Childhood Anemia and Risk for Acute Respiratory Infection, Gastroenteritis, and Urinary Tract Infection: A Systematic Review

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Abstract

Objective Children younger than 5 years, particularly children below 2 years, are among the most vulnerable groups for developing anemia and infections. This review is intended to assess the association between anemia and childhood acute respiratory infections (ARTIs), acute gastroenteritis (AGE), and urinary tract infections (UTIs).

Methods PubMed was searched for published articles from January 2000 to August 2021 in English using the following terms: anemia and acute respiratory tract infections in children; anemia and UTIs in children; anemia and AGE in children. The data extraction were conducted by two investigators using the same methodology. Using descriptive statistics, the data from different sources were synthesized, including medians and ranges.

Results A total of 426 articles and 27 original articles and 1 systematic review were included. Iron deficiency anemia is common among children between 6 months and 3 years of age. This age group can be considered a highly susceptible age for contraction of ARTI and AGE. Children below 5 years suffer five to six episodes of acute ARTI per year on average, and pneumonia accounts for the highest number of deaths, which is around 1.1 million each year. When considered, the odds ratio of anemia to increase the susceptibility of contracting lower ARTI would range from 2 to 5.7. Also, anemic children were 10 times more susceptible to developing acute recurrent ARTI and 4 times more susceptible to contracting pneumonia. Respiratory syncytial virus is the commonest viral etiology. Anemia would increase the risk of diarrhea by 2.9-fold in toddlers, while mild anemia, moderate anemia, and severe anemia would increase the susceptibility to contract AGE by 1.6, 1.6, and 8.9 times, respectively. Rotavirus is the commonest etiology. Some studies observed a protective effect of mild to moderate iron-deficient anemia from respiratory infections.

Conclusion Infectious disease imposes a heavy burden on the health sector in a country. The highest susceptibility for infections and the development of anemia would be due to inadequate nutrition supplementation to meet the demand during rapid body growth. Therefore, based on the available evidence, one can take the necessary steps to reduce the infectious disease burden by correcting the anemia status in children.

Keywords
- anemia
- children
- ARTI
- AGE
- UTI and risk for infections

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Introduction

A person can be considered anemic when the blood hemoglobin concentration is below 2 standard deviations below the mean for age.[1] Blood hemoglobin concentration is affected by different factors such as age, sex, altitude, ethnicity, active and passive smoking, and pregnancy. Therefore, these factors should be taken into the consideration and need to be adjusted before diagnosing anemia in a child.[2]

Ineffective erythropoiesis, hemolysis, and blood loss are the main mechanisms responsible for the development of anemia. The most common contributing factors for anemia are nutritional deficiencies, disease, and genetic hemoglobin disorders. The three most common causes of anemia worldwide are iron deficiency, hemoglobinopathies, and malaria. Around 80% of hemoglobinopathies occur in low- and middle-income countries. Sickle cell disorder is the most common hemoglobinopathy, and it is predominant in sub-Saharan Africa. The next in line is β- and α-thalassemia, predominant in South-East Asia.[3]

The World Health Organization estimates that approximately 2 billion people worldwide are suffering from anemia, of which 50% is due to iron deficiency.[4] It is also assumed that approximately 600 million preschool and school-aged children suffer from anemia worldwide.[5] Around 40 to 50% of children and adult women in the world are considered anemic, and among its numerous types, iron deficiency anemia is assumed to be affecting around 50% of school children and women, and approximately 80% of preschool children from 2 to 5 years old.[4] The prevalence of anemia among children under 5 years in nonindustrialized countries is estimated to be 39%, and in industrialized countries, it is 20%.[2] Anemia accounts for approximately 9% of the global total disability burden, and children under 5 years bear the highest burden of anemia.[3]

Iron deficiency anemia affects children in numerous ways, including growth, development, child mortality, and morbidity. Also, iron deficiency anemia during infancy and childhood can impair immunity, cognitive, and school performance. It is also suggested that anemia increases heavy metal absorption in children.[6]

Iron is an essential component to maintain proper immune function, but the relationship with the disease conditions is complex.[3] Iron plays a vital role in both innate and adaptive immunity. Intracellular iron promotes the release of reactive oxygen species via activation of NF-kB (Nuclear factor kappa B). The iron-dependent transcription factor and hypoxia-inducible factor-1 α promote macrophages for the production of antimicrobial peptides. Administration of iron to iron-deficient patients has been shown to increase tumor necrosis factor α (TNF-α), interleukin 10 (IL-10), and IL-6 mRNA expression in peripheral blood mononuclear cells. Some animal studies have shown that reduced iron levels for various reasons have shown low levels of mature B cells and impaired T-cell development.[7]

In contrast, too much iron in the body is shown to be detrimental to host defense mechanisms. Animal studies have shown low levels of IL-6 and TNF-α against *Salmonella* infections when iron was overloaded. Also, children with high amounts of intracellular iron have been shown to have low levels of circulating TNF-α in the circulation.[6,7]

