MINIREVIEW

Dengue in infants: an overview

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Received 13 February 2010; accepted 9 March 2010.
Final version published online 14 April 2010.
DOI:10.1111/j.1574-695X.2010.00670.x

Editor: Peter Timms

Keywords
dengue virus; dengue haemorrhagic fever; pathogenesis; antibody-dependent enhancement; cytokine tsunami; regulatory T cell.

Abstract

Dengue virus (DV) infection causes either a benign syndrome, dengue fever, or a severe syndrome, dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS), that is characterized by systemic capillary leakage, thrombocytopaenia and hypovolaemic shock. DHF/DSS occur mainly due to secondary infection by a heterotype DV infection in children and adults but in infants even primary infection by DV causes DHF/DSS. Clinical manifestations of DHF/DSS are more significantly associated with death in infants compared with older children. Vertical transmission of DV and anti-DV IgG has been well reported and is responsible for the pathogenesis of DV disease and its manifestations in infants. The complex pathogenesis of DHF/DSS during primary dengue in infants, with multiple age-related confounding factors, offers unique challenges to investigators. Dengue in infants is not often studied in detail due to practical limitations, but looking at the magnitude of DHF/DSS in infants and the unique opportunities this model provides, there is a need to focus on this problem. This paper reviews existing knowledge on this aspect of DV infection and the challenges it provides.

Introduction

Dengue viruses (DV) occur as four antigenically related but distinct serotypes transmitted to humans by Aedes aegypti mosquitoes. These viruses generally cause either a benign syndrome, dengue fever (DF), or a severe capillary leakage syndrome, dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) (Basu & Chaturvedi, 2008). DV affects humans of all age groups, worldwide. In some parts of the world it is mainly a paediatric public health problem, whereas in others such as Thailand dengue in infancy is also a serious medical concern (Pancharoen & Thisyakorn, 2001). Infant DHF/DSS was first reported in 1970 (Halstead et al., 1970). DHF/DSS occurs in infants < 1 year of age born to dengue-immune mothers and in children 1 year and older who are immune to one serotype of DV and are experiencing infection with a second serotype. In Asia, dengue disease predominantly affects children, in whom it is among the 10 leading causes of hospitalization and death (Halstead et al., 2002). Infants represent 5% of children hospitalized with DHF in Thailand (Pancharoen & Thisyakorn, 2001), Vietnam (Chau et al., 2008), Myanmar (Halstead et al., 2002), Indonesia (Graham et al., 1999), Sri Lanka (Lucas & Mendis, 2001) and India (Kabilan et al., 2003). Approximately one-quarter of these cases are DSS (Halstead et al., 2002; Kalayanarooj & Nimmannitya, 2003). In the Americas, the incidence of DHF is highest among infants in Venezuela (San Martín et al., 2010).

Prevalence of dengue disease in infants

Age-related differences have been identified in the prevalence of dengue diseases and their specific clinical manifestations. Infants are at high risk for DHF/DSS. In South East Asia, the age-specific incidence of infant DHF was 0.5 per 1000 persons over the age of 3–8 months, and it disappeared by age 9 months (Capeding et al., 2010). Data from the first published study to estimate age-specific dengue hospitalization rates for the Bangkok metropolitan area show that in 1964, the hospitalization rate for infants with DHF/DSS was twice that of children in Bangkok during the same year (Halstead et al., 1969). In a later report, infant DHF/DSS constituted 4.6–5.0% in Thai, Vietnamese, Myanmar and Indonesian infants and children hospitalized with DHF during 1995–1998 (Halstead et al., 2002). In Thailand, dengue in infancy (≤ 2 years of age) is a serious medical problem, constituting 7.7% and 2.9% (rates observed in two different hospitals) of DV infections (Pancharoen &
Thisyakorn, 2001). However, the death rate is low due to early diagnosis and prompt treatment (Witayathawornwong, 2001). Dengue in infancy has also been reported from Sri Lanka and India (Aggarwal et al., 1998; Lucas & Mendis, 2001). Dengue in infancy constituted 20% of total DV infections in an outbreak in Chennai, India. The major burden of DV disease lies in infants and children 5–9 years of age (Kabilan et al., 2003). Countries with a shorter or nonendemic history of DV circulation also report cases, principally in the adolescent and adult population. In countries where disease is endemic the distribution of the burden of disease is similar to that of DHF/DSS and/or severe clinical manifestations in both infants and children (da Cunha et al., 1995; Rahman et al., 2002). This difference may be due to variations in circulating DV serotype and strain or to changes in susceptibility to infection or enhanced disease due to immune status (Vaughn et al., 2000).

