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The use of Antibiotics for the Management of Severe Acute Malnutrition: A Review

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Abstract

Severe acute malnutrition contributes to the mortality of about a fifth of children who die before the age of five and those that are not killed by malnutrition are more likely to be affected by infectious diseases, which may impair their physical and cognitive development. Malnutrition predisposes the previous sufferer with poor overall health that can be life-long. Diseases such as Malaria, diarrhea, respiratory tract infections, HIV/AIDS and intestinal parasites related diseases are all observed to be attributed to malnutrition. The use of antibiotics for therapeutic management of severe acute malnutrition significantly reduced the mortality rates especially in complicated severe acute malnutrition. However, undernourished children with uncomplicated severe acute malnutrition should not be given antibiotics unless they show signs of clinical infection.

Key words: Antibiotics, Children, Malnutrition, Infection, parasite and Mortality.

Introduction

Malnutrition is typically the result of an inadequate diet and is one of the most common diagnosis among children in health facilities within sub-Saharan Africa and south Asia; it leads to greater risk of death or disability from common pediatric illnesses such as pneumonia and diarrhea diseases, and it poses long term health problems by compromising physical and intellectual development (Victoria *et al.*, 2008). More than 20 million children around the world suffer from severe acute malnutrition, which contributes to 1 million preventable deaths every year {Food and Nutrition Technical Assistance Project III (FANTA), 2014}. Acute childhood malnutrition affects about a tenth of the world's children under 5 years of age, particularly those living in circumstances of extreme poverty in the developing world (Ciliberto *et al.*, 2005). Nearly

6,500 children were found to be severely malnourished in 2015 at camps set up for people made homeless by Boko Haram insurgents as reported by health officials in northeast Nigeria {Agence France Presse (AFP), 2016}. Many studies have shown a high prevalence of clinically significant infections among children hospitalized for severe malnutrition (WHO, 2007). Diseases such as Malaria, diarrhea, respiratory tract infections, HIV/AIDS and intestinal parasites related diseases are all observed to be attributed to malnutrition (Andrew and Fiona, 1989). This observation has led to treatment guidelines recommending the use of routine antibiotic agents even for children treated as outpatients (WHO, 2007), although outpatients are presumably much less likely to have a systemic infection than are patients with complicated cases that require in patient care. Most children with severe acute malnutrition can now be treated in rural health posts throughout the developing world (Collins *et al.*, 2006). To provide scientific evidence on the most effective treatment for severe acute malnutrition, specifically the use of antibiotics in treatment, help to improve recovery from severe acute malnutrition and reduce mortality (FANTA, 2014).

Malnutrition

Malnutrition makes a major contribution to the global disease burden, accounting for more than one-third of child deaths worldwide. Malnutrition can be classified as mild, moderate or severe based on anthropometry (measurement of the size, weight and proportions of the human body), biochemistry and clinical assessment (Picot *et al.*, 2012).

Malnutrition is a dietary condition resulting from inadequate or excess of one or more of the essential nutrients in a diet, or the inability to absorb and metabolize nutrients due to disease condition. It is a

condition which occurs when there is deficiency of certain vital nutrients in a person diet (Young, 2012). The nutrients involved include: calorie, protein, carbohydrates, vitamins or minerals (UNICEF, 2010). It is a category of diseases that includes under-nutrition and over-nutrition (WHO, 2012). The term hunger, which describes feeling of discomfort from not eating, has been used to describe under nutrition, especially in reference to food insecurity (Black *et al.*, 2008).

Types of Malnutrition

There are two major types of malnutrition which are the primary malnutrition and secondary malnutrition.

Primary Malnutrition

Is one in which the body lacks the essential nutrients necessary to maintain good health; primary malnutrition occurs in most part of the world where in most of the population is undernourished because of famine poverty and limited crop production (McGuire and Beerman, 2007).

Secondary Malnutrition

Is one which occurs as a result of disease condition, here the nutrients are available but because of the health condition or infection, the body cannot absorbed or utilizes the available nutrients. Secondary malnutrition has been observed among medical and surgical patients who are treated in hospital for prolonged period of time (McGuire and Beerman, 2007).

