Why Is a Child Not a Miniadult for Infections?

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Abstract: The presentation of an infectious disease in a child is likely to differ from an adult and will differ at different ages of the child. In addition to differences in immune response, there are significant differences in anatomy, physiology, metabolism, and behavior that affect susceptibility, course of disease, severity, and treatment. This is the first of a series of reviews that examine differences in disease presentation for different demographics. This short review will look at some of the parameters that ask, "Why is a child not a miniadult for infections?"

Key Words: children, infectious disease, immunology, COVID-19

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Most textbooks and manuscripts generalize the description of the presentation and treatments for infectious diseases to adult White male patients. With the vast differences in COVID-19 presentation in patients of different ages, race, color, and sex, it is clear that the classical textbook description of infectious diseases for a White adult male patient is insufficient. For a child, the presentation may be similar or very different than an adult and different for different aged children (Table 1). For COVID-19, children are more likely to be asymptomatic but potentially prone to multisystem inflammatory syndrome in children.[1] Epstein-Barr virus (EBV) causes infectious mononucleosis in a teen or adult but may only cause pharyngitis in a child. Hepatitis B virus (HBV) may cause no symptoms in a child as opposed to hepatitis in an adult, but children are more prone to chronic disease. This is the first of a series of reviews that examine differences in disease presentation for different demographics. This short review will look at some of the parameters that ask, "why is a child not a miniadult for infections?"

ANATOMY/PHYSIOLOGY

The anatomy, physiology, and metabolic demands of children are very different from adults, causing many infectious diseases to present differently in a child. First, children need proportionally higher volumes of water to maintain equilibrium and are more susceptible to volume depletion. Children are smaller and have less volume with a much higher body surface area–to–mass ratio and therefore have relatively higher fluid loss, which is not readily measurable, from the skin, the respiratory system, and excreted in stool (insensible fluid loss). They also have a higher total body water percentage (75% of total weight in infants and 60% in children compared with 50%–60% in adults). Coupled with their inability to communicate needs ("I'm thirsty"), inability to hydrate themselves, and their immature renal function that limits the ability of an infant to conserve water, they become much more susceptible than adults to life-threatening dehydration due to gastroenteritis, especially from rotavirus, *Escherichia coli, Vibrio cholera,* and other agents.

Metabolic demands are 2 to 3 times greater in neonates and infants, and therefore, they have greater caloric demands, especially during illness. Neonates and infants with sepsis are more prone to hypoglycemia because of increased glucose requirements and the higher metabolic rate coupled with decreased glycogen stores in their less developed liver. This is quite often exacerbated by the decreased oral intake that can accompany illness. In older children, as with adults, hyperglycemia is often seen with sepsis.

Several anatomical differences make children more prone to respiratory distress from respiratory infections than adults. Children are more prone to positional airway obstruction because they have proportionally larger tongues, natural flexion of the neck when in supine position due to their proportionally larger head, a prominent occiput, and relatively lax cervical support. Children also have a more compliant chest wall and a less rigid, narrower trachea that are more susceptible to distending and compressive factors.[2] Overall, smaller airway diameter results in more severe symptoms from respiratory infections due to airway inflammation and increased mucus production. Children have a larger heart size relative to the thoracic cavity volume and overall smaller lung capacity, which decreases the pulmonary reserve, making them more prone to hypoxia with respiratory infection. In addition, young infants are obligate nose breathers and can have significant respiratory distress due to obstruction by nasal secretions. Just based on these anatomical differences, children are more susceptible to serious presentations due to diphtheria, *Haemophilus influenzae B* epiglottitis, parainfluenza croup, and respiratory syncytial virus (RSV). Children are also quicker to decompensate with respiratory distress from respiratory infections due to decreased respiratory reserves, as described, and inadequate compensatory mechanisms. In addition, the immature kidneys of infants cannot compensate as well for respiratory alkalosis/acidosis. All of these factors combine to make infants and children more susceptible to respiratory distress and even respiratory failure with respiratory infections. These factors help make respiratory distress/failure the leading cause of cardiac arrest in children as opposed to a primary cardiac event.[3]