### Manifestations of dengue disease in infants

Dengue is a well-documented public-health burden in many developing countries. Any of the four serotypes of DV can cause a spectrum of outcomes in humans, ranging from asymptomatic infection to mild and clinically significant severe disease (DHF/DSS), which is characterized by systemic capillary leakage, thrombocytopenia and hypovolaemic shock (Table 1). The burden of severe illness lies predominantly in infants 4–9 months of age (Halstead et al., 2002). Severe clinical manifestations of DHF/DSS and DSS alone are more prevalent in infants, followed by children and then adults (Hammond et al., 2005). Manifestations such as convulsions and hepatic dysfunction more commonly affect infants than older children, and the fatality rate is four times higher in infants (Kalayanarooj & Nimmanitya, 2003). Only the frequency of internal haemorrhage increases with age, affecting one in seven adults (Hammond et al., 2005). The risk of presenting with signs of DHF/DSS by year of age was calculated and it was seen that infants and children aged 5–7 years are at significant risk for severe dengue, whereas in adults and adolescents 14 years and older, the risk is significantly less (odds ratio < 0.5) (Hammond et al., 2005). Haematocrit of < 30% is seen at a higher frequency among infants (infants < 35%; older children < 19.5%). Mean platelet count for infants (56 900 mm$^{-3}$) is significantly less than that for older children, and nearly 51.1% of infants have platelet counts of < 80 000 mm$^{-3}$ (Kabilan et al., 2003). Total white blood cell count and total lymphocyte count is significantly higher in infants than in children. Coryza, nausea/vomiting, rash, petechiae and other haemorrhagic manifestations are significantly higher in infants and younger children than in older children (Witayathawornwong, 2005). High-grade fever, hepatomegaly (Soundravally et al., 2010), rashes, oedema of the lower extremities, retro-orbital puffiness, vomiting and convulsions are commoner in infants than in older children (Kabilan et al., 2003). Infants with DHF/DSS present with some bleeding (87.5% of cases), cyanosis and ascites (37.5%) and shock (25%), as well as hepatomegaly (Martínez et al., 1993).

### Vertical transmission of DV

Transplacental transmission of DV has been reported either by virus isolation (Thaithumyanon et al., 1994) or by detection of viral nucleic acid (Phongsamart et al., 2008). Some researchers have demonstrated the presence of anti-DV IgM in sera of a newborn as documentary proof of vertical transmission of the virus (Fernández et al., 1994). DV infection during pregnancy poses significant risk to both mother and child, while maternal antibodies are not harmful to the foetus or newborn (Table 2). A recent report from Malaysia (Chin et al., 2008) reported vertical transmission of acute dengue. A subject delivered a normal term baby girl

| Findings                        | Reference(s)         |
|--------------------------------|----------------------|
| High death rate                | Kalayanarooj & Nimmanitya (2003) |
| DHF/DSS                        | Hammond et al. (2005), Kabilan et al. (2003), Martínez et al. (1993), Witayathawornwong (2005) |
| Thrombocytopenia               | Poli et al. (1991), Kabilan et al. (2003), Witayathawornwong (2005) |
| Raised total leucocyte count   | Hammond et al. (2005), Kabilan et al. (2003), Witayathawornwong (2005) |
| Lymphocytosis                  | Hammond et al. (2005), Kabilan et al. (2003), Witayathawornwong (2005) |
| Severe clinical manifestations | Hammond et al. (2005). |
| (shock, plasma leakage, internal haemorrhage) | Witayathawornwong (2005) |
| Cynosis                        | Martínez et al. (1993) |
| Convulsion                     | Kabilan et al. (2003) |
| Hepatic dysfunction and hepato-megaly  | Kabilan et al. (2003), Soundravally et al. (2010) |
| Splenomegaly                   | Hammond et al. (2005), Kabilan et al. (2003) |
| Ascites                        | Martínez et al. (1993) |
| Nausea/vomiting                | Kabilan et al. (2003) |
| Rash/petechiae                 | Kabilan et al. (2003), Witayathawornwong (2005) |
| High-grade fever               | Kabilan et al. (2003), Martínez et al. (1993), Witayathawornwong (2005) |
| Oedema of lower limbs          | Kabilan et al. (2003), Martínez et al. (1993) |
| Retrobulbar puffiness          | Kabilan et al. (2003), Martínez et al. (1993) |
| Coryza                         | Witayathawornwong (2005) |
by spontaneous vaginal delivery and recovered uneventfully without peripartum haemorrhage despite the presence of thrombocytopenia. The baby girl developed low-grade fever on day 4 and except for the transient thrombocytopenia, recovered uneventfully following 3 days of mild illness (Chin et al., 2008). Presentation in infants can be mild, i.e. mild fever subsiding after 1 week uneventfully to hepatomegaly, thrombocytopenia and coagulopathy, or can involve bleeding disorder, respiratory distress, DHF/DSS and death. Clinical features of neonatal DV infections show that fever and vasomotor problems (blotches) are the dominating traits followed by hepatomegaly, thrombocytopenia and coagulopathy, or can involve bleeding disorder, respiratory distress, DHF/DSS and death. Antibodies produced by DV infections can be divided into (1) type-specific neutralizing antibodies, (2) cross-reactive non-neutralizing antibodies and (3) cross-neutralizing antibodies.

