are malnourished and in developing countries malnutrition claims about half of the death each year of children under five years. (2, 3)

Re-introduction of feeding after a prolonged period of fasting or starvation can result in a serious complication which is called Re-feeding syndrome. This potentially lethal condition can be defined as severe fluid and electrolytes shift associated with metabolic abnormalities in malnourished patient undergoing re-feeding whether orally enterally or parenterally (4).The biochemical hallmark of this syndrome is hypophosphataemia in addition to other electrolytes disturbance like potassium and magnesium with or without derangement in serum glucose. The incidence of re-feeding syndrome is unknown largely because no accepted definition exists. (1)

Risk factors for re-feeding syndrome

Children with prolonged under nutrition over weeks and months, prolonged periods of "nil by mouth" as in hospitalized patients, mal-absorption such as inflammatory bowel disease and coeliac disease, oncology patients undergoing chemotherapy and radiotherapy, Anorexia nervosa, chronic diarrhea and vomiting' increase metabolic demands such as malignancy and recent major surgery, chronic diuretics users and laxative misuse.(5-8)

Criteria for determining patients at high risk of developing re-feeding syndrome; Patient has two or more of the following: BMI less than 16 kg/m^2,

unintentional weight loss greater than 10%-15% within the last 3-6 months, little or no nutritional intake for more than 5-10 days, Low levels of electrolytes (potassium, phosphate, or magnesium) prior to feeding, history of drugs abuse like insulin, chemotherapy, antacid diuretics and laxatives. [4, 8]

So the most important aspect of treatment of this syndrome is to correct electrolytes disturbances, monitoring of vital signs and prevent further complications. [4, 9]

2.Patients and Methods

This is a prospective study; was carried out to evaluate malnourished children who underwent re-feeding in the Nutritional Rehabilitation Center (NRC) in Basra General Hospital. Ninety nine children with moderate-severe malnutrition were studied over seven months duration (from the first of February till the end of August 2010) their ages ranged from 2-36 months. Exclusion criteria; Patients discharged on their family responsibility (26 cases) and dead patients (2 cases) early on admission before day four and children with systemic diseases as congenital heart disease, CNS disease and renal diseases.

Data collection**:** Information was obtained from mothers through a direct interview using simple and clear language. A standard questionnaire was filled for each child as: name, age, sex, residency and date of admission and discharge. Initial diagnosis was recorded as (acute gastroenteritis, pneumonia, chronic diarrhea, fever and poor weight gain).Patients were classified as high risk groups when two or more of the following risk factors present:1.poor or little intake prior to the admission. 2. loss 10-15% of the body weight in the previous 3-6 months that was recorded from follow-up cards of primary health center or from the hospital if the patient was previously admitted to the hospital.3.Electrolytesdisturbances prior to re-feeding (hypokalemia, hypophosphatemia and hypomagnesemia).[4, 8]

All children assessed clinically for signs of re-feeding like tachycardia dyspnea, tachypnea, edema, and abdominal distention. As well as child anthropometric data was assessed and applied to appropriate charts. Two blood samples were aspirated on first day of admission before feeding and on fourth day after re-feeding of therapeutic milk.

The following biochemical data were measured: serum phosphorus, potassium, magnesium and serum glucose. Other investigations like serum protein, cholestrol, blood urea, S.GOT and S.GPT were not done due to difficulties in obtaining blood sample in critically ill patients**.**

Data were collected using SPSS software, (version 16). Comparison was performed using chi square, *P* value of less than 0.05 was considered as statistically significant, *P* value <0.01 as high significant and <0.001 as extremely significant.

This study was carried out to assess the frequency of re-feeding syndrome in malnourished children managed in NRC and the electrolytes derangement correlation to the child related variables as age, sex, initial diagnosis, duration of hospitalization and nutritional status.

3.Results

Nutritional status in relation to child related variables.

Seventy one malnourished children were included in the study. Thirty four (47.8%) were males and 37(52.2%) were females; their ages ranged from 2-36 months (mean10.6±2.3); 54(76%) of them were ≤ 12 months. Fifty nine (83%) of studied children were from Basra city center. Infants 2-6 months of age were more frequently underweight and wasted (56.3%, 55.3%) respectively. There was decreased frequency of underweight and wasting with increasing age, statistically significant result (*p* value < 0.05). Table (1)

Table (2) demonstrates that; only 2 (2.8%) of patients were admitted to NRC for complaint of poor weight gain, while those with acute gastroenteritis constitute 46(64.7%), other diseases; were pneumonia 11(15.4%), chronic diarrhea 8(11.2%) and fever 4(5.6%).Fifty four (76%) of admitted patients stay in hospital for 1-7 days and less frequency for longer duration.

