Clinical Commentary Review

The Influence of Immune Immaturity on Outcome After Virus Infections

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Maturation of the adaptive immune response is typically thought to improve outcome to virus infections. However, long-standing observations of natural infections with old viruses such as Epstein-Barr virus and newer observations of emerging viruses such as severe acute respiratory syndrome coronavirus 2 responsible for COVID-19 suggest that immune immaturity may be beneficial for outcome. Mechanistic studies and studies of patients with inborn errors of immunity have revealed that immune dysregulation reflecting inappropriate antibody and T-cell responses plays a crucial role in causing bystander inflammation and more severe disease. Further evidence supports a role for innate immunity in normally regulating adaptive immune responses. Thus, changes in immune responses that normally occur with age may help explain an apparent protective role of immune immaturity during virus infections. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:641-50)

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In a world teeming with microbes, a competent immune system is critical for survival. In the young, innate immunity plays an important role in host defense by recognizing and responding to pathogen-associated molecular patterns. As children age, adaptive immunity matures and takes an increasingly important role in fighting off infections. When encountering a microbe for the first time, T- and B-lymphocytes, bearing uniquely rearranged antigen receptors that recognize specific microbial antigens, expand and mediate effector functions such as killing of virus-infected cells. After resolution of infection, the formation of immunological memory enables a more swift and
Abbreviations used
ACE2- Angiotensin-converting enzyme 2
ADE- Antibody-dependent enhancement
CRP- C-reactive protein
DENV- Dengue virus
EBV- Epstein-Barr virus
FI-RSV- Formalin-inactivated respiratory syncytial virus
HLH- Hemophagocytic lymphohistiocytosis
IIE- Inborn errors of immunity
IFN- Interferon
IVIG- Intravenous immunoglobulin
MERS-CoV- Middle East Respiratory Syndrome coronavirus
MIS-C- Multisystem inflammatory syndrome in children
NK- Natural killer
pDC- Plasmacytoid dendritic cell
POL III- Polymerase III
ROS- Reactive oxygen species
RSV- Respiratory syncytial virus
SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2
VZV- Varicella-zoster virus

robust response on subsequent re-encounter with the microbe. Because maturation of adaptive immune responses occurs over the first few years after birth, many infections are more severe in infancy and early childhood. A classic example is that of measles virus infections, which is associated with more severe complications in those children younger than 5 years old.

In the ideal situation, adaptive immunity complements and amplifies innate immunity to provide a powerful and targeted way to rid the body of pathogens. However, the line between a protective and a pathological response from this "mature" arm of the immune system can be a delicate one. When unrestrained or in the wrong place at the wrong time, activated T- and B-lymphocytes can cause collateral tissue destruction resulting in end-organ damage or even death. Thus, immune immaturity, with its less robust adaptive immune responses, can seemingly lessen the risk of morbidity and mortality to some infectious diseases.

The concept of pathological adaptive immune responses can apply broadly to all types of infectious diseases including bacterial and parasitic infections. Nevertheless, because lymphocytes are important in antiviral defense, the consequences of their dysregulation are more apparent for virus infections. For that reason, in this review, we focus on virus infections that seemingly "buck the trend" by being less severe in young infants and children as compared with older individuals. We start with the example of the 1918 influenza pandemic, an "old" virus infection, which illustrates how different factors could determine disease outcome, but where it is likely that pathological adaptive immune responses at least partially explain the increased mortality in young adults. Next, we delve into how dysregulated antibody responses cause disease using the examples of Dengue virus (DENV) and respiratory syncytial virus (RSV). We then turn to dysregulated T-cell responses using the example of Epstein-Barr virus (EBV) and age-related changes in innate immunity against varicella-zoster virus (VZV). Finally, we end with a new virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in which hyperactivated T-cell responses, defective innate immunity, and dysregulated B-cell responses are together linked to cause severe disease especially in older individuals. Thus, using the examples above, this review highlights the “upside” of immune immaturity and examines the mechanistic roles of immune status and age in increasing the risk of contracting severe clinical disease to viruses, which are more complex than first thought.