Other Forms of Malnutrition

Protein – Calorie Malnutrition or Protein Energy Malnutrition

The term severe malnutrition is often used to refer specifically to protein energy malnutrition (PEM) (Christopher *et al.*, 2008). The combined effect of malnutrition and infection in young children is referred to as protein – calorie malnutrition. The protein energy malnutrition has two severe forms known as Marasmus and Kwashiorkor (Young, 2012). Kwashiorkor which is a lack of proteins only

(Young, 2012); also known as displaced child is mainly caused by inadequate protein intake results in low concentration of amino acids (Nikolaos, 2011). Marasmus as a lack of protein and calorie (Young, 2012); can result from sustained diet of inadequate energy and protein which traditionally is seen in famine, significant food restriction, or more severe cases of anorexia (Nikolaos, 2011). Both Conditions are characterized by extreme wasting of the muscle and a gaunt expression.

Micronutrient Deficiency

It is a deficiency condition which occurs when the body is deprived of some of the essential nutrients like vitamins and minerals, the absence of which can result to various deficiency disorders like pellagra (Vitamin B₃ deficiency), beriberi (Vitamin B₁ deficiency) and others (Christopher *et al.*, 2008).

The major function of vitamins in the biological system is the role of cofactor in enzymatic transformations. Their absence can deny the nutrients from being metabolized, thereby resulting in secondary malnutrition. For example, pyridoxal phosphate which is the active form of Vit. B₆ acts as coenzyme in the transfer of alpha amino groups to alpha-keto groups.

Causes of Malnutrition

Major causes of malnutrition include poverty and food prices, dietary practices and agricultural productivity, with many individual cases being mixture of several factors like alcoholisms, drug addiction, depression and digestive disorders. Practical condition of a country is another cause, but various scales of analysis have to be considered in order to determine the sociopolitical cause of malnutrition. For example, the population of a community may be at risk if it lacks health related services, but on a smaller scale certain households or individuals may be at even higher risk due to differences in income levels, access to land or levels of education (Fotso and Kuate-defo, 2005).

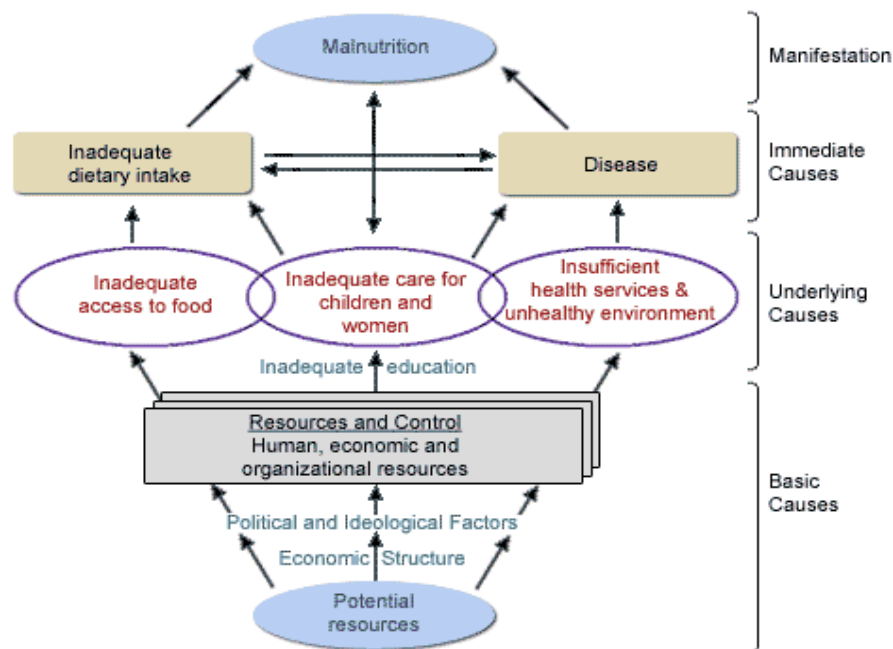


Figure 1. UNICEF Conceptual Framework on the causes of Malnutrition

Poverty and Food Price

Poverty and the cost of food has always been a major contributing factor to malnutrition. Where family survives at a very low income, they may be able to obtain the entire necessary and healthy nutrient required for growth and maintenance of sound health. Although, food and agricultural organization (FAO) has estimated that 80% of malnourished children are living in developing countries that produced food (Gardner and Halweil, 2000). However, Sen (1981), states that malnutrition and famine were more related to problems of food distributions and purchasing power. The use of biofuels as a replacement for traditional fuels may leave less supply of food for nutrient and also raises the price of food.