VITAL SIGNS AND LABORATORIES

Normal vital signs, such as blood pressure, heart, and respiratory rate, differ between children and adults and vary with their age, sex, and height. For example, normal vitals for an infant up to 3 months of age include a blood pressure of 65 to 85/45 to 55 mm Hg, a respiratory rate of 30 to 60 breaths per minute, and a heart rate of 110 to 160 beats per minute.[4] Such vitals in an adult would indicate hypotension, tachypnea, and tachycardia and suggest septic shock. In children, septic shock may initially present as tachycardia, with or without tachypnea, and hypotension is typically a late finding because children initially use compensatory mechanisms to maintain blood pressure and perfusion. Awareness of the difference in these vital signs is important to correctly evaluate a child for an infectious process. In addition, the higher respiratory rates will result in higher insensible fluid losses from the respiratory tract, and as mentioned previously, this causes children to

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TABLE 1. Infections With Different Presentations in Immunocompetent Children and Adults

Infections	Child Presentation	Adult Presentation
Adenovirus	Infant—pharyngitis, coryza, otitis media, pneumonia; diarrhea children—URI, pneumonia; pharyngitis, conjunctivitis; diarrhea, mesenteric adenitis; hemorrhagic cystitis	Acute respiratory distress, conjunctivitis
Bordetella pertussis	<6 mo—apnea; respiratory distress, can be fatal	Prolonged cough
EBV	Variable, but can be asymptomatic or very mildly symptomatic with only 1 symptom, such as pharyngitis	Mononucleosis
Group A Streptococcus	Rheumatic heart disease rare in children <3 yo	Rheumatic heart disease
Hepatitis A virus	<6 yo—commonly asymptomatic	Jaundice (can last up to 6 mo)
HBV	Mild or asymptomatic; however, 90% of children <1 yo develop chronic hepatitis	Hepatitis
Herpes simplex virus	Infants—skin, eye, mouth disease, meningitis, liver failure, pneumonia, myocarditis, cerebral hemorrhage, death	oral, genital lesions
Mumps	Orchitis less common in prepubertal male individuals	Unfavorable outcomes more common
Parainfluenza	Croup, respiratory distress	Mild cough, congestion
Parvovirus B19	Young child—erythema infectiosum, usually mild illness	Acute polyarthropathy with or without rash
Rotavirus	Life-threatening diarrhea	Mild diarrhea
RSV	<3 mo—can present with apnea <2 yo—bronchiolitis often with severe respiratory distress	Mild cough, congestion
Salmonella	Invasive disease more common in infants <1 yo	Invasive disease less common (until >60 yo)
SARS-CoV-2	Less severe than in adults; possible MIS-C	Asymptomatic to ARDS, death
VZV	Varicella with typically only skin involvement, but infrequently can progress to serious and even fatal disease	Pneumonia and serious presentation more common

ARDS indicates acute respiratory distress syndrome; MIS-C, multisystem inflammatory syndrome in children; mo, months of age; URI, upper respiratory tract infection; yo, years of age.

be at higher risk for dehydration, particularly during a respiratory infection, when respiratory rate may be increased and food and fluid intake is likely to be decreased.

Although the normal temperature range for infants and children is the same as adults, fever or hypothermia may be the only initial sign of a serious infection in a newborn, and only 50% of infected newborns have elevated temperatures with infection.[5] As mentioned previously, children have a greater ratio of body surface area to mass and therefore are at higher risk of excessive heat loss. As with adults, heart rate and respiratory rate can increase in presence of fever. The presence of fever in an infant or small child can increase the respiratory rate by as much as 5 to 7 breaths per minute per every degree Celsius above normal for children older than 12 months and as much as 7 to 11 breaths per minute in children younger than 12 months.[6] Therefore, tachycardia and tachypnea should be assessed in the context of temperature.