Iron is an essential element required for the growth of many pathogens. Therefore, the idea that iron deficiency increases the susceptibility of the host to infections has been controversial. Moreover, some studies have shown that iron deficiency increases susceptibility to infections, while some have shown that iron supplementation can increase the risk of tuberculosis and malaria. Therefore, it is clear that there needs to be further studies to decide the optimal iron level needed for the adequate immune response against pathogens.[7] Acute infections are common among children and are associated with high morbidity and mortality. Acute respiratory tract infections (ARTIs), urinary tract infections (UTIs), and gastroenteritis (GE) are common infectious entities in children.[8] Out of the annual burden of 10 million deaths among children under 5 years, a large proportion is associated with infectious diseases. Among the postneonatal deaths due to infections, estimates and uncertainty bounds include 22% of deaths attributed to diarrhea (14–30%), 21% to pneumonia (14–24%), 9% to malaria (6–13%), and 1% to measles (1–9%). There is a high burden of infectious diseases among developing countries. Some of the major social determinants affecting the under-5 years' mortality and morbidity include poverty and malnutrition.[9] ARTI can be identified as a significant cause of death in children under 5 years, and anemia is the commonest cofactor in children seeking medical advice, especially in developing countries.[10]

Past experiments have failed to establish an essential relationship between infectious disease and iron deficiency anemia as a risk factor.[7] However, some studies have successfully shown an existing relationship between anemia and risk of infections and recurrent infections. Under-5 age group, particularly infants and children below 2 years, are among the most vulnerable groups to developing anemia and infections.[3] This review is intended to assess the association between anemia and childhood acute infections.

Materials and Methods

PubMed was searched for published articles from January 2000 to August 2021 in English using the following terms: anemia and acute respiratory tract infections in children; anemia and urinary tract infections in children; anemia and acute gastroenteritis in children. The abstracts and case reports were also included. Database searches were followed by manual searches of bibliographies of selected references. Since the numbers of studies are limited, all articles were included for the review.

Using descriptive statistics, the data from different sources were synthesized, including medians and ranges. The searches and data extraction were conducted by two investigators using the same methodology. In cases of disagreements, results were reconciled through mutual discussion. Using Comprehensive Meta-Analysis (CMA) software odds ratios (OR), standardized mean differences were calculated.