Patients and risk factors for re-feeding syndrome.

Forty two (59.1%) of malnourished children were classified as high risk patients due to having two or more risk factors for re-feeding syndrome.The most common risk factor was decreased or little oral intake for (5-10) days (90.4%), loss of body weight during the previous 3 months (71.4%) and electrolytes disturbance prior to re-feeding (33.3%). As shown in Table(3). Hypokalemia was the most common electrolytes disturbance prior to re-feeding in 6(8.5%) of patients followed by hypophosphatemia and hypomagnesemia 5(7%), 3(4.2%) respectively. Acute GE was the most common presenting illness.

Biochemical monitoring and clinical signs related to re-feeding.

Twelve (16.9%) of the studied children developed clinical signs during re-feeding. The most frequent sign was abdominal distention (7%) followed by dyspnea and tachypnea (4.2%), tachycardia (2.8%) and oedema of the hands and feet (2.8%).Monitoring of serum electrolytes with re-feeding revealed that 34 (47.8%) of malnourished children show electrolytes disturbances and hypophosphatemia being the most frequent constitute (43.6%). While hypokalemia and hypomagnesemia account for (39.4%) and (26.7%) respectively. Ten (14%) of malnourished children

develop either hypoglycemia or hyperglycemia with re-feeding. Table (4).

Electrolytes monitoring in studied children.

Table (5)shows there is a significant reduction in serum electrolytes(Ph, K) in malnourished children who underwent re-feeding in fourth day with non significant reduction in serum glucose and magnesium.

Electrolytes disturbance among malnourished children with and without re-feeding syndrome.

There is a significant reduction of serum electrolytes(Ph, K) in malnourished children with re-feeding syndrome. While there is no significant difference in serum glucose and magnesium in malnourished children with and without re-feeding syndrome. As shown in Table (6)

Relation of serum phosphorus to the child related variables.

Table (7) shows that there is a statistically significant reduction of serum Ph in 31(46.3%) patients; more common in infants 2-6 months of age (55%) followed by toddlers less than 18 months old age (54.6%), male sex 20 (58.9%) and those with acute gastroenteritis 28(60.9%). As well as hypophosphatemia is more common in children with prolonged duration of hospitalization more than seven days 13(76.5%), severe underweight 23 (53.5%), severe wasting 23(57.5%) and is more in high risk group 23(54.8%), *p* value<0.05.

Relation of serum potassium level to the child related variables.

There a statistically significant reduction of serum potassium in 28 (36.4%) of patients, more in male sex 19(55.9%) and those with acute gastroenteritis 25(54.4%). Value<0.05. Hypokalemia was more pronounced in severely wasted patients 23(57.5%) and in high risk patients 21(50%), *p* value<0.05. Table (8)

Relation of serum magnesium level to the child related variables.

Serum magnesium was normal in 52 (73.3%) of malnourished children with re-feeding only decreased in 19(26.7%) of the patients. It was statistically not significant to any of the child related variables. Table (9)

Relation of serum glucose to the child related variables.

Table (10) shows serum glucose was normal in 61 (85.9%) of malnourished children with re-feeding only decreased in 3(4.2%) and increase in 7(9.8%). It was statistically not significant.

Correlation analysis of electrolytes status and selected variables.

The correlation of selected variables with frequency of hypophosphatemia, hypokalemia, Hypomagnesemia during re-feeding using logistic regression analysis has revealed that there was a significant correlation of hypophosphatemia with initial diagnosis and age. *P* value< 0.05.

As well as there was a significant correlation of hypokalemia with initial diagnosis, age and duration of hospitalization. *P* value <0.05.

While Hypomagnesemia and hypo or hyperglycemia show no significant result. Table (11).

Re-feeding electrolytes disturbances hypokalemia and hypophosphatemiatend to occur in young age group with acute GE. In addition hypokalemia tend to occur in malnourished patients with short duration of hospitalization.

Table (1) Nutritional status in relation to child age, sex and residency.