In addition to physical signs, the relevant complete blood count for a child with infection can differ from that of adults because the number of circulating neutrophils varies with age of the child. White blood cell count (WBC) ranges from 9000 to 30,000/mm^3 in full-term neonates with narrowing of the normal range from 6000 to 17,000/mm^3 in those aged 6 month to 2 years and further from 4500 to 13,500/mm^3 in those aged 6 to 12 years. In addition, the normal ranges for percentages of neutrophils and lymphocytes on a complete blood count differential also vary with age in children. A normal WBC in a child may be mistaken for abnormal if adult normal parameters (4500–11,000/mm^3) are used.[7] Being familiar with these values is essential to determine the diagnosis and appropriate treatment of an infection in a child. Typically, infection is indicated by leukocytosis in adults, but in neonates, neutropenia is a better predictor of sepsis than leukocytosis.[5] Using adult normal parameters and typical patterns of WBC response to infection may result in overdiagnosis or underdiagnosis of a serious infection in a child.

IMMUNOLOGY

The immune response in children changes as they age because of development of the system and with its education by exposure. Many changes occur as the neonate transitions from being a fetus protected by the womb to an individual exposed to the microbial world. The first such exposure comes as the baby traverses the birth canal and interacts with the mother's normal vaginal flora. This can initiate the development of the baby's personal microbiota but may also include pathogens, such as group B streptococcus or herpes simplex virus, for which protections are insufficient and the consequences can be tragic.

Initiation of the immune system occurs in utero with the presence of B and T cells from week 22 of gestation. At birth, the neonate makes a big transition from the protected environment of the womb to the challenges of the microbial world.[8,9] At birth, the complement system is functional as are other innate protections, but the immune system is geared more toward tolerance and repair rather than antimicrobial and cytolytic responses. Much of the tolerance is meant to limit or prevent responses to maternal proteins and cells and the extensive tissue remodeling that accompanies the rapid growth during this period. Although there are an abundance of T cells, the regulatory T cells (Treg) dominate and the rest of the T cells are waiting to be educated by normal flora and other exposures. Interestingly, specific bacteria are sufficient to initiate T-cell development, for example, the polysaccharide A of *Bacteroides fragilis*.[10] The neonatal immune system creates a bias against the responses driven by interferon-γ (T_H1) that activates macrophages and cytolytic T cells important for combat against intracellular infections, such as viral infections. Instead, the system favors the T_H17-driven responses that support epithelial cell defenses, including antimicrobial peptide production, and neutrophil responses to promote rapid antibacterial and antifungal protections. This bias against T_H1 responses, the immaturity of their CD8 cytolytic T

cells, and the naivete of the immune repertoire make the neonate exceptionally sensitive to intracellular infections, including the TORCH (toxoplasma, other [syphilis, varicella zoster, parvovirus B19], rubellavirus, cytomegalovirus, herpes simplex virus, and human immunodeficiency virus) infections. These TORCH infections acquired in utero or perinatally and the immune response to them can have severe sequelae in the rapidly growing brain of the fetus and infant.

Before and for the first 4 to 6 months, antibody protections are mostly limited to the maternal IgGs obtained through the placenta for systemic protections and IgAs in breast milk for protection of the gastrointestinal (GI) tract. The maternal immunoglobulin repertoire is dependent on exposure and often does not provide sufficient protections for all significant pathogens. A lack of antirotavirus IgA in mother's milk may be one reason that rotavirus is such a problem in neonates and young infants, whereas rubella-immunized mothers provide protections to the fetus and neonate. Antibody production begins before birth, during the third trimester,[11] but these antibodies are predominantly generated by innate B1 B cells and are low affinity IgMs that may have some weak cross-reactivity with microbial antigens, but are not very protective. Maturation of the classical B2 B cells and a potent antibody response begins soon after birth, as the B1 B-cell response recedes to more normal levels. Even so, antibody production requires exposure to antigens, an IgG response requires at least 7 days to mature, and the clonal selection of a more sophisticated and higher affinity response takes more time and possibly multiple exposures. This provides a long window of time for infection to occur and spread.