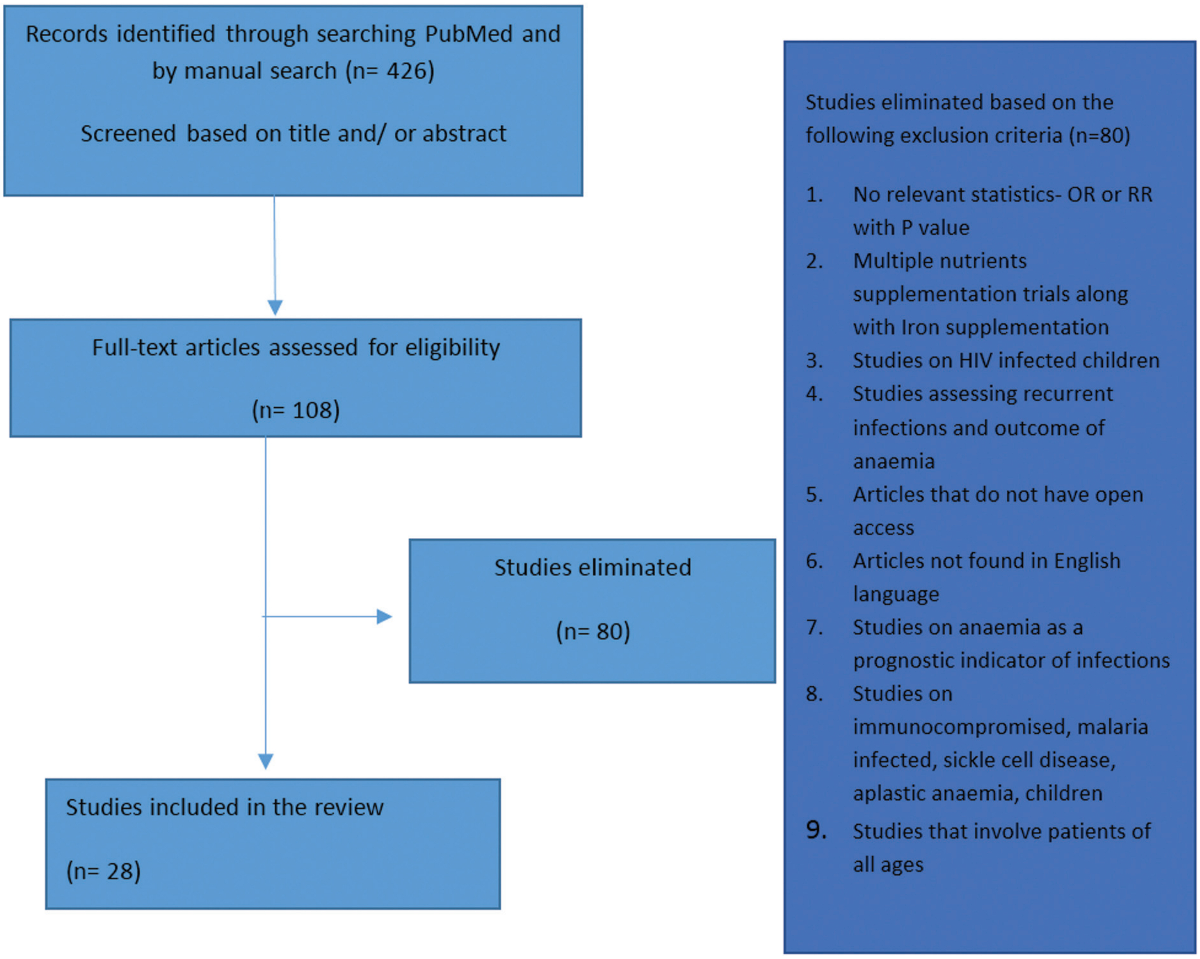

Fig. 1 Summary of the literature review.

Results

PubMed searches and manual searches for studies on childhood anemia and development of ARTI, GE, and UTI found 426 articles screened based on title and abstract. A total of 108 full-text articles were assessed for their eligibility, and 80 articles were excluded based on the exclusion criteria mentioned in the following. Thus, 27 original articles and 1 systematic review were included in the review (►**Fig. 1**).

This review highlights the results and conclusions based on different studies to identify an existing relationship between anemia and the risk of infections.

Anemia and Risk for Development of ARTIs

In Israel, Shmonah et al evaluated the association between childhood iron deficiency anemia and recurrent acute otitis media frequency. They assessed the impact of restoring normal hemoglobin levels on the frequency of episodes of acute otitis media. The study was done among 680 children who get frequent episodes of acute otitis media. The study showed a significant difference between the hemoglobin concentrations of the study group and the control group ($p < 0.01$). Therefore, the study concluded that children with anemia have a higher prevalence of acute otitis media episodes than nonanemic children. It also found a direct relationship between the degree of anemia and the number of acute otitis media episodes. Also, it showed that improving the hemoglobin level significantly decreased the frequency of episodes of acute otitis media in children (►**Table 1**).[11]

Another study was done in the Department of Pediatrics, Amrita Institute of Medical Sciences and Research Centre Kochi, Kerala, India. The study aimed to analyze the association of hemoglobin level with the risk of acute lower respiratory tract infection (LRTI) among children. It was a prospective study, and 100 children aged 9 months to 16 years were included. Age- and sex-matched 100 children without respiratory infections were taken as controls. The study revealed that 74% of the study group and 33% of the control group were anemic. Of the anemic cases, 60% had iron deficiency anemia, 10% had chronic inflammation, and 4% had hemolytic diseases. Furthermore, among the controls, iron deficiency anemia, anemia due to chronic disease, and hemolytic anemia were 30%, 2%, and 1%, respectively. The study concluded that low hemoglobin level is a risk factor for acute LRTI irrespective of the etiology of the anemia ($p = 0.000$). The study also concluded that children with anemia were 5.75 times more at risk of getting LRTI than the controls.[12]

Another prospective case–control study was done in Mysore, India, to identify modifiable risk factors for acute

Table 1 Summary of studies included in assessing the association between anemia and risk of infections

Country	Study period	Sample size	Cases (*n*)	Control (*n*)	Age	Anemic cases	Anemic percentage	Cases (anemic)	Percentage	Control (anemic)	Percentage	Study reference
Israel	1986–1998	880	680	200	18 mo to 4 y	139	15.79	136	20	3	1.5	11
Israel (Bedouin)	November 1989 to December 1992 and December 1994 to March 1997	293			Newborn to 18 mo	128	43.68					24
India (Kerala)	March 2003 to February 2004	200	100	100	9 mo to 16 y	107	53.5	74	74	33	33	12
India (Wardha)	January 2005 to December 2005	990			<3 y		80.3%					25
Mysore (India)	March 2005 to August 2005	208	104	104	1 mo to 5 y	87	41.82	80	76.92	7	6,73	13
Nepal (Pokhara)	March 2006 to March 2007	290	150 (140 in actual cases group)	140	1 mo to 5 y	126	43.44	96	68.6	30	21.42	14
Lebanon	September 2009 to April 2010	200	100	100	9 mo to 12 y	48	24	32	32	16	16	15
India (Kashmir)	March 2011 to February 2012	220	110	110	1 mo to 5 y	102	46.36	71	64.5	31	28.2	10
Nepal	July 2013 to June 2014	200	100	100	6 mo to 5 y	106	53	72	72	34	34	16
Egypt (Benha)	January 2014 to December 2014	100	50	50	9 mo to 6 y	60	60	38	76	22	44	17
Egypt	February 2014 to February 2015	300	150	150	6–12 y							18
Romania	2016–2017	192	166	26	1–3 y	104	54.2	98	59	6	23	19
Egypt (Benha)	May 2016 to May 2017	200	100	100	<5 y	112	56	74	74	38	38	20
Nepal	September 2016 to September 2017	200	100	100	<5 y	108	54	66	66	42	36	21
India (Mumbai)		220	110	110	9 mo to 5 y	114	51.81	74	67.3	40	36.4	22
Karad (India)	2017–2019	130	P: 21		2–60 mo	P: 2	P: 3.64					23
			SP: 79			SP: 37	SP: 67.27					
			VSP: 30			VSP: 16	VSP: 29.09					

Abbreviations: P, pneumonia; SP, severe pneumonia; VSP, very severe pneumonia.