Table 2. Foetal risks and dengue disease in pregnancy

| Associated risks         | References                                |
|--------------------------|-------------------------------------------|
| DHF/DSS                  | Poli et al. (1991), Chye et al. (1997), Chong & Lin (1989) |
| Stillbirth/death         | Poli et al. (1991), Chye et al. (1997), Carles et al. (1999) |
| Thrombocytopenia         | Poli et al. (1991), Chin et al. (2008), Chye et al. (1997) |
| Low-grade fever          | Poli et al. (1991), Chin et al. (2008), Chye et al. (1997) |
| Hepatomegaly             | Poli et al. (1991), Chye et al. (1997) |
| Splenomegaly             | Kabilan et al. (2003)                      |
| Coagulopathy             | Poli et al. (1991), Chye et al. (1997) |
| Bleeding disorder        | Poli et al. (1991)                         |
| Respiratory distress     | Poli et al. (1991)                         |
| Vasomotor dysfunction    | Poli et al. (1991)                         |
| Sepsis-like illness      | Restrepo et al. (2003), Phongsamart et al. (2008) |
| Low birth weight         | Restrepo et al. (2003)                     |
| Premature birth          | Restrepo et al. (2003)                     |
| Foetal distress          | Restrepo et al. (2003)                     |
| Nonassociated risks      |                                          |
| Peripartum haemorrhage   | Chin et al. (2008)                        |
| Teratogenic effect       | Chong & Lin (1989), Carles et al. (1999)   |
| Abortion                 | Chong & Lin (1989), Carles et al. (1999)   |
| Intrauterine growth retardation | Chong & Lin (1989), Carles et al. (1999)   |
| No long-term sequelae    | Phongsamart et al. (2008)                 |

Antibody response during DV infection

DV genome is a single-stranded positive sense RNA which is translated as a single polyprotein that is cleaved by proteases of viral and host origin, to yield 10 viral proteins including the C and M proteins, the E glycoprotein, and seven nonstructural proteins (NS1, NS2A/B, NS3, NS4A/B, NS5). The antibody and T-cell responses to individual viral proteins are variable. Anti-E antibodies are the main response against DV that inhibit viral binding to cells, neutralize viral infectivity in vitro, protect mice from DV challenge on passive transfer and show a variable degree of cross-reactivity among the DV serotypes. Antibodies against NS1 can trigger complement-mediated lysis of DV-infected cells in vitro and protect mice from DV challenge.

Antibody-dependent enhancement (ADE) of DV infection

Antibodies produced by DV infections can be divided into (1) type-specific neutralizing antibodies, (2) cross-reactive non-neutralizing antibodies and (3) cross-neutralizing antibodies.
antibodies among the four DVs (Kurane & Takasaki, 2001; Stephenson, 2005). The cross-reactive, non-neutralizing antibodies remaining from earlier heterogeneous DV infection enhance the cellular uptake of DV and enhance the infection. They are also called enhancing antibody and cause ADE of infection (reviewed by Chaturvedi et al., 2005).

