

# Neonatal Sepsis in the Very Low Birth Weight Preterm Infants: Part 1: Review of Patho-physiology

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## Abstract

*Background:* Over the last fifty years neonatal care has made tremendous progress; increasing survival, reducing morbidity, developing newer modalities of care and therapy for the very low birth weight (VLBW) and premature infant. However, mortality from neonatal sepsis in this group of infants has remained between 18-20% in the developed world and around 80% in the developing world for last three decades with little sign of decline. There is also clear evidence that VLBW infants who survive infection in the neonatal period are at significantly greater risk of neuro-developmental delay; making sepsis the most important cause of mortality and morbidity in this group of infants today.

*Objective:* The objective of this review is to highlight the reasons for this lack of success in combating neonatal sepsis successfully. These can be attributed to four main reasons: 1) poor host defences, 2) clinician's inability to diagnose sepsis early and accurately [due to lack of or general availability of highly sensitive and specific markers], 3) clinician's poor understanding of the 'process' i.e.

*patho-physiology of neonatal sepsis, thus not being able to institute early 'goal' directed therapy, and 4) total reliance on killing the pathogen(s) with inadequate attention to correcting the consequences of the inflammatory process itself.*

*This review presents a brief epidemiological background to neonatal infections in the VLBW infants, discusses host defence systems and how immune compromised VLBW infant combats infection by describing the patho-physiological 'process' of sepsis in detail. It is our belief that understanding the heterogeneity and complexity of host response and the defence systems is fundamental in formulating management strategies.*

*Conclusion:* By discussing patho-physiology, current available diagnostic tests and presenting an evidence based management 'care bundle' it is hoped to change clinician's paradigm to use more immune and molecular markers for diagnosis and monitoring of the infection process and in management considering adjunctive therapies that boost host defences.

*It is recognised that while this review is static i.e. it presents evidence as we understand it today, sepsis is a dynamic process. Our understanding, ability to diagnose and manage neo-natal sepsis is constantly changing and will continue to change and evolve. By presenting this review it is hoped that over a period of time more of our practices would become evidence based and dogma abandoned.*

**Keywords:** Neonatal sepsis, patho-physiology, diagnosis, management, very low birth weight infant (VLBW).

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## Introduction and Background

Neonatal sepsis remains the unconquered frontier of modern neonatal medicine today, despite advances in knowledge, technology and therapeutic armamentarium available. Blood stream infection rates in hospitals (in the

developed world) range from 10-25% for all neonates to around 50% in preterm very low birth weight (VLBW) infants.<sup>1,2</sup> Exact figures for the developing world are not known but are considerably higher. World Health Organisation estimates that of the four million neonatal deaths all over the world every year, over 35% are due to infection in the neonatal period;<sup>3</sup> this translates to approximately two deaths per minute! Whilst most of these deaths take place in the developing world where mortality from sepsis may be as high as 85%, in the developed world neonatal mortality from sepsis has remained around 20% for nearly three decades.

This two part review deals with babies born weighing 1500 Grams or less or earlier than 32 weeks of gestation who have the highest rate of mortality and twenty times greater chance of developing infection (often multiple) between birth and first month of life.<sup>4,5</sup> Though under reporting is common, prevalence of confirmed neonatal bacterial infection and or meningitis is reported to be between 1-5/1000 live births but in the preterm and VLBW infants it maybe as high as 1/230 live births.<sup>6</sup> Blood stream infections rates in neonates range from 40% in the community and 10-25% of those admitted to hospital for all neonates and up to 50% in extremely preterm infants.<sup>1</sup> Whilst overall gestation specific survival has consistently improved over the years, mortality from neonatal sepsis in the VLBW infants has not declined from 18-20% for the last three decades in UK, USA or Australia.<sup>7</sup> Worryingly Barbara Stoll *et al.*<sup>8</sup> in a study of over 6000 infants weighing 1000 Grams or less have confirmed earlier studies.<sup>9-11</sup> that VLBW infants who survive at least one proven sepsis episode in the neonatal period have 30-80% increased odds for neuro-developmental impairment and a 30-100% increase in odds for poor head growth (an indirect reflection of poor neurological development) at 18-22 months. This is also true for infants with Coagulase Negative Staphylococcus (CONS) or culture negative sepsis hitherto thought to be benign due to low mortality

but who show similar poor neuro-developmental outcome at 18-22 months.

High incidence of both suspected early onset sepsis (EOS) {within 72 hours of birth} and late onset sepsis (LOS) {infection after 72 hours of birth} and high levels of mortality and morbidity has led to over 50% of VLBW infants being investigated and treated with antibiotics.<sup>5</sup> Escobar and colleagues<sup>12</sup> have estimated that in United States alone as many as 600,000 infants are screened to 'rule out' sepsis while an estimated 130,000-400,000 are treated with antibiotics every year though less than 20,000 actually have proven infection!! This is a serious concern; because it not only promotes development of resistant bacterial flora but also increases length of hospital stay and care of cost.