Variables	Underweight No. (%)	Wasting No. (%)	*P* value
Age (months)			<0.05
2-6	40 (56.3)	36 (55.4)	
-12	14 (19.7)	13 (20)	
-18	11 (15.5)	10 (15.4)	
>18-36	6 (8.5)	6 (9.2)	
Sex			>0.05
male	34 (47.8)	31 (47.6)	
Variables	Underweight No. (%)	Wasting No. (%)	P value
Age (months)			<0.05
2-6	40 (56.3)	36 (55.4)	
-12	14 (19.7)	13 (20)	
-18	11 (15.5)	10 (15.4)	
>18-36	6 (8.5)	6 (9.2)	
Sex			>0.05
male	34 (47.8)	31 (47.6)	
female	37 (52.2)	34 (52.4)	

Table (2) Distribution of patients in relation to initial diagnosis and Duration of hospitalization

Variables	No. (%)
Initial diagnosis	
Acute gastroenteritis	46 (64.7)
Pneumonia	11 (15.4)
Chronic diarrhea	8 (11.3)
Fever	4 (5.7)
Poor weight gain	2 (2.8)
Duration of hospitalization (days)	
1-7	54 (76)
>7	17 (24)
Total	71 (100)

Table (3) Classification of patients into high and low risk groups.

Risk factors	High risk patients (42) No. (%)	Low risk patients (29) No. (%)
Decrease or little oral intake for 5-10 days.	38 (90.4%)	5 (17.2%)
Loss of 10-15% of body weight during the previous 3 months.	30 (71.4%)	4 (13.7%)
Electrolytes disturbance prior to re-feeding(on first day)	14 (33.3%)	0 (0%)

Table (4) Biochemical data and clinical signs related to re-feeding.

Variables	No.(%)
Electrolytes disturbance	34(47.8%)
Hypophosphatemia	31(43.6%)
Hypokalemia	28(39.4%)
Hypomagnesemia	19(26.7%)
Hypo or hyperglycemia	10(14%)

Table (5) Electrolytes monitoring in first and fourth day of hospitalization.

Variables	Day 1 Mean (±SD)	Day 4 Mean (±SD)	*P* value
S.Phosphorus	1.3 0.2	0.9 0.25	<0.01
S.Potassium	3.2 0.4	2.6 0.7	<0.01
S.Magnesium	0.95 0.3	0.7 0.2	>0.05
S.glucose	4.5 1.6	4.2 1.8	>0.05

Table (6) Electrolytes disturbance among malnourished children with and without re-feeding syndrome

Variables	Malnourished patients with re-feeding syndrome Mean (±SD)	Malnourished patients with no re-feeding syndrome Mean (±SD)	*P* value
S.Phosphorus	0.7 0.26	1.6 0.4	<0.05
S.Potassium	2.5 0.8	3.7 0.64	<0.05
S.Magnesium	0.75 0.3	0.92 0.2	>0.05
S.glucose	3.8 0.64	3.6 0.42	>0.05

Table (7) Relation of serum phosphorus level to the child related variables.

Variables	Serum phosphorus day four		Total
	NormalNo. (%)	DecreasedNo. (%)	
*Age (months)			
2-6	18(45)	22(55)	40
-12	12(85.7)	2(14.3)	14
-18	5(45.4)	6(54.6)	11
>18-36	5(83.3)	1(16.7)	6
*Sex			
Male	14(41.1)	20(58.9)	34
Female	26(70.2)	11(29.8)	37
*Initial diagnosis			
Acute GE	18(39.1)	28(60.9)	46
pneumonia	10(90.9)	1(9.1)	11
Chronic diarrhea	7(87.5)	1(12.5)	8
fever	3(75)	1(25)	4
Poor weight gain.	2(100)	0(0%)	2
*Duration of hospitalization (days)			
1-7 days	36(66.6)	18(33.4)	54
> 7 days	4(23.5)	13(76.5)	17
*Underweight			
Moderate	20(71.4)	8(28.6)	28
Severe	20(46.5)	23(53.5)	43
*Wasting			
Moderate	19(76)	6(24)	25
Severe	17(42.5)	23(57.5)	40
*Risk factors			
High risk	19(45.2)	23(54.8)	42
Low risk	21(72.4)	8(27.6)	29
Total	40	31	71

*p value<0.05

Table (8) Relation of serum potassium level to the child related variables.

Variables	Serum potassium day four		Total
	Normal No. (%)	DecreasedNo. (%)	
Age (months)			
2-6	20(50)	20(50)	40
-12	12(85.7)	2(14.3)	14
-18	6(54.5)	5(45.5)	11
>18-36	5(83.3)	1(16.7)	6
*Sex			
Male	15(44.1)	19(55.9)	34
Female	28(75.6)	9(24.4)	37
*Initial diagnosis			
Acute GE	21(45.6)	25(54.4)	46
pneumonia	10(90.9)	1(9.1)	11
Chronic diarrhea	7(87.5)	1(12.5)	8
fever	3(75)	1(25)	4
Poor weight gain.	2(100)	0(0%)	2
Duration of hospitalization (days)			
1-7	34(62.9)	20(37.1)	54
> 7	9(52.9)	8(47.1)	17
Underweight			
Moderate	21(75)	7(25)	28
Severe	22(51.1)	21(48.9)	43
*Wasting			
moderate	19(76)	6(24)	25
Severe	17(42.5)	23(57.5)	40
*Risk factors			
High risk	21(50)	21(50)	42
Low risk	22(75.8)	7(24.2)	29
Total	43	28	71

P value<0.05

Table (9) Relation of serum magnesium level in relation to the child related variables.