Dietary Practices

A lack of breast feeding can lead to malnutrition in infants and children which may contribute to a number of infectious diseases such as; gastroenteritis, pneumonia, malaria and measles which increase nutrient requirements (Brady, 2012). Mothers abandon breast feeding because they do not know how to get their baby to hatch on properly or suffer pain and discomfort in the process. Deriving diet from a single source, such as eating almost exclusively on corn or rice can cause malnutrition. This may be from a lack of education about proper nutrition, or from only having access to a single food source (Burchi *et al.*, 2011).

Malnutrition does not only mean hunger, therefore, overfeeding or excess nutrient is also a contributing factor as well (Gardner and Halweil, 2000). Many parts of the world have access to a surplus of non-nutritional food, in addition to increased sedentary lifestyles. In turn, this has created a universal epidemic of obesity. Yale psychologist Kelly Grownndt calls this a “toxic food environment” where fat and sugar laden foods have taken precedent over healthy nutritious foods (Gardner and Halweil, 2000).

Agricultural Productivity

Food shortages can be caused by lack of farming skills such as crop rotation, or by a lack of technology or resources needed for higher yields found in modern agriculture such as nitrogen fertilizers, pesticides and irrigation. As a result of widespread poverty, farmers cannot afford fertilizers at market prices, leading to low agricultural production. Agricultural yield can be reduced in an area that suffers draught, desert lands, rugged to topography thereby contributing to undernutrition (Dugger, 2007).

Effects of Malnutrition

Malnutrition increases the risk of infectious disease, and moderate malnutrition weakens every part of the immune system. For example, it is a major risk factor in the onset of active tuberculosis (Schaible *et al.*, 2007). Protein and energy malnutrition and

deficiencies of specific micronutrients (e.g. iron, zinc and vitamins) increase susceptibility to infection (Stillwaggon, 2008).

Malnutrition affects HIV transmission by increasing the risk of transmission from mother to child and also increasing replication of virus. According to the World Health Organization, malnutrition is the biggest contributor to child mortality, present in half of all cases by which six million children die of hunger every year. Underweight births and poor or non-existent breastfeeding causes an increase in mortality. Also it exacerbates the problems of diseases, causes disease and can be fatal on its own.

Infection and Malnutrition

The general interactions of nutrition and infection have been recognized for many years as individuals becomes susceptible to developing infections due to

malnutrition which may become particularly extensive and serious. Conversely, it has been widely accepted that certain infections have profound influence on nutritional status, mediated by changes in dietary intake, absorption, nutritional requirements (especially for energy and protein) and loss of endogenous nutrients (Andrew and Fiona, 1989). The types of bacteria most commonly found in surveillance studies of bacteremia among malnourished children corroborates the notion that the significant invasive bacterial infections among these children are due to translocation across compromised mucosal surfaces (both respiratory and intestinal) that are known to be diminished among these patients. It is not surprising that HIV infection severely hampers a child's ability to recover from SAM (Manary *et al.*, 2012).