THE 1918 INFLUENZA PANDEMIC

One of the earliest examples of an infectious disease whose epidemiology suggested a protective effect of immune immaturity was the 1918 H1N1 influenza pandemic. In most years, influenza virus infections pose the highest risk of death to the very young and the elderly. For the very young, the increased risk has been attributed to an underdeveloped immune system that fails to control virus replication, as well as physiological differences such as smaller airways more easily compromised during respiratory infections. For the elderly, the increased risk has been attributed to immunosenescence, an age-related deterioration of the immune system characterized by dysregulation involving both defective activation and chronic proinflammatory responses. Additional factors predisposing to worsened outcome include pregnancy and comorbid conditions such as chronic pulmonary or cardiovascular diseases that diminish cardiac and respiratory reserve particularly in the elderly. Nevertheless, when contrasted to other influenza virus outbreaks, worldwide mortality to the 1918 H1N1 influenza pandemic exhibited not the typical “U-shaped” curve but rather an unusual “W-shaped” curve with an additional peak in deaths coming from otherwise healthy young adults.

Understanding this unusual pattern of mortality requires an appreciation for disease pathogenesis. Experimental infections of mice and monkeys with a reconstructed 1918 H1N1 virus established its extreme virulence, with a lower dose required for death, and characterized by increased immune cell infiltrates, proinflammatory cytokine production, and cell death within the lungs. These observations complement those from autopsies of patients who died during the 1918 influenza pandemic, which frequently revealed similar pathological findings and secondary bacterial pneumonias. Because the reconstructed 1918 H1N1 virus exhibits increased virus replication, the increased virus products might have driven the worsened clinical severity. However, in other studies, influenza virus load within the respiratory tract has not correlated with clinical severity and outcome. Thus, the increased immunopathology might not necessarily have solely resulted from increased replication.

Several explanations have been proposed to account for the unusual age distribution of deaths. One explanation is that older adults had protective antibodies from previous exposures to related H1 influenza viruses that were circulating before 1889, and that these were missing in the younger adults. However, this explanation cannot account for the increased mortality in younger adults, especially in males. Their participation in World War I efforts increased their exposure to the virus because of travel and contact with large numbers of infected persons. In this group, concomitant infection of influenza virus with tuberculosis (which itself was associated with higher male mortality around that time) has been suggested to predispose to secondary bacterial pneumonias due to preexisting colonization of cavity lung lesions. However, this cannot be the only explanation as in some parts of the world, females had higher mortality from 1918 H1N2 influenza than males.

A clue might be found in careful epidemiological studies that established an exact peak mortality at 28-year-old adults. This
observation suggests that some widespread event occurred 28 years earlier that influenced later outcome to infection with 1918 H1N1 in fluenza virus. One intriguing possibility is that the increased immunopathology in this age group could have instead resulted from cross-reactive T cells induced by the Russian influenza pandemic of 1889-1890, as depicted in Figure 1, A. According to this model, infection with the 1890 (suspected H3Nx) influenza virus resulted in the development of memory T cells that could recognize 1918 H1N1, due to shared T-cell epitopes. Although the difference in H3 and H1 would mean no development of cross-reactive protective antibodies, the cross-reactive T cells could contribute to a dysregulated immune response on subsequent 1918 H1N1 infection. Alternatively, infection with 1890 H3Nx influenza virus either in utero or during infancy—during a window of time critical for normal T-cell maturation—could have resulted in deletional tolerance of T cells. The resulting “holes” in the T-cell repertoire could contribute to inadequate ability to control subsequent 1918 H1N1 influenza virus infection.

Although these explanations for the increased lethality in young adults are scientifically satisfying, other epidemiological observations about the 1918 influenza pandemic remain unexplained. For example, the reason(s) for the decreased mortality in school-aged children even in geographically isolated, infection-naive populations, as occurred in Alaska during the 1918 H1N1 influenza pandemic, are unknown. Similar unexplained phenomena have also been observed for other viruses, including measles, VZV (causing chickenpox), and EBV. One can speculate that these observations reflect differences in innate immunity, which are most robust in this age group and deteriorate with age. Certainly, the importance of innate immunity in this age group is suggested by the life-threatening virus infections presenting during childhood of patients with inborn errors of immunity (IEI). In the case of life-threatening influenza virus, this has been observed with the identification of inherited TLR3, IRF7, and IRF9 deficiencies, which impair type I interferon (IFN) antiviral immunity.