LRTI among children 1 month to 5 years of age. A total of 104 children with acute LRTI were taken as cases and 104 healthy children as controls. The study identified several sociodemographic, nutritional, and environmental risk factors. The authors found that anemia was a significant nutritional risk factor ($p < 0.05$) for acute LRTI.[13]

Another prospective study has been done in the Pediatric Department of Manipal Teaching Hospital, Pokhara, Nepal. The study aimed to evaluate low hemoglobin concentration as a risk factor for developing acute LRTI in children. It was done among 150 cases and 140 controls belonging 1 month to 5 years ago. The study showed that anemia is a significant risk factor for acute LRTI ($p < 0.001$). Iron deficiency anemia was the leading cause and anemic children were found to be 3.2 times more susceptible to developing acute LRTI than the controls.[14]

A prospective comparative study was conducted in the Department of Pediatrics at Makassed General Hospital, Beirut, Lebanon, aiming to determine the relationship between anemia and LRTI. They have employed 200 infants and children from 9 months to 12 years. A hundred cases with ARTIs and 100 age- and sex-matched healthy controls were taken for the analysis. The study identified anemia as a risk factor for LRTI (OR, 2.08; 95% confidence interval [CI], 1.03–4.20; $p = 0.004$), revealing that anemic children are twice more susceptible to LRTI than the others. Also, the anemic children had significantly higher rates of recurrent chest infections ($p = 0.001$). Iron deficiency anemia was found to be the most common type of anemia.[15]

Another prospective case–control study has been performed among 220 children 1 month to 5 years of age in Kashmir, Northern India. The study aimed to assess whether a low hemoglobin level in children is a risk factor for acute LRTI. According to the study, anemia was found among 71 (64.5%) in the study group and 31 (28.2%) in the control group, and a higher risk to contract acute LRTIs (4.6 times) was detected among anemic children (OR, 4.63; $p < 0.01$). Iron deficiency was predominant among anemic patients, consisting of 78.9% of total anemic cases ($p < 0.01$).[10]

Another case–control study in Nepal recruited 200 children aged 6 months to 5 years to assess anemia as a risk factor for acute LRTI. The study showed that 72% of cases and 34% of controls were anemic. Anemia was significant (OR, 4.99; 95% CI, 2.73–9.1), and iron deficiency anemia was predominant.[16]

Another case–control study was done in Egypt to determine the relationship between iron deficiency anemia and pneumonia among children. The study included 50 children with pneumonia and 50 age- and sex-matched controls. Age of the participants ranged from 9 months to 6 years. Anemia was a significant risk factor for pneumonia (OR, 4.03; 95% CI, 1.71–9.49; $p = 0.001$). Iron deficiency was the most predominant type of anemia. The recurrent acute LRTI was significantly more common among anemic than nonanemic children (OR, 15.55; 95% CI, 4.88–49.53; $p < 0.001$).[17]

A prospective study was done in Egypt to identify the association between iron statuses as a predisposing factor for pneumonia. It was carried out in the Pediatric Department, Al-Azhar University Hospital, Damietta, from February 2014 to February 2015, recruiting 300 children. These children were divided into two equal groups based on the presence or absence of pneumonia. The study group showed a significant decrease in hemoglobin levels compared with the controls ($p = 0.001$). The study concluded that iron deficiency anemia was significantly found among children with pneumonia; hence, early and accurate identification of iron deficiency in children and treating iron deficiency would decrease pneumonia in children.[18]

One retrospective study performed in Romania comprising toddlers (1–3 age group) aimed to identify a significant association between anemia and ARTI and its associated risk factors. The study group comprised 166 toddlers with acute LRTI and 26 controls without ARTIs. The statistical analysis showed a significant association between LRTI and anemia ($p = 0.001$; χ^2 test). Furthermore, the study showed a significant association between anemic status in a rural area ($p = 0.023$; χ^2 test) and nonnatural nutrition ($p < 0.001$; χ^2 test).[19]