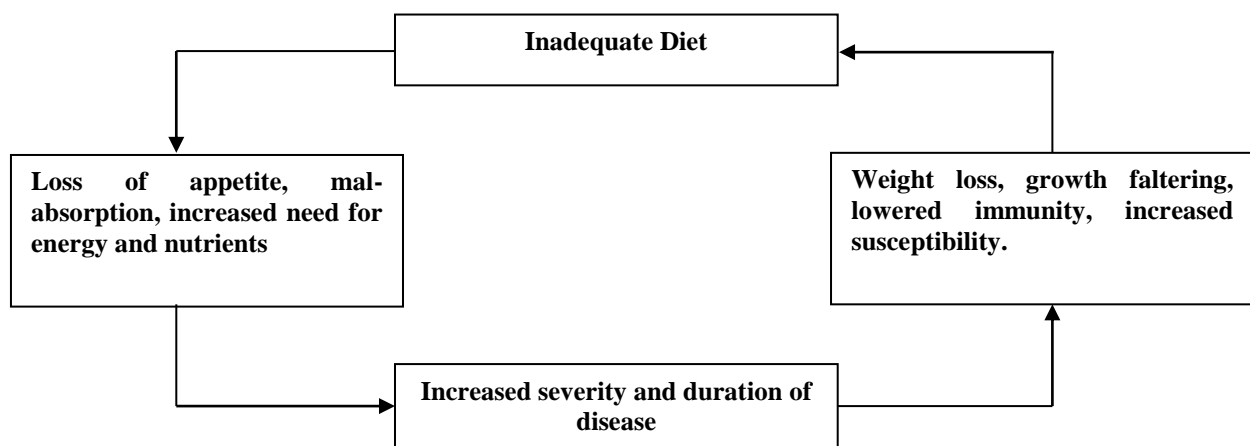


Figure 2. Infection - Malnutrition Cycle (Andrew and Fiona, 1989).

Acute Malnutrition

In acute malnutrition, the amount of one or more macronutrients available to body tissues is inadequate to sustain optimal function. Macronutrient deficiency may result from inadequate diet, poor absorption of ingested nutrients, or the presence of a chronic inflammatory condition that increases requirements for nutrients while promoting a nutrient wasting and catabolic state (Mark and Heidi, 2008). Acute malnutrition occurs as a result of sudden reductions in food intake or diet quality and combined with pathological causes. Acute malnutrition occurs when the body doesn't receive the nutritional support it requires, a condition to which it adapts by reducing physical activity and slowing the process involved in proper organ function, cell and tissue maintenance. The body begins to consume its own tissue in search of the nutrients and energy it needs to survive, targeting

muscle and body fat first (Yip and Sharp, 1993). Body's metabolism begins to slow, thermal regulation is impaired and immune system capacity diminished. Acute malnutrition often results from immediate problem, a crisis included by illness or deprivation due to seasonal shortages, sudden catastrophe and other such reasons (Yip and Sharp, 1993).

Acute malnutrition has been defined in various ways, and has been referred to by various names including: protein-energy malnutrition, wasting, kwashiorkor and marasmus. Acute malnutrition, or wasting, is defined using anthropometric cut-offs and clinical signs. The currently accepted definitions, set out by the World Health Organization (WHO) are as follows:

Moderate acute malnutrition (MAM), defined as Weight-for-Height Z-score (WHZ) between -2 and -3 or mid-upper arm circumference (MUAC) between

115-125 mm, affects 32.8 million children worldwide, 31.8 million of whom reside in low and middle-income countries (Black *et al.*, 2013).

Global acute malnutrition (GAM) refers to both MAM and SAM together and is used as a measurement of nutritional status at a population level, often as an indicator of the severity of an emergency situation.

Severe acute malnutrition (SAM), defined as WHZ < -3SD or MUAC <115 mm, and/or the presence of bilateral pitting edema which is a significant public health concern as it affects approximately 19 million children across the globe every year (Black *et al.*, 2013). Forms of SAM include kwashiorkor, marasmus and marasmic kwashiorkor with severe wasting as defining feature; approximately 310,000 deaths among children < 5 years of age in Africa, Asia and Latin America were attributed to severe wasting in 2004 (Picot *et al.*, 2012). The contribution of severe acute malnutrition to the overall burden of childhood morbidity and mortality is enormous and the degree of wasting is positively correlated with an increase in the risk of death (Black *et al.*, 2008; 2013). It also contributes to the mortality of about a fifth of children who die before the age of five and those that are not killed by malnutrition are more likely to be debilitated by infectious disease also their physical and cognitive development is often impaired (Hult *et al.*, 2010). Retrospective studies on children malnourished in the 1966-69 Biafra war reveal that even when malnutrition does not persist; it predisposes the previous sufferer with poor overall health that can be life-long (Hult *et al.*, 2010). In Bangladesh, malnourished girls that survive to adulthood frequently continue to be undernourished and bear children at risk of undernutrition (Ahmed *et al.*, 2012).

Antibiotics

Antibiotics are agents that either kills or inhibits the growth of microorganism that were formerly described as substances produced by microorganisms that are antagonist to the growth of other microorganisms in high dilution (Young, 2012). Antibiotics are a group of medicines that are used to treat infections caused by bacteria and are sometimes called antibacterial.