Possibly, the most obvious reason that children are more susceptible to infectious diseases is that they are immunologically naive and are continuously being exposed to infection at day care, in school, and from friends and relatives. Young children get 4 to 8 viral respiratory infections per year on average.[12] In addition to being immunologically naive, children younger than 5 years and especially younger than 12 months generate less antiviral type 1 interferon in response to viral infection than adults because of a more limited response by their plasmacytoid dendritic cells.[13,14] These are the cells and cytokines that promote flu-like symptoms during the prodrome period of a viral infection and are especially important for defense against RSV, influenza, SARS-CoV-2, and other respiratory viruses.

There is an interesting conundrum in that some infections are milder in children than teens or adults. These include HBV, varicella zoster virus (VZV), and EBV. Hepatitis B virus is milder or asymptomatic in children but more likely to establish chronicity because of insufficient resolution by a T-cell response.[15] Similarly, EBV infection may be less pronounced because of less of a T-cell response.[16] For VZV, the adult immune and inflammatory response in the lung, the initial site of virus infection, puts the adult at much greater risk of serious pneumonia before the virus can even spread and cause its classic rash. Although there are no definitive answers, it is possible that the initial inflammatory response to these infections is more mild or children may be able to more effectively control the infection earlier than adults to preclude the need for a more active inflammatory response later. The latter possibility may be due to "trained immunity,"[17] a newly described phenomenon in which repetitive exposure to a specific type of infection can enhance the response of innate cells. For virus infections, this would include interferon producing cells and NK cells, which may undergo epigenetic changes to respond faster and more efficiently toward generic viral infections.

Vaccine-induced protections provide the means for preventing disease early in life[18–20] and ideally, should be provided according to the recommended vaccine schedule (https://www.cdc.gov/vaccines/schedules/hcp/index.html). Some vaccines can be administered within the first 2 months, but other vaccines must be administered later because of a combination of factors. These factors include possible interference by maternal antibodies, immaturity of immune cells and structures, and the suppression of T_H1 cell–mediated responses, which limit the nature of the protections and the longevity of the immunity. In addition, the immunizations must be temporally spaced to optimize the response. For example, polysaccharide vaccines are poor immunogens at younger than 1 year but are excellent immunogens when conjugated to proteins, as for *Streptococcus pneumoniae*, *Hemophilus influenzae B*, and *Neisseria meningitidis*. The efficacy of the live rotavirus vaccine in infants, which is given between the ages 2 and 8 months, compared with the live measles, mumps, rubella, or varicella vaccines, which are initially given at the ages of 12 to 15 months, is likely due to differences in the mode of presentation, the levels of maternal antibody, and the type of protective immune response that must be elicited by the vaccine (secretory IgA for rotavirus and IgA-, IgG-, and cell-mediated immunity for the others). For these reasons, determination of the format and schedule of administration of vaccines requires testing in infants and children and cannot be extrapolated from older children or adults.

BEHAVIORS

Children of all ages behave differently from adults, and some of those behaviors increase exposure to microbes and, therefore, infection (Table 2). Young infants explore their environment by touching and mouthing objects as part of normal development. Children are also more prone to excessive digital probing of their nostrils and more likely to cough or sneeze without covering their nose/mouth and, if they do, less likely to wash their hands. Children are also not yet aware of the risks of touching contaminated surfaces and substances, including stool. Infants do not have the gross motor skills to wash their hands effectively and young children do not always do a thorough job of hand hygiene. All these behaviors make children more at risk of contracting and spreading respiratory and fecal-oral microbes. Toileting behaviors also contribute to increased risk of infection. Poor or inappropriate wiping (eg, wiping from back to front instead of front to back) increases risk for urinary tract infections in girls upon contamination of the urethra with fecal bacteria. Adolescents are more likely than adults to believe that they are "indestructible," leading to risky behaviors, increasing their risk for certain infections, including sexually transmitted infections.

In addition to the behaviors that put children at higher risk of contracting infections, there are also behaviors that make diagnosis of infections more difficult in children, in particular preverbal children. Infants and young children are not able to verbalize symptoms as well as adults and therefore may present with vague symptoms, such as fussiness, decreased appetite, or lethargy. An infant or young child cannot say that they have abdominal pain

TABLE 2. Behaviors of Children/Adolescents That Increase Risk for Infection

Putting objects/hands in mouths
Digital nostril probing
More likely to touch contaminated objects/surfaces (including stool/inside diaper or underwear)
Poor wiping techniques after toilet usage
Less efficient/complete handwashing techniques
Feelings of invincibility

or sore throat, and instead, a parent may note crying with feeding or refusal to eat or drink. An infant or young child cannot say that they have a headache or ear pain, and instead, a parent may note fussiness or excessive crying. Delay in identifying or associating the nonspecific symptoms and subtle signs of an infection in neonates and other pediatric patients may result in increased morbidity and mortality.