A cross-sectional case–control study was done in Benha, Egypt, to determine iron deficiency anemia as a risk factor for acute LRTI in children younger than 5 years. In total, 100 cases and 100 age- and sex-matched controls were included. Seventy-four percent of cases and 38% of controls were anemic, and 60% of cases and 24% of controls had iron deficiency anemia. Compared with controls, anemia was high in the cases (OR, 4.64; 95% CI, 1.99–10.80), and iron deficiency anemia was the most common type of anemia among cases than controls (OR, 4.75; 95% CI, 2.02–11.14). The study concluded that anemic children are four times more susceptible to developing acute LRTIs (OR, 4.75; 95% CI, 2.02–11.14). Also, in both cases and control, anemic children were 27 times more likely to develop recurrent acute LRTI (OR, 27.60; 95% CI, 9.52–79.95). Also, recurrent acute LRTI was high in children with iron deficiency anemia than non–iron deficiency anemia (OR, 10.26; 95% CI, 3.91–26.81).[20]

A retrospective study was conducted to identify the association of anemia with acute LRTI in children below 5 years of age at a pediatric ward of a tertiary hospital in Lalitpur, Nepal. It was done by recruiting 100 cases of acute LRTI and 100 age- and sex-matched controls. Anemia ($p = 0.002$) and acute LRTI ($p = 0.005$) were predominant in the 3 to 23 months' age group. Anemia was a significant risk factor for acute LRTI (OR, 2.68; 95% CI, 1.51–4.75; $p < 0.001$). It also revealed that in the presence of anemia, the development of acute LRTI was increased by 2.68 times compared with nonanemic patients.[21]

A prospective study was done in Mumbai, India, to assess anemia as a risk factor for acute LRTI in children aged 9 months to 5 years. In this study, 110 cases and 110 controls were included for the analysis; the study found that anemia is a significant risk factor for acute LRTI (OR, 3.59; $p < 0.001$) and anemia increases susceptibility to develop LRTI by 3.59 times.[22] Another study, which was conducted in Karad, India, assessed the clinical profile, risk factors, and outcomes of ALRIs in children. A prospective observational study employed 130 children aged between 2 and 60 months with ALRIs (pneumonia, severe pneumonia, and very severe pneumonia). A significant association ($p < 0.05$) was found between malnutrition, anemia status, and acute LRTI in these children. Anemia was found to be a significant risk factor for severe pneumonia ($p < 0.05$) and very severe pneumonia ($p < 0.05$).[23]

Effect of Anemia on the Severity of Pneumonia

A study was done in Quito, Ecuador, to determine the possible interaction effects between ambient air pollution and malnutrition, particularly anemia as risk factor for pneumonia in children. The study suggested that a higher degree of exposure to air pollution in anemic children was significantly associated with increased hospitalization due to pneumonia (OR, 6.82; 95% CI, 1.45–32; $p = 0.015$). They have observed that the OR for hospitalization due to pneumonia in children with higher exposure to air pollution has increased from 3.68 to 6.82 in the presence of anemia. Furthermore, no difference in hospitalization by pollution exposure status was observed among nonanemic children (OR, 1.04; $p > 0.05$). The study concluded that anemia might interact with air pollution to increase hospitalization due to pneumonia.[24]

Studies Assessing Anemia and the Etiology of ARTIs, AGE, and UTI

Among anemic children with acute LRTI, *Staphylococcus aureus* was identified as the most common pathogen,[23] while another study revealed *Klebsiella* spp. as the commonest etiology, and *Staphylococcus* spp., *Streptococcus pneumoniae*, *Acinetobacter* spp., and *Escherichia coli* were found significantly.[14] One study identified that in anemic children 43% of ARTIs were viral in origin, and respiratory syncytial virus (RSV) was the most common etiology. Among anemic children with acute gastroenteritis (AGE), an etiology was detected in 65% of cases, and from them, rotavirus was the commonest. Among UTI patients with anemia, an etiology was detected in 82% of cases, and *E. coli* was the commonest.[9–11]

Pathophysiology: Anemia as a Risk Factor for Contracting ARTI and AGE

The exact mechanism of anemia as a risk factor for developing infections is debatable. One proposed pathophysiology is that neutrophils have a reduced capacity to kill bacterial pathogens such as *S. aureus* due to reduced myeloperoxidase activity. The reduction in absolute number and the proportion of T cells in the circulation has defective DNA synthesis due to decreased ribonucleotide reductase activity.[13]

Hemoglobin is essential in oxygen and carbon dioxide transport and acts as a buffer for nitric oxide. Also, it stabilizes the oxygen pressure in tissues. A reduction of hemoglobin concentration qualitatively or quantitatively would affect normal body functions.[10–13] Alveolar macrophages are said to be obtaining iron from metabolized red blood cells and the plasma. Hence, in anemic states, their action can be retarded. These could be the possible pathophysiology behind the increased risk of ARTI in an anemic state.[10–18]

Iron is also essential for iron proteins such as hepcidin, lactoferrin, siderocalin, haptoglobin, hemopexin, Nramp1, ferroportin, and transferrin receptors, which have crucial roles related to innate immunity.[18] Iron is required for the proliferation and maturation of cells in the immune system, specifically the lymphocytes, which carry out specific immune responses against infections.[8] Also, studies suggest significant impairment in bacterial killing by polymorphonuclear leucocytes in individuals with iron deficiency.[25] Also, anemia results in low oxygen-carrying capacity in the pulmonary vascular system and reduces the response against pulmonary infections.