The first antibiotic discovered was called penicillin by Alexander Fleming in 1928. Synthetic antibiotic chemotherapy as science and development of antibacterial began in Germany with Paul Ehrlich in late 1880s (Calderon and Sabundagyo, 2007). There are various antibiotics available and they come in various different brand names. Antibiotics are

usually grouped together based on how they work. Each type of antibiotic only works against certain types of bacteria. Antibiotics are classified based on their mechanism of action, chemical structure for spectrum of activity. Most target bacterial functions or growth processes. Those that target the bacterial cell wall include (penicillin and cephalosporins) or the cell membrane (polymyxins), or interfere with essential bacterial enzymes (Rifampycin, lipiarmycin, quinolones and sulfonamides). Macrolides, lincosamides and tetracycline are those that target protein synthesis (Fingberg *et al.*, 2004). Further categorization is based on their target specificity; narrow spectrum antibacterial target specific types of bacteria such as Gram-negative or Gram-positive bacteria. Whereas broad – spectrum antibiotics affect a wide range of bacteria (Srivastava *et al.*, 2011).

Antibiotics and Severe Acute Malnutrition

The primary management for severe acute malnutrition was based on inpatient rehabilitation with fortified milk formulas for the children with severe wasting, kwashiorkor, and case of fatality rates among hospitalized children that is as high as 50% worldwide (WHO, 1999). However, international consensus guidelines now recommend the use of ready-to-use therapeutic food (RUTF) — usually a fortified spread consisting of peanut paste, milk powder, oil, sugar, and a micronutrient supplement — in outpatient settings as the preferred management for uncomplicated cases of severe acute malnutrition (WHO, 2007). Despite the markedly better outcomes observed with this revised outpatient regimen, progress in treatment has been slow with the most successful intervention being fortified peanut-paste and milk powder-based Ready-to-Use Therapeutic Food (Ciliberto *et al.*, 2005); 10 to 15% of children still do not recover, even in the context of rigorously controlled clinical trials (WHO, 2007). RUTF alone however cannot guarantee cures; therefore treatment to augment this therapy is surely needed (Trehan *et al.* 2013). The recent information about the antibiotic resistance patterns for the most commonly translocating bacteria; β -lactam antibiotics particularly third-generation cephalosporins, such as cefdinir seem to be the optimal choice for severely malnourished children (Manary *et al.*, 2012). It was recently reported that a home-based course of beta-lactam antibiotics reduced mortality and increased recovery of malnourished children in Malawi whereas antibiotics were recommended for hospitalized patients due to severe malnutrition whom almost invariably have symptomatic infections. (Trehan *et al.* 2013).

Antibiotics therefore, should be used more generally in severe malnutrition for outpatients irrespective of concomitant infectious disease because certain bacterial species may exacerbate or even cause Kwashiorkor (Trehan *et al.* 2013). A handful of broad-spectrum antimicrobials, namely tetracycline, the aminopenicillins, chloramphenicol as well as sulphonamides with and without trimethoprim were the mainstay of bacterial infections in Africa in the latter half of the 20th century. These drugs remain effective against susceptible bacteria but justified or questionable therapeutic and preventive use combined with unsanctioned use in the informal health sector has provided the selective pressure for present-day resistant strains that have all but replaced the susceptible. This selection accounts for the situation today in which previously easy-to-treat infections are costly or impossible to treat in many patients (Okeke *et al.*, 2007). All antimicrobial irrespective of how strongly justified selects for resistance, therefore the decision to use an antibiotic in a given condition must be weighed against the cost of resistance to the community. Routine outpatient administration of antibiotics represents significant selective pressure that could result in unforeseen consequences as up to 50% of children are malnourished in some settings (Trehan *et al.*, 2013). Resistance has undermined the outcome of bacillary dysentery and cholera and has become a common feature among bacteria implicated in persistent childhood diarrhea and pneumonia that for many patients operate in a mutually detrimental cycle with malnutrition (Okeke *et al.*, 2007). Newer, more expensive drugs such as the fluoroquinolones and third-generation cephalosporins are not accessible to many poor patients who die or are disabled by treatable infections. These relatively expensive medicines represent the last resort for most African countries which have no alternatives even though resistance to them is already commonplace (Lamikanra *et al.*, 2011). Manary *et al.* (2012) confirmed the clinical sense that children with marasmic kwashiorkor are at particularly high-risk and warrant aggressive care, perhaps including earlier and/or more frequent follow-up. Furthermore, if the availability of antibiotics for malnourished children is limited, one strategy may be to reserve them for children with marasmic kwashiorkor or marasmus, as the relative benefit for children with kwashiorkor alone appears smaller. Alcoba, *et al.* (2013) in their meta analysis provided little evidence to continue with the routine amoxicillin therapy in children with uncomplicated SAM especially in low HIV prevalence populations. Gough *et al.* (2014) also provided an evidence that