ANTIMICROBIAL TREATMENTS

The choice and dosage of antimicrobial for a child will differ from an adult based on anatomical, behavioral, and other parameters that affect pharmacokinetics and patient compliance. Many antimicrobials that are considered safe for use in adults are not considered safe for children or only approved for use in older children. The fluoroquinolones are a good example of a first-line therapy used for adult infections that is not routinely used in children because of increased concern for adverse effects and differences in pharmacokinetics.[21] The calcium chelating property of tetracyclines limits their use during pregnancy and children younger than 8 years.[22] Even for the more common pediatric antimicrobials, an adult dosage could be an overdose for a child. Different sized adults typically have the same bioavailability of medication, whereas in children, the dosage must be calculated based on weight or body surface area. For healthy children without comorbid conditions, specifically renal disease, the dosages are standardized for each medication based on components, although the dosage used can vary based on the disease process. Calculated dosages for children are adjusted for specific microbes and locations of infection to ensure that they exceed the minimum inhibitory concentration but do not exceed the maximum adult dosages.[23]

Oral versus intramuscular administration and flavoring (bubble gum flavored vs grape) are real considerations for treating children. For example, amoxicillin is commonly prescribed for children with streptococcal pharyngitis although oral or intramuscular penicillin is the recommended first-line treatment for adults. Amoxicillin has the advantage that it is administered orally (bubble gum flavored) rather than as an injection and only requires 1 to 2 doses per day instead of 3 to 4 times per day dosing with oral penicillin.

COVID-19

An excellent example of the difference in disease presentation between children and adults is COVID-19. Children aged between 12 months and 18 years are much more likely to have asymptomatic or mildly symptomatic (single symptom) disease, which can lead to difficulty with diagnosis. More severe cases are more common in neonates and infants.[24,25] Gastrointestinal symptoms are more common in children than in adults, also leading to increased difficulty with diagnosis, as GI symptoms may be attributed to other illnesses. In addition, there does not seem to be a significant difference in severity based on sex in children, as seen with adults.

It is still unknown exactly why illness in children is less severe, but the most commonly proposed theory at this time is related to less expression of the angiotensin-converting enzyme 2 receptor in children compared with adults. Another current thought is that children may have a more effective innate immune response to combat the virus due to trained immunity. A better initial defense with protective cytokines and responses may lessen the need for a more vigorous or inappropriate response later that could lead to acute respiratory distress syndrome.[26,27] Multisystem inflammatory syndrome in children is the most serious complication being documented for COVID-19 at this time, with symptoms similar to those of Kawasaki disease and toxic shock syndrome. The cause for this is not known.

Children younger than the ages of 6 or 7 are also much less likely to transmit SARS-CoV-2, although older children seem to transmit at a similar rate as adults. Less transmission is possibly due to less virus production, less air expulsion, which could be due to smaller lung volume, or less tendency for coughing. Even with potentially less transmission per child, as schools reopen, opportunities for transmission are likely to increase. As such, children are an important group to vaccinate, enhancing herd immunity and preventing the spread of the virus to their teachers and families. The differences in infectivity and disease presentation combined with physical variations and differences in immune response for children warrant inclusion of children in trials of any SARS-CoV-2 vaccine.

CONCLUSIONS

Children are not miniadults for disease presentation or treatment of infections because they are smaller, their anatomy and physiology are different, and, most importantly, their immune system and immunological exposure history are less mature. In addition, children have different behaviors and lead different lives than adults, which put them at risk for different infections from their peers and their environment. Even larger differences distinguish infants from older children and adults. Diagnosis and treatment must be customized to accommodate the differences in size and physiology of children.

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