DHF occurs almost exclusively in two settings: (1) children and adults who become infected with a second DV serotype after an initial ‘primary’ DV infection with a different serotype, and (2) infants with primary DV infections whose mothers have some DV immunity. The ADE model suggests that in individuals who develop DHF, although there are some antibodies against DV in their blood, these antibodies do not neutralize the virus, but rather they bind to it and enhance its uptake by certain Fc receptor-bearing monocytes/macrophages, thus increasing viral burden that results in more severe disease (reviewed by Halstead, 2003, 2009).

Secondary infections cause 40 times more DHF cases than primary infections. Neutralizing antibodies can reduce viraemia levels, whereas cross-reactive non-neutralizing (enhancing) antibodies may increase them. Individuals once infected with one serotype of DV are usually protected from subsequent infection with the same serotype (homotypic infection) (Halstead, 2003). Cross-protection against infections with different serotypes (heterotypic infection) is only shown in the short term following infection. A report shows that some individuals who had neutralizing antibodies against DV2 developed symptoms upon infection with DV2, suggesting that neutralizing antibodies do not always work for protection from the subsequent homologous infection (Endy et al., 2004). Neutralizing antibody is important for protection against DV infection, as passive transfer of polyclonal and monoclonal (MAbs) neutralizing antibodies can confer protection from lethal challenge in a murine model (Chaturvedi et al., 1977, 1978).

One study reported that enhancing antibodies do not correlate with viraemia level (Laoprasopwattana et al., 2005). It has been demonstrated that all MAbs showing enhancing activities also show neutralizing activities. Addition of commercial rabbit complement or fresh human sera into the ADE assay systems abolishes the enhancing activities of all MAbs (Yamanaka et al., 2008). The complement component C1q restricts ADE by antiflavivirus antibodies in an IgG subclass-specific manner in cell culture and mice. IgG subclasses that bind C1q avidly induce minimal ADE in the presence of C1q, whereas subclasses that bind C1q weakly enhance infection (Mehlhop et al., 2007). The site of attachment of antibody to DV may be a determinant of ADE. Humanized MAbs directed at the fusion loop near the junction of domain I and II of the DV2 envelope protein enhance DV4 viraemia in rhesus monkeys (Goncalvez et al., 2004, 2007), while the domain III antibodies mediate neutralization and protection functions (Pierson et al., 2008).

DV infection of THP-1 cells via ADE suppresses nitric oxide radicals, by disrupting the transcription of the iNOS gene transcription factor, IRF-1, and blocking the activation of STAT-1. It also suppresses the transcription and translation of interleukin (IL)-12, interferon (IFN)-γ and tumour necrosis factor (TNF)-α, while the expression and synthesis of the anti-inflammatory cytokines IL-6 and IL-10 are enhanced. Thus, besides facilitating the entry process, DV infection via ADE also alters innate and adaptive intracellular antiviral mechanisms, resulting in unrestricted DV replication in THP-1 cells (Chareonsirisuthigul et al., 2007). This is similar to the decreased nitric oxide and increased IL-10 blood levels seen in DHF patients (Ubol et al., 2008; Chaturvedi & Nagar, 2009). Furthermore, DV infection of the FcR-bearing mast cell/basophil KU812 cell line through ADE results in a massive induction of apoptosis (Brown et al., 2009). The abundance of IFN type I gene transcripts in peripheral blood mononuclear cells from Vietnamese DSS patients was lower than in those from DHF patients without shock (Simmons et al., 2007b). The role of ADE in DHF/DSS is summarized in Fig. 1.

**Maternally derived anti-dengue IgG in infants**

The role of maternal dengue-specific antibodies in the development of DHF/DSS caused by DV2 in infants was reported by Kliks et al. (1988). Evidence of DV infection and very low geometric mean titres against all dengue serotypes in children at 6 months of age and beyond was demonstrated. DV infection rates increase from 12 months of age
onward. Maternal IgG antibodies are known to cross the placental barrier, providing protection to newborns against infections. Antibody titres in newborns are proportional to maternal antibody level (Perret et al., 2005). The first report of dengue antibodies crossing the placental barrier in humans was that of Ventura et al. (1975), but these antibodies were not suspected to sensitize infants to DHF/DSS. Cord blood leucocytes from neonates with maternal dengue antibody supported DV2 replication in vitro; those from neonates without maternal antibody did not. Marchette et al. (1979) reported that cord blood of infants born to dengue-immune mothers contained a potent enhancing factor, which gradually decayed with age and which was absent from neonates born to nonimmune mothers. This supported the hypothesis that severe primary DHF with shock seen in Bangkok infants is related to maternal immune status (Marchette et al., 1979).