antibiotics are not the most viable option for the treatment of malnutrition outside of highly vulnerable populations in which antibiotic treatment is already routinely recommended for treatment and prevention of infections even though their result have shown that antibiotic treatment has a growth promoting effect, particularly for ponderal growth in prepubertal children from undernourished populations in low and middle income countries whereas Linear growth seems less responsive to antibiotics.

Routine use of amoxicillin for 7 days to all the children with uncomplicated SAM is recommended by the WHO in addition to the nutritional rehabilitation but there is no clear rationale for this because there is no available data of high prevalence of bacteremia, urinary infection or other bacterial infections among these children (Mathew, 2016). Furthermore, Isanaka *et al* (2016) discovered no benefit of routine antibiotics use with respect to nutritional recovery from uncomplicated severe acute malnutrition in Niger and recommended eliminating the routine use of antibiotics in protocols for the treatment of uncomplicated severe acute malnutrition especially in regions with adequate infrastructure for surveillance and management of complications.

Management

Practitioners and WHO experts endorse community-based management for uncomplicated SAM while still advising that children who are severely malnourished and have medical complications should be treated in an appropriate health facility (Lenters *et al.*, 2013).

Antibiotics should be given to every severely malnourished patient, even if they do not have clinical signs of systemic infection (EFMH), 2007). Nevertheless, despite the absence of clinical signs, they are nearly all infected, particularly if they require Phase 1 treatment (poor appetite), these infections are treated blindly. Small bowel bacterial overgrowth occurs in all these children. These enteric bacteria frequently are the source of systemic infection by translocation across the bowel wall. They also cause malabsorption of nutrients; failure to eliminate substances excreted in the bile, fatty liver, intestinal damage and can cause chronic diarrhoea. The antibiotic chosen for routine treatment must be active against small bowel bacterial overgrowth. Because the children with kwashiorkor have free iron in their blood, bacteria that are not normally invasive, such as *Staphylococcus epidermidis* and “exotic bacteria”

can cause systemic infection or septicaemia (EFMH, 2007). If staphylococcus is suspected then an antibiotic active against staphylococcus should also be used. The position of antibiotic administration to children who pass their appetite tests and go straight to Phase 2 is less clear. They probably do not have a major systemic infection; however, they usually have small bowel bacterial overgrowth and at least these bacteria should be suppressed for optimal response to treatment. Thus, at the moment these children are usually given antibiotics systematically in a similar fashion to those who require Phase 1 treatment initially (EFMH, 2007).

Oral amoxicillin or ampicillin, addition of chloramphenicol or gentamycin or changing to amoxicillin/clavulanic acid (Augmentin) and Fluconazole (systemic anti-fungal) is added for any patient who has signs of severe sepsis or systemic candidiasis as first line, second line and third line treatment respectively {Ethiopia-Federal ministry of health (EFMH), 2007}. However, it is recommended to follow the WHO guidelines for the management of children with severe acute malnutrition (Zerihun *et al.*, 1991). Wherever possible antibiotics should be given orally or by Nasogastric tube Infusions containing antibiotics should not always be used because of the danger of inducing heart failure (EFMH, 2007).

Conclusion

The addition of antibiotics to therapeutic regimens for severe acute malnutrition is associated with a significant improvement in recovery and reducing mortality rates especially in complicated severe acute malnutrition. Undernourished children of less than 5 years but do not have severe acute malnutrition should not routinely be given antibiotics unless they show clinical signs of infection. However, diagnosis and documentation of infection for appropriate drug selection is highly recommended.

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