In summary, influenza virus infections, and in particular the 1918 H1N1 influenza pandemic, illustrate the complex interplay among microbes, nonimmune factors such as human physiology and epidemiology, and immune responses, in determining outcome to virus infection (Figure 1, B). For the remainder of this review, we will focus on specific immune mechanisms that are best illustrated during other virus infections, and how they provide insight into the effects of immune immaturity on clinical outcome.
DENGUE VIRUS

Influenza virus infections demonstrate a situation in which cross-reactive antibodies elicited by a previous influenza infection can protect against subsequent infection by a related influenza virus strain sharing a similar hemagglutinin. By contrast, DENV infections demonstrate that prior antibodies can sometimes be detrimental. DENV infections are usually asymptomatic or mild, but can sometimes cause fever, increased vascular permeability with shock, and complications such as hemorrhage, end-organ damage, and death. Differences in protein sequence among the 4 distinct serotypes of DENV can contribute to their different clinical manifestations including disease severity. Infection with any particular serotype of DENV promotes longer lasting protection from subsequent infection with the same serotype including protection against severe disease. However, cross-protection against infection with a different serotype is short-lived, and the risk of severe disease on a second infection is actually increased to a different serotype although not for subsequent infections. Other factors that contribute to increased risk of severe disease include age, timing between DENV infections, and host genetic variation. In addition, infants of immune mothers also have increased risk of severe disease during primary DENV infection at an age when maternal antibodies wane. Thus, depending on the context, immune immaturity can be either protective or worsen outcome of DENV infection.

These effects were postulated and later shown in humans to result from antibody-dependent enhancement (ADE). As shown in Figure 2, the effects on a subsequent heterologous DENV infection result from either insufficient levels of neutralizing antibodies, and/or the presence of cross-reactive antibodies that bind but do not neutralize virus of the different serotype. When such a scenario occurs, circulating immune complexes, composed of non-neutralizing antibodies with infectious virus particles, bind to activating Fcγ receptors on monocytes, macrophages, and dendritic cells. This binding enhances virus uptake into the host cell, causing a large number of FcγR-bearing cells to quickly become infected by DENV. Additional downstream effects after uptake of these immune-complexed viruses include suppression of type I IFN and proinflammatory signaling. On the other hand, large aggregates of antibodies complexed with DENV can also engage FcγR1IB, which exerts inhibitory effects to antagonize ADE-mediated phagocytosis. This inhibition requires a very high concentration of neutralizing antibodies, which is not the case during a secondary heterologous DENV infection, especially as the time interval since primary infection lengthens. However, it should be...
noted that the concentration of neutralizing antibodies would increase for subsequent infections, accounting for the rarity of severe disease with third and fourth infections. Finally, a polymorphism in the activating FcγRIIA (p.His131Arg) lowers binding affinity for IgG and is protective against severe DENV infection, further supporting the idea of immune complex-FcγRIIB-driven pathogenesis.19-21 In this light, early administration of high-dose intravenous immunoglobulin (IVIG) after DENV exposure might protect high-risk patients from severe disease by increasing the size of immune complex aggregates to promote engagement of FcγRIIB, although this possibility has not been carefully investigated.