Variables	Serum magnesium day four		Total
	NormalNo. (%)	DecreasedNo. (%)	
Age (months)			
2-6	27(67.5)	13(32.5)	40
-12	13(92.8)	1(7.2)	14
-18	7(63.6)	4(36.4)	11
>18-36	5(83.3)	1(16.7)	6
Sex			
Male	21(61.7)	13(38.3)	34
Female	31(83.7)	6(16.3)	37
Initial diagnosis			
Acute GE	29(63)	17(37)	46
pneumonia	10(90.9)	1(9.1)	11
Chronic diarrhea	8(100)	0(0%)	8
fever	3(75)	1(25)	4
Poor weight gain	2(100)	0(0%)	2
Duration of hospitalization (days)			
1-7	43(79.6)	11(20.4)	54
> 7	9(60)	6(40)	15
Underweight			
Moderate	24(85.7)	4(14.3)	28
Severe	28(65.1)	15(34.9)	43
Wasting			
Moderate	19(76)	6(24)	25
Severe	23(57.5)	17(42.5)	40
Risk factor			
High risk	27(64.2)	15(35.8)	42
Low risk	15(78.9)	4(21.1)	19
Total	52	19	71

P value>0.05

Table(10) Logistic regression of different variables with electrolytes derangement due to re-feeding.

Hypophosphatemia			
Variables	*B	*SE	*P*-value
Initial diagnosis	0.536	0.297	<0.05
Age	−0.575	0.310	<0.05
Hypokalemia			
Initial diagnosis	0.514	0.284	<0.05
Age	−0.543	0.298	<0.05
Duration of hospitalization	−1.524	0.666	<0.05

SE* Standard Error B* Regression coefficient

Discussion

All studied children were malnourished managed in NRC as a strategy for combating childhood malnutrition. Their nutritional status was ranging from moderate to severe malnutrition.

Previous WHO survey in Iraq in 2003 showed that malnutrition affects a significant proportion of children (9.2% of children aged less than two years were > -2SD of weight for length). [10]

In Basra; it was found that (20.6%) of children were moderately and severely wasted in a study carried out by Saleem [11]. Forty percent of the children admitted to NRC were moderately malnourished because the admission criteria were adjusted according to ward capacity. About 76% of admitted children were below 12 months of age; this is in agreement with other survey carried out in India by Uttar *et al.,* and Saxena *et al.,* respectively. [12, 13]

Higher frequency of malnutrition was from Basra city center possibly because of availability of other Nutritional Rehabilitation Centers in Basra districts; or difficulty of referral to the city center.

Residency was not significantly associated with malnutrition; this is in agreement with other study conducted by Banerjee *et al.,*[14], but in contrast to finding of Joyce et al and smith et al whom reported that children from rural areas were more undernourished than those from urban areas. This is due to better nutritional status of urban children is probably due to cumulative effect of more favorable socioeconomic conditions especially maternal and prenatal health, birth care, quality of complementary feeding and immunization of children.[15,16]

Initial diagnosis was studied; only (2.8%) of patients admitted with complaint of poor weight gain because parents didn't regard underweight as serious problem.

Acute diarrheal diseases were more prevalent in children admitted to NRC; this is probably due to starvation diarrhea, decreased activity of intestinal brush border and decreased pancreatic enzymes secretion. Followed by respiratory tract infections same findings were found by Esi*et al.,* in Ghana. [17]

Management of malnutrition according to WHO is about six weeks. In the present study; higher frequency of children admitted for less than 7 days, only one out of four stayed for ≥ one week. This is probably explained by; large family's size where the mother is the only caregiver and the father is daily-wage worker and they are unable to stay for long duration. This is in agreement with a study carried out in India by Mamidi *et al.,*[18]

This study shows that high risk group patients with poor oral intake in previous 5-10 days before re-feeding was the most common risk factor for developing re-feeding electrolytes disturbances (hypophosphatemia and hypokalemia). This in agreement with a study was done in critically ill patients in an intensive care unit in USA by Paul et al, showed that about 1/3 of patients developed re-feeding hypophosphatemia, with the poor nutritional intake is the most risk factor.[19]