**ADE and DHF in infants**

DHF in children and adults is typically associated with secondary infection caused by a DV serotype distinct from that present when an individual is first exposed to DV (Graham et al., 1999). In contrast, DHF occurs in primary DV infections in infants born to dengue-immune mothers (Simmons et al., 2007a). The bimodal age distribution of DHF was one of the earliest clues that alerted researchers to the immune enhancement theory. The age peaks occur at 7 months and 3–5 years. Children with secondary infections and DHF have higher initial plasma viral loads (Wang et al., 2006).

Kliks and colleagues’ investigation of DHF in infants found that maternal dengue 2 neutralization antibody titre and age of the infant were strongly correlated. The actual age at which DHF/DSS occur in infants correlates with the age at which maximum enhancing activity for dengue infection in mononuclear phagocytes is predicted. This critical time for the occurrence of DHF/DSS was observed to be approximately 2 months after the time calculated for maternal dengue-neutralizing antibodies to degrade below a protective level. In addition, sera of mothers of infants with DHF/DSS enhanced DV infection to a slightly greater degree than did sera from mothers of infants with pyrexia of unknown origin and toddlers with DHF/DSS. This showed that maternal dengue antibodies play a dual role by first protecting and later increasing the risk of development of DHF/DSS in infants who become infected by dengue 2 viruses (Kliks et al., 1988). At birth, maternal antibodies protect infants from dengue infection. As IgG antibodies are catabolized, a period of risk to enhanced infection ensues, followed in turn by the loss of enhancing antibodies and a corresponding decline in risk for DHF/DSS (Kliks et al., 1988, Fig. 2). Enhancement of infant infection by cord blood antibodies is also described in naturally infected kittens born to queens immune to feline infectious peritonitis virus (Horzinek & Osterhaus, 1978).

Maternal dengue antibody decay has been studied. A 1-year follow-up period reported that maternal haemagglutination inhibition antibodies against DV disappear by the age of 9 months in 99% of cases (Watanaveeradej et al., 2003). In another study, 13% of 9-month-old infants still had lower titres of neutralizing antibody against at least one DV serotype. One infant had undifferentiated febrile illness due to DV2 infection 6 weeks after having been seen to have neutralizing antibodies against all four serotypes (Pengsaa et al., 2003). In healthy Vietnamese infants, there was a strong temporal association between the Fc-dependent, DV infection-enhancing activity of neat plasma and the age-related epidemiology of severe dengue. A prospective, nested case-control study of primary DV3 infections during infancy has shown a full range of disease severity (Libraty et al., 2009). Disease severity in infants with primary infections is associated with a robust immune response, possibly as a consequence of higher viral burdens in vivo (Chau et al., 2008). Total IgG and DV-reactive IgG were higher in cord plasma than in the mother’s plasma. Maternal DV-neutralizing and E protein-reactive IgG titres decline to below measurable levels in > 90% of infants by 6 months of age, while DV-reactive IgG with whole DV virions persist until 12 months of age in 20% of infants. DV infection in infants is frequently subclinical but there is a window between 4 and 12 months of age where virion-binding but non-neutralizing IgG could facilitate ADE (Chau et al., 2009). DV-infected cells release a high proportion of immature prM-containing virions that lack the ability to infect cells. However, they become highly infectious upon interaction with prM antibodies. During a secondary infection or primary infection of infants born to dengue-immune mothers, immature particles have the potential to be highly infectious and hence may contribute to the development of severe disease (Rodenhuis-Zybert et al., 2010).