RESPIRATORY SYNCYTIAL VIRUS

The experience with DENV infections has shown that under certain circumstances antibodies generated after exposure to natural infections can have detrimental effects. Although rare, antibodies elicited by some vaccine formulations have also been observed to exert detrimental effects.22 One example involves RSV, which causes bronchiolitis with high morbidity and mortality in the very young, especially in premature infants and those with chronic lung disease or congenital heart disease. Passive immunization with palivizumab, a neutralizing monoclonal antibody against the RSV fusion glycoprotein, prevents severe disease. However, in 1967, infants were administered a formalin-inactivated RSV (FI-RSV) vaccine, which did not protect but instead caused enhanced disease.23 On subsequent natural infection with RSV, many hospitalizations for severe disease occurred, as well as the deaths of 2 immunized toddlers. Autopsies revealed extensive peribronchiolar deposition of C4d, a marker of immune complex-mediated complement fixation. Mouse models of immunization and challenge showed that both complement and FI-RSV-elicited antibodies contributed to pathogenicity.24,25 Overall, these observations indicated that FI-RSV primes for a pulmonary Arthus reaction to promote enhanced RSV disease, as depicted in Figure 3. Additional studies in mice also showed that CD4 T cells, through their skewing away from a protective antiviral TH1 cytokine profile, also contributed to FI-RSV-mediated disease.24,25 These poor outcomes set back the field, and an effective vaccine against RSV has still not been achieved despite decades of work. Current efforts have shifted away from an inactivated virus vaccine strategy to a live virus/virus vector vaccine strategy. Finally, similar problems have been observed for a formalin-fixed measles vaccine formulation that was associated with severe atypical disease. It is believed that formalin denaturation of virus antigens and/or the adjuvants used impair the ability to make protective neutralizing
antibodies, thereby contributing to the deleterious effects. Thus, in these situations, immunological naivete appears relatively protective.

**EPSTEIN-BARR VIRUS**

By the time people reach adulthood, most have been infected by EBV. As with many other viruses, infection during childhood is usually asymptomatic or mild. However, infection during adolescence or adulthood often causes infectious mononucleosis, characterized by fever, lymphadenopathy, pharyngitis, and an increase in the peripheral blood of responding atypical mononuclear cells. Less frequently, hepatosplenomegaly and/or other complications (including hepatitis, cytopenias, myocarditis, or meningoencephalitis) can occur. On resolution of clinical disease, the virus remains in a latent state within memory B cells for the remainder of life, but can periodically re-emerge from latency if cell-mediated immunity is compromised. Impaired long-term control can lead to EBV-associated malignancies such as Hodgkin lymphoma and EBV-associated lymphoproliferative disease. In chronic active EBV, the virus can be driven to replicate within natural killer (NK) cells and T cells, contributing to development of aggressive NK- and T-cell lymphomas.

For control of EBV during primary infection, and for continued suppression to prevent virus reactivation, a robust immune response is required. Both NK cells and CD8 T cells, which kill virus-infected cells, as well as CD4 T cells producing cytokines that help regulate CD8 T cells and activated B cells that can serve as antigen-presenting cells to promote T-cell responses, are important for host defense against EBV. NK-T cells may possibly also contribute to host immunity. Adaptive immunity, in particular, is especially important for long-term control of EBV, as shown in patients who are immunosuppressed after organ transplantation who have increased risk of EBV-associated lymphoproliferative disease. In addition, many inherited primary immunodeficiencies with defective cellular function, including those that impair T-cell receptor signaling or T-cell costimulatory pathways, predispose to severe EBV disease.

Although robust T-cell immunity is crucial for control of EBV, studies of children with IEI have revealed that when dysregulated, unrestrained hyperactive T-cell responses can cause immunopathology. Such patients have a fulminant course of primary disease, characterized by hemophagocytic lymphohistiocytosis (HLH), bone marrow failure, and death unless hematopoietic stem cell transplantation is performed. Inherited mutations in genes responsible for this phenotype involve those important for interactions between T cells and (infected) B cells as well as those for optimal T-cell cytotoxicity. Defective killing of EBV-infected cells results in increased virus replication that stimulates other responses including production of proinflammatory and immunoregulatory cytokines such as IFN-γ, IL-6, TNF, and IL-10. This toxic “cytokine storm” provides rationale for immunosuppressant treatments and identifies targets for possible therapeutic intervention. For example, efficacy of anti-IFN-γ to treat HLH, which is most frequently caused by EBV, is currently being evaluated in a clinical trial. Thus, immunological maturity may function as a double-edged sword, conferring powerful antiviral effects but also deadly tissue-damaging effects.
VARICELLA-ZOSTER VIRUS