Iron deficiency, as well as malnutrition, is known to increase the risk of contraction of GE. The gastric epithelium, which has a high turnover rate, requires adequate nutrition to maintain its mucosa's integrity and absorptive functions.[8] Lack of tissue iron in chronic state results in defective epithelial formation.[25] Also, the general weakening of the immune responses due to anemia would increase the risk of GE.

Anemia was not identified as a risk factor for developing UTI in children even though immunity is impaired in an anemic state. In the pathogenesis of UTI, hydration plays a vital role along with structural abnormalities in the urinary tract.[8]

Pneumonia impairs tissue oxygenation. Hypoxia is said to increase mortality in pneumonia by two- to fivefold. Meanwhile, anemia also results in low oxygen delivery to tissues. Therefore, an anemic child would experience more significant hypoxia during an episode of pneumonia than a nonanemic child. Also, when a child has a higher exposure to air pollutants, the oxygen saturation is said to decrease significantly ($p < 0.001$). Therefore, it can be assumed that anemia and pollution exposure have an additive effect in increasing hypoxia in a child with pneumonia, resulting in severe disease.[23]

Studies Assessing Both ARTI and AGE in Children

A study has been performed among Bedouin infants in Israel to find an association between anemia and infection. In this study, 293 families and newborns from the Bedouin population were included and followed up for 18 months. The number of diarrhea and respiratory disease episodes and the total number of days of diarrhea were noted. The study showed that anemia at 6 months is an independent risk factor for diarrhea and respiratory illness from 7 to 18 months of age even after controlling environmental and socioeconomic factors. Anemia at 6 months of age was found to increase diarrheal episodes by 2.9 times (95% CI, 1.6–5.3; $p = 0.001$) and respiratory illness by two times after that age (1.1–3.7; $p = 0.03$).[26]

A cross-sectional study was done in Wardha district, India, to investigate the prevalence of acute childhood morbidities and the factors determining those and to assess the mothers' health-seeking behaviors. The study revealed a 59.9% prevalence of acute morbidities, including fever, cough and cold, pneumonia, diarrhea, and dysentery. These morbidities were significantly associated with anemia as well as grades of anemia. Severe anemia was associated with the highest prevalence of morbidities (90.9%), while moderate anemia, mild anemia, and nonanemia were found to have morbidity prevalence of 63.7%, 62.4%, and 52.1%, respectively ($p < 0.05$). Children with mild anemia, moderate anemia, and severe anemia were 1.56 (95% CI, 1.09–2.23), 1.57 (95% CI, 1.14–2.17), and 8.9 (95% CI, 1.17–70.83) times at risk of developing an ARTI or AGE compared with children with normal hemoglobin.[27]

Anemia and Persistent Diarrhea

A study was done in Pondicherry, India, to identify risk factors for persistent diarrhea and deaths. The study included 120 children between 1 month and 10 years of age, and revealed that anemia was a risk factor for persistent diarrhea in univariate analysis ($p = 0.002$; OR, 3.74; 95% CI, 1.55–9.15). However, it was not significant in multivariate analysis.[28]

Anemia and Development of UTI

Numerous studies have described the tendency of children with sickle cell anemia to develop UTI. However, the pathophysiology was due to the change in renal blood flow, causing renal papillary necrosis and inability to concentrate and acidifying urine precipitating microorganism growth.[29]

Children with sickle cell anemia are more susceptible to bacterial infections than the healthy population. Nevertheless, several identified causes for the increased risk are functional asplenia, defaulted complement activation system, micronutrient deficiencies, predisposing genetic factors, and mechanical risk factors.[30] Severe anemia is one of the complications of sickle cell disease, and it is associated with several infections in these patients, including upper respiratory tract infections, malaria, osteomyelitis, acute chest syndrome, sepsis, and UTIs.[31] There are numerous studies done to assess the infection risk of children with sickle cell disease, but those studies are not included in this review.

In this study, 46 out of 96 (47.9%) cases of UTI had anemia. The study reported that the development of UTI anemia was neither a risk factor nor a protective factor (OR, 1.03; 95% CI, 0.78–1.40; $p = 0.09$).[31]

Hemoglobinopathies and Acute Respiratory Tract Infections

Hemoglobinopathies would lead to an immunocompromised state. Also, children with sickle cell anemia may develop respiratory complications such as acute chest syndrome following viral influenza. The most extensive study with administrative data from the United States assessed the burden of influenza with sickle cell disease and found children with sickle cell disease were hospitalized with influenza at a rate 56 times that of children without sickle cell disease (95% CI, 48–65). The review summarized several high-quality observational studies and showed that sickle cell disease is associated with increased severity and frequency of influenza.[32]