**Cellular immunity and DV infection**

The cellular immune response is a coordinated differentiation of heterogeneous populations of antigen-specific T cells (both CD4 and CD8) that effectively eradicate pathogens and provide protection against reinfection. Antigen-exposed T cells have been identified as three subsets: short-lived effector T cells, central memory T cells (Tcm) and effector memory T cells. The early delineation of these cells is regulated through specific transcription factors and cytokines; the latter are also responsible for the maintenance of Tcm cells. The heterogeneity of CD 4 T cells that play a role in DV infection is summarized in Fig. 3.
Little is known about the generation of the T-cell pool in healthy children. Normally, peripheral blood naive T-cell numbers are high in newborns and decline with increasing age, while memory T-cell numbers appear less dependent on age. It has been shown that during foetal life, mature T-cell responses can be elicited by viral and parasite infections (King et al., 2002; Marchant et al., 2003). T cells capable of producing IFN-γ increase progressively with age (Härtel et al., 2005). A significant age correlation has been observed in the expression/release of IFN-γ, IL-2, IL-4 and TNF-α. The mRNA levels of these cytokines increase from the neonatal period to infancy. The expression of IL-5 and IL-10 is usually not correlated. The expression of IL-12 in monocytes is also age-correlated (Härtel et al., 2005). Schönland et al. (2003) have suggested that increased T-cell division in young mice and children may be driven by high IL-7 levels, other growth factors and antigen exposure in the first year of life. The physiological immaturity of the immune system at birth has been attributed to the prevalence of suppressor factors during foetal life and antigenic naivety. The regulatory T cells (Treg) consist of a heterogeneous collection of cells that have the ability to suppress the activation and proliferation of other T cells and the immune response as a whole. Treg cells can inhibit protective antiviral responses and enhance disease progression. These cells can block T-cell activation, limiting viral replication as well as consequent immunopathology. Furthermore, inhibition of antiviral T-cell responses by Treg cells could lead to viral persistence and more rapid disease progression (reviewed by Chaturvedi et al., 2007). Treg cells are known to be present at higher frequency during human foetal ontogeny (Cupedo et al., 2005) and may be important in the context of perinatal infection.

**Role of T cells in DV infection of infants**

Cellular immune responses in infants with DV infection have not been well studied. Dengue immunopathogenesis has focused on the sequential DV infection phenomenon, suggesting that severe disease results from amplified cytokine release caused by dengue infections occurring in the presence of T-cell memory (Rothman & Ennis, 1999). This model cannot explain DHF/DSS during a first dengue infection (Fig. 4). Plasma levels of cytokines/chemokines are generally higher in infants with DSS. Antigen-driven inflammatory cytokine release is hypothesized to contribute to dengue capillary-leakage syndrome. Chemokine expression may be an early event in dengue and might play a role in immunopathogenesis. The concentrations of cytokines...
(IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNF-α) and chemokines (IP-10, MCP-1, MIG and RANTES) in plasma samples from (except that of RANTES) infants with DSS are high. This is consistent with a relationship between the magnitude of immune inflammation and capillary leakage (Chau et al., 2008). [Correction made on 23 April after online publication: IL-10 corrected to IP-10 in this paragraph.] Plasma levels of IP-10 correlate with viraemia, and RANTES and MIG correlate with hepatic dysfunction during acute primary dengue in infants. Plasma levels of other cytokines or chemokines in infants are not significantly correlated with viral loads, NS1 levels or other measures of disease severity including thrombocytopenia, haematocrit and dengue disease grade. In infants, IP-10 is significantly correlated with plasma DV loads in the same sample. IP is expressed by hepatocytes in DV-infected mice and promotes infiltration of natural killer cells into hepatic tissue (Chen et al., 2006). IP-10 and DV appear to compete for attachment to heparin sulphate on the cell surface, suggesting that IP-10 might have anti-DV activity beyond its immunological properties (Chen et al., 2006). Plasma levels of RANTES and MIG are associated with liver transaminase levels, which may suggest a relationship between hepatic dysfunction and these chemokines, activities of which include the recruitment of lymphocytes to sites of infection. DHF in secondary infections is also associated with both significantly greater plasma concentrations of inflammatory cytokines (Chaturvedi et al., 2000; Juffrie et al., 2001) and increased frequencies of activated lymphocytes, compared with those in patients with milder disease (Mongkolsapaya et al., 2003), presumably in response to higher viral burdens in DHF.

Cellular immune activation is associated with dengue severity during primary infection of infants as well as during secondary infection of older children (Juffrie et al., 2001). The concept of antigen-driven immune activation in infants is consistent with observations in older children with secondary infection, in whom relatively high early viraemia levels and robust activation of lymphocytes and inflammatory cytokine responses have been found to be associated with disease of greater severity (Juffrie et al., 2001). Infants with primary acute DHF show a significant positive association between dengue severity and markers of lymphocyte activation (Chau et al., 2008). NS3133/C0142-specific CD8+ cells may play a role in the immunopathogenesis of...
secondary infection, where responses can be expected to be earlier and dominated by robust serotype-cross-reactive responses, although these cells contribute little to the resolution of viraemia or immunopathogenesis in infants with primary dengue (Mongkolsapaya et al., 2003).