Similar to the situation with EBV, chickenpox is usually limited (to rash, fever, and malaise) in young children but is more severe in adolescents and adults, who before the adoption of widespread vaccination were found to have a higher rate of hospitalizations and complications such as varicella pneumonia, cerebellar ataxia or encephalitis, and even death. After resolution of primary disease, long-term control of latent VZV by T cells is important. When poorly controlled, virus reactivation occurs, leading to herpes zoster (shingles) with postherpetic neuralgia in the elderly. Furthermore, VZV is associated with vasculopathy and stroke in certain IEI characterized by impaired T-cell immunity such as DOCK8 deficiency. Although the potential contribution of immunopathological responses has not been well studied in adults with severe primary varicella disease, another possibility to consider is that immune immunity may appear protective due to a relative lymphocytosis in young children. This property accounts for a higher overall NK-cell cytotoxicity, which could contribute to overall stronger innate responses in the young. In addition, young children have higher numbers of plasmacytid dendritic cells (pDCs), which are important producers of antiviral type I IFN elicited during virus infections. Both NK cells and pDC have important roles in controlling VZV and other herpes group viruses, as shown by IEI such as GATA2 deficiency that lack these innate immune cells and which are associated with severe primary varicella or EBV infections.

Other IEI with defects in innate immunity have revealed that in children, mechanisms of virus sensing to activate type I IFN responses are critical for VZV immunity. Mutations in 2 genes, POLR3A and POLR3C, which encode for subunits of the RNA polymerase III (POL III), enhance susceptibility to severe VZV by impairing the ability of POL III to detect viral AT-rich DNA and trigger an effective IFN response. Interestingly, aging impairs TLR9-dependent DNA sensing for antiviral IFN responses. The mechanism involves an aging-related increase in reactive oxygen species (ROS) that interferes with downstream upregulation of IRF7 for signal transduction. When treated with an antioxidant, this defect could be reversed in aged pDCs. Together, these findings suggest another “upside” of immune immaturity, whereby an age-related increase in ROS directly damages antiviral immunity, increasing the susceptibility of the elderly to certain viral diseases.

SARS-CoV-2

SARS-CoV-2, which is responsible for the recent novel coronavirus pandemic (COVID-19), causes asymptomatic or mild infection in most exposed people. However, some individuals develop severe disease, characterized by pneumonia with profound hypoxemia, and complicated by acute respiratory failure or other end-organ damage, thromboembolic events, and death. Predisposing factors for severe disease include male sex, comorbid conditions (such as obesity and chronic pulmonary or cardiovascular disease), and older age. Interestingly, although children can be infected with SARS-CoV-2, they appear less susceptible to the severe clinical manifestations of COVID-19 disease. For example, in one French study, children were 25 times less likely to require hospitalization and 500 times less likely to die after contracting COVID-19 than adults. This apparent protection may in part be due to the less likely occurrence of comorbid conditions in children, as well as decreased expression in children of the angiotensin-converting enzyme 2 (ACE2) receptor for SARS-CoV-2 entry into and infection of cells.

The generally milder disease course and better outcome in children acutely infected with SARS-CoV-2 is similar to that previously seen for the related SARS-CoV. A retrospective review of cases during the SARS outbreak that ended in 2003 revealed that in addition to the fewer pediatric cases than expected, symptoms in children were generally less or nonspecific, supplemental oxygen or intensive care unit admission was less frequently required, and no fatalities were observed. In comparison, experience with Middle East Respiratory Syndrome coronavirus (MERS-CoV) infections in children has been limited, although disease in children also seems less severe unless comorbidities are present.

Curiously, however, weeks after an often asymptomatic or mild SARS-CoV-2 infection, when there is little or no detectable virus, a minority of children can develop a life-threatening hyperinflammatory condition termed multisystem inflammatory syndrome in children (MIS-C). MIS-C resembles Kawasaki disease or toxic shock syndrome. It is characterized by fever, elevation of systemic inflammatory markers such as C-reactive protein (CRP) and IL-6, prominent gastrointestinal symptoms, cardiovascular involvement (such as myocarditis, coronary artery dilatation, and cardiogenic shock), skin and mucous membrane involvement, but relatively little respiratory involvement. Treatment includes immunomodulators such as IVIG and corticosteroids standardly used in Kawasaki disease, as well as IL-6- or IL-1-receptor antagonists.