Studies with Iron Supplementation and Follow-up to Assess the Infections

A study was done in Colombo, Sri Lanka, to identify the effects of iron supplementation on iron status and morbidity among children with or without infection. The study was done in a community where the prevalence of anemia is high. It was a longitudinal, randomized, controlled, double-blinded supplementation trial done on children aged 5 to 10 years, attending the outpatients' department of Children's Hospital, Colombo, Sri Lanka. A total of 420 children were taken and stratified based on age and sex, and oral iron or a placebo was given randomly on a ratio of 3:1. The occurrence of ARTI and AGE was assessed every 2 weeks. Following 8 weeks of supplementation, the children were reassessed. The children with infections who received iron had 29% fewer ARTI episodes than those who received a placebo and infectious episodes that were 40% less severe than those who received a placebo. The study results showed that iron supplementation improved body iron status and reduced the contraction of infections in children. Also, supplementation of iron may improve the quality of life of these children while ensuring good school attendance.[33]

Another study was done in children aged 2 to 48 months to identify whether long-term oral iron supplementation would increase the risk of childhood infections. However, this study did not assess the efficacy of iron supplementation on laboratory indices of iron status. The study showed a higher number of episodes and number of days of dysentery in <12-month-old than 12- to 24-month-old children. The study concluded that daily oral iron supplementation to young children reduces the incidence of dysentery, watery diarrhea, or ARTI.[34]

Another study among Cambodian children aged 6 to 24 months showed efficacy and safety of administration of iron and folic acid with and without the complement of 14 essential micronutrients. The study revealed that acute respiratory infectious episodes ($p = 0.014$) were less frequent in those who received the multiple micronutrient formulation than in placebo. In contrast, watery stools ($p = 0.002$) were more frequent with supplementation with iron and folic acid alone than in the placebo control group.[35] Another study was done among infants in Santiago, Chile, and found that the incidence of ARTI and diarrhea was not increased after supplementation of iron-fortified milk.[36] A study assessed the relationship between childhood anemia and the frequency of recurrent acute otitis media and found that correction of hemoglobin concentration would have reduced the frequency of recurrent acute otitis media episodes ($p < 0.05$).[11]

Anemia and Development of Recurrent Infections in Children

The study assessed the development of acute otitis media episodes among children with iron deficiency anemia and showed that the improvement of the hemoglobin concentration would significantly reduce the number of episodes of acute otitis media.[11] Some studies revealed that anemic children are more prone to contract recurrent chest infections[15,17,20] and anemic children were 10 times more susceptible to contraction of recurrent chest infections than nonanemic children ($p < 0.05$).[20]

Studies That Do Not Support the Hypothesis: Anemia Is a Risk Factor for Developing ARTIs, AGE, and UTI in Children

A study in Maputo province, rural southern Mozambique, assessed the epidemiology and clinical presentation of RSV infection and showed that anemic children have less frequently contracted RSV infections ($p < 0.05$). Moreover, contraction of RSV infections was less in children with moderate (OR, 0.4; 95% CI, 0.2–0.4) and severe anemia (OR, 0.2; 95% CI, 0.1–0.5).[37] A study that assessed the risk factors for the contraction of severe acute LRTI among children younger than 5 years has concluded that anemia is not a significant risk factor.[38]

A study was done on children in Kilimanjaro, Tanzania, to assess the association between iron deficiency anemia, the contraction of infectious diseases, and cell-mediated immunity. The study showed that the diagnosis of infectious diseases was more common among children with iron deficiency anemia; however, the association was insignificant. Moreover, the incidence of ARTI was lowest among patients with moderate iron deficiency, with an adjusted hazard ratio of 0.24 ($p = 0.030$). The study concluded that iron deficiency had no adverse outcome on cell-mediated immunity, and moderate iron deficiency would protect against ARTI.[39]

Discussion

Prevalence of anemia changes from low- to high-income countries, from urban to rural areas, and across the globe with the consumption of a nonnatural diet. In low- and middle-income countries such as India, anemia is increasingly prevalent among preschool children.[22] There have been studies to prove the association of anemia with the development of ARTI, GE, and UTI.[1–8]

Iron deficiency is a global health problem, and iron deficiency anemia is common among children aged 6 months to 3 years. Similarly, this age group can be considered a highly susceptible age for contraction of acute LRTIs and AGE.[10] Moreover, at the same time, acute LRTI is the leading cause of mortality among children < 5 years of age,[15] which is associated with 16% of deaths, and it is more common in developing countries.[21] Children below 5 years suffer five to six episodes of acute LRTI per year on average, and pneumonia accounts for the highest number of deaths, which is around 1.1 million each year.[22] The highest anemic population in the world is found in Southeast Asia,[20] while pneumonia is also prevalent in Southeast Asia and Africa.[20]

One study identified that the age group 3 to 23 months has the highest number of acute LRTI patients from 1 month to 5 years,[10] which was in line with studies conducted on children < 5 years and 9 months to 5 years age and found 3 to 23 months' age group is vulnerable to develop both acute LRTI and anemia.[21,22] Another study identifies that ages between 2 months and 1 year have the greatest number of ARTIs. Moreover, the highest susceptibility to infections and the development of anemia would be due to inadequate nutrition supplementation to meet the demand during rapid body growth.[14] A study from India recruiting children from 9 months to 16 years showed the maximum incidence of ARTI among children < 6 years,[12] and this would imply that the incidence of acute LRTI decreases with age.[22]