Also there is an observational study

performed in ICU in France by Vignuad *et al. that* demonstrated about 1/4 of studied patients with anorexia nervosa developed electrolytes disturbances of re-feeding with severe malnutrition being the most important risk factors. [20] In addition there was another prospective study which was performed in Australia by Whitelaw et al. demonstrated that more than 1/3of malnourished anorexic patients developed re-feeding hypophosphatemia. [21]

Other risk factor for patients who developed re-feeding syndrome is loss of the body weight in 3-6 months before re-feeding, this in agreement with a study performed in USA by Sheean *et al.,*[22].

In this study abdominal distension was the most common clinical sign of re-feeding syndrome; this is due to muscles weakness and gastric dysmotility caused by electrolytes disturbances (hypophosphatemia and hypokalemia). Same result was concluded from a study performed in USA by Kellogg *et al.,*[23] In contrast to a study conducted in Mexico by Gonzalez *et al.,* revealed that neuromuscular complication, respiratory muscles weakness with dyspnea and tachypnea are the most common clinical sign.[24]

The present study reported a high frequency of re-feeding electrolytes disturbances in infants and toddlers < 18 months old age, this is due to the extracellular fluid level is more in this age group than in older children so they are affected more by fluid and electrolytes derangement. This in agreement with a study done in USA by Kellogg *et al.,* whom demonstrated that re-feeding electrolytes disturbances and clinical signs occur in infants more than older children.[23]

The current study has revealed that hypophosphatemia being the most common electrolytes disturbance followed by hypokalemia. This in agreement with many studies; were performed in USA, Mexico, and Taiwan demonstrated that all malnourished patients developed hypophosphatemia and most of them developed hypokalemia,[19, 23-25]. Another study done in Mexico by Hernandez et al revealed that the incidence of re-feeding electrolytes disturbances with hypomagnesemia more than hypophosphatemia and hypokalemia. [26]

This study has confirmed that the re-feeding hypophosphatemia and clinical signs of this syndrome tend to be manifested in severe under nutrition and wasting, while hypokalemia tend to occur in severe wasting only. This in agreement with a study which was performed in Ohio USA by Adam et al. who concluded that all patients developed re-feeding hypophosphatemia were severely malnourished.[27]

Another prospective study was performed in China by Fan *et al.,* which demonstrated that patients admitted to hospital with severe malnutrition developed hypophosphatemic re-feeding syndrome.[28] Re-feeding syndrome may be manifested in the first 3-7 days of initiating feeding this is probably the time need to switch from using up body stores to using food [9]. Current study has conclude that re-feeding syndrome electrolytes disturbances tend to occur in first four days of re-feeding; this in agreement to many studies carried out in China and India [28,29].

There was another clinical study performed in Kuwait by Al Sharkawy*et al.,* in 13 months old male toddler with history of severe malnutrition develops lethal electrolytes disturbance (hypokalemia, hypophosphatemia and hypomagnesemia) on 3rd day of starting nutritional rehabilitation. [30] Another study was performed in Mexico by Hernandez *et al.,* showed that all patients with mild to severe malnutrition received nutritional support; 48% of them develop electrolytes disturbances and tend to occur in severe malnutrition and >1/2 of them occur during third day of initiating feeding. **[26]**

A study was carried out in Mexico by Gonzalez *et al.,* Showed that the incidence of the re-feeding syndrome was 24.5%; it was more frequent in the enteral group and it took place 72 hours after starting the nutritional support[24].

The present study revealed that re-feeding hypophosphatemia associated with prolonged duration of hospitalization, this is due to many complications that developed as a result of electrolytes disturbance, this in agreement with a study performed in USA by Kellogg *et al.,*[23]

It is found that re-feeding glucose disturbance occurred in only (14%) of studied children with hyperglycemia being more common, this is probably due to daily monitoring of serum glucose from 1st day of start feeding and change the amount of feeding accordingly. This in agreement with other studies done by Hernandez *et al.,* and Gonzalez *et al.,*[26, 24].in contrast to study carried out by Kellogg et al who showed that glucose disturbance occur in about half of studied children with hyperglycemia being more common.[23]

Our recommendations are; doctors and other health care providers should be aware of patients at risk of re-feeding complications. As well as clinical status must be monitored carefully during re-feeding especially vital signs (heart rate and respiratory rate) as well as Monitoring serum phosphate, potassium, magnesium and glucose before and during re-feeding.

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