The delayed MIS-C presentation in children can be contrasted to acute presentations in some severely affected adults, who can exhibit hyperinflammation manifesting either as disproportionate and prolonged worsened pulmonary inflammation, or in a biphasic pattern characterized by a brief period of improvement followed by worsened pulmonary inflammation with respiratory decline. The hyperinflammation can extend beyond the lung, resulting in vascular complications affecting multiple organs with elevated systemic markers such as CRP, cytokines (IL-1β, IL-6, TNF, and others), and chemokines drawing in both innate and adaptive immune cells. Altogether, patients can develop a cytokine storm similar to what is seen in the related condition macrophage activation syndrome. Immunomodulators directed against various cytokine and corticosteroids to tamp down the cytokine storm have been used and are currently undergoing clinical trials to assess for efficacy. Similar hyperinflammatory responses have also been observed for SARS-CoV and MERS-CoV.

The delayed timing of MIS-C, when compared with the earlier timing of hyperinflammatory responses during acute SARS-CoV-2 infection in adults, suggests that severe COVID-19 disease in either age group reflects in large part hyperactivated adaptive immunity. This could occur regardless of any other nonimmune factors that may also cooperatively contribute to disproportionately severe disease outcome in adults. The hyperactivated adaptive immunity may be more likely to occur earlier and more often in adults due to cross-reactive T cells previously elicited by past exposure to seasonal coronaviruses. The data do not address whether these cross-reactive T cells are more likely to be pathogenic versus protective. Whether ADE contributes to COVID-19 disease pathogenesis has also not been determined, although this could be a potential complication of convalescent plasma.
In addition, and somewhat surprisingly, the immune cell hyperactivation may be caused by impaired innate immunity that in turn disrupts immunoregulation normally mediated by antiviral type I IFNs. Recent mouse models of experimental SARS-CoV-2 infection, similar to results in mouse models of experimental SARS-CoV and MERS-CoV infections, support this concept. Impaired type I IFN responses were shown to lead to inappropriate recruitment of myeloid cells into the lung with proinflammatory effects contributing to immunopathology. In humans with SARS-CoV-2 infection, critical illness is similarly associated with defective type I IFN production, increased inflammatory cytokines, and increased critical illness with variable effects on virus load. Recently, we have identified genetic defects in type I IFN signaling genes, as well as autoantibodies against type I IFNs that phenocopy the former, which can account for the defective type I IFN production during life-threatening critical acute COVID-19 infection of some adults. Interestingly, many of these defects were found in older people who had no prior history of severe infections to other viruses, suggesting that increased pathogen virulence and comorbidities may also contribute to outcome. Because autoantibodies generally increase with age, this phenomenon may also contribute to the apparent protection against COVID-19 disease with immune immaturity. Together, these findings lead to a model of disease pathogenesis as depicted in Figure 4. Similarly, identifying IEI in children with MIS-C may additionally help provide insights into disease pathogenesis associated normally with overlapping hyperinflammatory adult presentations.

CONCLUSIONS

Epidemiological observations have shown that children tend to fare better than adults when challenged by certain common viruses including EBV and emerging viruses such as SARS-CoV-2. Because maturation of adaptive immune responses—which proceeds as children age—is crucial for optimal control of virus infections, these examples, perhaps counterintuitively, point to underappreciated aspects of how the immune system interacts with microbes within the body to determine clinical outcome. Unraveling these complexities at a mechanistic level has revealed that adaptive immunity is not always protective, but can sometimes itself cause excessive tissue damage. Furthermore, accumulating evidence indicates that defects in innate immunity, which is normally strongest in young children, can not only compromise the ability to limit virus replication, but can also dysregulate adaptive immune responses to cause disease. Altogether, these and additional insights are being advanced by studying humans with rare IEI. Nevertheless, it should be acknowledged that considerable challenges remain in trying to tease apart age-dependent changes in the immune system from normal age-related physiological changes in other tissues, including other confounding factors such as preexisting medical conditions associated with increasing age. Further research is
needed to better understand their relative contributions to clinical outcome for virus infections in the young versus older individuals.

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