Pathogenesis of DHF/DSS in infants

The findings described here indicate that maternally derived DV-reactive IgG determines the viral load and the pathogenesis in infants through ADE. Infection with DV through ADE inhibits induction of iNOS/nitric oxide and IFN-γ in dendritic cells/macrophages. In several studies, increased susceptibility of newborns to various infections has been attributed to a deficient secretion of IFN-γ (reviewed by Hartel et al., 2005). Treg cells can suppress protective antiviral responses and accelerate disease progression. On the other hand, they can block T-cell activation, thus limiting viral replication and activation-associated immunopathology. It is interesting to note the findings of Simian immunodeficiency virus (SIV) infection in infant macaque monkeys that have a large number of highly suppressive Treg cells. These cells directly inhibit the CD4+ T-cell response to SIV, which is associated with a transient CD8+ T-cell response and limited antibody production (Hartigan-O’Connor et al., 2007). Suppressor T cells are known to be present in both mice and humans infected with DV (Tandon et al., 1979; Chaturvedi, 1984; Chaturvedi et al., 2007; Lühn et al., 2007). Similar mechanisms may work in infant patients with DHF/DSS, which may partly explain the vulnerability of human infants to DV infections. High viral burden in vivo may elicit consequent immune activation, which may be associated with disease severity and may contribute to dengue-related vasculopathy. In this situation, the burden of viral antigen and the magnitude of the immune response are important determinants of the clinical response. It has been suggested that high peak viraemia is necessary but not sufficient to cause plasma leakage; memory DV-specific T cells induced during a primary DV infection are reactivated by the heterologous viral serotype during a secondary infection to expand to high levels and produce a skewed cytokine profile (Rothman, 2009), resulting in a cytokine tsunami (Chaturvedi et al., 2007; Chaturvedi & Nagar, 2009). During pregnancy, small number of various types of cells are transferred between the mother and the foetus via the placenta or breast-feeding (Zhou et al., 2000). They include maternal erythrocytes, platelets, granulocytes and lymphocytes (Desai & Creger, 1963). Mold et al. (2008) have reported that substantial numbers of maternal cells cross the placenta to foetal lymph nodes, inducing the development of CD4+CD25+FoxP3+ Treg cells that suppress foetal antimaternal immunity and persist at least until early adulthood. Furthermore, Michaëllson et al. (2006) have reported that foetal T cells are highly responsive to stimulation in the absence of Treg cells. It is worth investigating whether DV-specific memory cells also cross the placenta, and if so whether in sufficient numbers to initiate a cytokine tsunami. Several other explanations may be offered for faster disease progression in infants. This may be due to a lower intensity of adaptive T-cell responses resulting in unrestricted viral replication as the infants have lower frequencies of antigen-specific T helper (Th) cells with a Th2 cell bias. Furthermore, infant dendritic cells express lower levels of the major histocompatibility complex and adhesion molecules, their ability to produce IL-12 is lower and due to the limited expression of adaptor proteins and the limited activation of downstream signalling molecules the responses to Toll-like receptor ligation are reduced. This may compromise the priming of the T-cell response to DV in infants (Table 3).
Conclusions and future perspectives

A large body of data suggests that DHF/DSS occurs during secondary dengue infections in adults and children and that the main inducers in this situation are ADE and memory T cells. The situation in infants is complex as DHF/DSS may accompany primary DV infection; the maternally derived specific IgG may be present but are memory T cells also present? It is not known how DV infection influences T-cell dynamics in infants. The complex pathogenesis of DHF/DSS during primary dengue in infants, with the confounding differences in age-related vascular physiology and immunological maturity, maternally derived memory cells and overwhelming Treg response, offers a unique challenge to investigators. The results in infants may not be directly applicable to older children/adults with secondary infections. Reduction of the viral burden by antiviral drugs or suppression of immune activation may help to improve clinical outcomes in infants (and also in children and adults) with dengue. Further studies will show whether interference with the regulatory control of CD4+ T cells can assist in control of dengue disease. Newer strategies are needed for the prevention and treatment of DHF/DSS. The magnitude of DHF/DSS in infants and the uniqueness of this model provide immense challenges for understanding pathogenesis. There is need to focus more attention on dengue disease in infants.

Acknowledgements

U.C.C. is grateful to the Indian National Science Academy, New Delhi, for financial assistance as an INSA Honorary Scientist, and Dr Rachna Nagar for help with the preparation of this manuscript. We declare no conflict of interest.

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