Studies in children aged 6 months to 5 years and 9 months to 16 years revealed age and sex were not significant for contraction of acute LRTI,[12,16] while some studies signified no gender discrepancies related to contraction of acute ARTIs.[10,16] Some studies identified a male predominance,[14,23] and the possible reason for such may be the preference given by families for male children, which is common among Asian cultures.[23] Some experts suspect the low prevalence of acute LRTI in female children would be due to the inherent immunity with an additional "X" chromosome.[22,23]

Children aged 2 to 12 months had the highest number of severe viral pneumonia, while those aged 13 to 60 months had very severe form. Having the highest incidence of severe pneumonia in children below 1 year could be due to poor immunity, poor nutritional status, narrow and smaller airways, frequent exposure to infections, and more susceptibility to bacterial and viral infections.[23]

Irrespective of the cause of anemia, many studies have identified anemia as a risk factor for the contraction of acute LRTI.[12] And some studies specifically identified that iron deficiency anemia as a risk factor for developing acute LRTI,[14,23] particularly pneumonia.[23] The early diagnosis and prevention of anemia would help reduce the incidence of acute LRTI. The studies have recommended the importance of screening for low hemoglobin levels in all infants at the age of 9 to 12 months and, if clinically indicated, additional screening before the age of 5 years. Moreover, the study recommends commencing therapeutic oral iron supplementation if screening tests are not available and depending on clinical suspicion of iron deficiency anemia.[22]

In summary, the ORs of anemia to increase the susceptibility to contracting acute LRTI would range from 2 to 5.7.[10,12,14–16,20–22] Moreover, anemic children were 10 times more susceptible to developing acute recurrent chest infections[20–22,29,31,34] and 4 times more susceptible to contracting pneumonia.[3–7,17,18] Identifying the modifiable risk factor would help reduce mortality.[8,9,15–21,33] Anemia would increase the risk of diarrhea by 2.9- to 3.3-fold in toddlers,[26,29,34] while mild anemia, moderate anemia, and severe anemia would increase the susceptibility to contract AGE by 1.6, 1.6, and 8.9 times, respectively.[27,29–31] The studies reported that the development of UTI anemia was neither a risk factor nor a protective factor[8,11,16–18,28] (►**Table 2**).

Studies have been conducted to assess the effect of iron supplementation on infection risk and morbidity, which may help in proving our hypothesis. Some studies showed that iron supplementation reduces the incidence of ARTIs.[33] Some studies observed a protective effect from mild to moderate iron-deficient anemia to respiratory infections. This dietary iron deficiency would have developed a nutritional adaptation against infections. However, iron deficiency has other adverse effects, such as growth retardation and cognitive and motor function impairment in children.[39,40]

Table 2 Summary of the systematic review

	Type of infection		
	Acute lower respiratory tract infections	Acute gastroenteritis	Urinary tract infections
Odds ratio for the contraction of infections among anemic children	2–5.7	2.9–3.3	0
References	10,12,14–16,20–22	8,9,15–21,32	8,11,16–18,30

It is difficult to identify iron deficiency anemia during infections as body iron status might get affected by the inflammatory process. Per the latest studies, iron deficiency anemia can be identified more reliably with transferrin saturation, which does not affect other factors such as inflammation, infection, age, sex, or pregnancy.[15] Our study did not consider the methodology that the researchers used to identify anemia in children.

The contribution of viral pathogens in these infections maybe not be adequately analyzed in some studies due to the unavailability of molecular and antigen detection facilities.[23]

Conclusion

Anemia, particularly iron deficiency anemia, can significantly contribute to morbidity and mortality among children worldwide. Apart from the direct contribution of anemia to mortality and morbidity, it can be identified as a risk factor for infections among children. Numerous studies are proving this association, and some studies have failed to identify any existing association.

ARTIs, including pneumonia, can be identified as the number one killer among children worldwide. Most studies have been done to identify a relationship between ARTIs and anemia, particularly iron deficiency anemia. Some studies have shown a strong association between anemia and contraction of ARTIs and AGE. There was 2 to 5.7 times risk of contracting LRTI among children with mild to moderate anemia and 8.9 times risk of contracting AGE among children with severe anemia.

A few studies have proved that there is no significant association between anemia and UTIs in children. No articles were found proving this association. Studies were done to prove an association between anemia and infections by prospectively studying the risk of infections following iron supplementation. While most of the studies managed to prove an association, some studies proved a negative association.

Infectious disease imposes a heavy burden on the health sector in a country. Therefore, the available evidence can help us in taking the necessary steps to reduce the infectious disease burden by correcting the anemia status in children. Correcting nutritional anemia may break the vicious cycle of anemia leading to infections and infections leading to anemia.

Conflict of Interest
None declared.

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