Newborn infants are normally colonised within 48 hours to first few days after birth by both Gram-negative and Gram-positive organisms and *Candida* species, this process is much quicker if they require resuscitation at birth or are admitted to neonatal units. EOS most frequently is with organisms like *GBS*, *E.Coli*, *Staphylococcus aureus*, and *Klebsiella* species whilst LOS is mainly with coagulase negative staphylococcus (CONS), *Serratia* and *Citrobacter* species.<sup>4</sup> (Table 1).

Table 1. Most frequent bacteria causing neonatal infection

| From the Mother                 | From the Environment              |
|---------------------------------|-----------------------------------|
| (pre/perinatal)                 | (postnatal/nosocomial)            |
| <i>Escherichia coli</i>         | <i>Staphylococcus aureus</i>      |
| Group B streptococci            | <i>Staphylococcus epidermidis</i> |
| <i>Staphylococcus aureus</i>    | <i>Escherichia coli</i>           |
| <i>Streptococcus pneumoniae</i> | <i>Pseudomonas aeruginosa</i>     |
| <i>Listeria monocytogenes</i>   | <i>Serratia</i> species           |
| <i>Ureaplasma urealyticum</i>   | <i>Citrobacter</i> species        |
|                                 | <i>Enterobacter</i> species       |
|                                 | <i>Salmonella</i>                 |

It appears that worldwide Gram-negative sepsis is on the increase in VLBW infants,<sup>13</sup> in some reports accounting for more than half of EOS and one third of LOS.<sup>14,15</sup> It is well known that in developing countries Gram-negative infections form the bulk of both EOS and LOS,<sup>16</sup> but interestingly in a recent cohort of VLBW (< 1000 Grams) infants born at or before 28 weeks of gestation, *E.Coli* was the most common organism causing EOS in Norway.<sup>17</sup> Most infections occur in infants who have one or more of the known 'risk factors'.

We<sup>4,18,19</sup> and others have identified 'risk factors' that predispose VLBW infants to sepsis, these include; prolonged rupture of membranes (> 18 hours), presence of chorioamnionitis, repeated vaginal examination in labour, maternal urinary tract infection during pregnancy, need for resuscitation at birth, birth weight less than 1500 Grams and or gestation of or below 31 weeks. Other factors include umbilical catheterisation, long line insertion, total parenteral nutrition (TPN), poor hand washing practices, use of H<sub>2</sub> blockers and prolonged or un-necessary use of antibiotics.

Institution of continued surveillance policies in neonatal units have led to better understanding of pattern of sepsis in individual units and in neonatal networks but the critically important comprehensive understanding (*of host defences and the patho-physiology of the sepsis cascade*) is often not fully appreciated in formulating a management plan. This perhaps is the most important reason for continued high mortality and morbidity in neonatal sepsis.

We<sup>4</sup> have suggested the following as possibly the four main reasons for continued mortality and morbidity from neonatal sepsis;

- 1) Poor understanding of the host defences of the VLBW infant
- 2) Inability to diagnose sepsis accurately and early.
- 3) Imprecise understanding of patho-physiology of sepsis leading to inadequate ma-

agement strategies such as 'goal directed' therapy which has been successfully applied in adults with sepsis.

- 4) Total reliance on killing the infecting pathogen/s (with a particular 'course' of antibiotics) while paying little or inadequate attention towards correcting the consequences of the inflammatory process itself and/ or boosting host defence.

In first part of this review I shall discuss host defence mechanisms and patho-physiology of neonatal sepsis in detail. In part two we define sepsis and discuss how to investigate and manage sepsis in the VLBW infants according to current evidence concluding by suggesting a pragmatic 'care bundle'.

It should be made clear at the outset that though there are many commonalities between bacterial, viral and fungal infections in the newborn this review deals only with bacterial infection.

#### Host Defence in the VLBW Infant

Main function of the human defence system is to protect the host from invading pathogen/s. For this, the first line of defence are the physical barriers e.g. keratinised skin, mucus membranes and chemicals in the form of enzymes and other substances (e.g. secretory IgA) that inhibit bacterial adhesion to the host or have a direct anti-bacterial action. Epidermal barrier of the skin matures around 32-34 weeks of gestation accelerating rapidly after birth<sup>20</sup> this process can be accelerated by applying oil on premature skin.<sup>21</sup> Mucosal defence is largely dependent on the protective layer provided by secretory IgA (sIgA) that is low in pre-term VLBW infants<sup>22</sup> increasing with feeding of colostrum and in response to environmental factors by 2-5 weeks after birth.<sup>23</sup> Use of H<sub>2</sub> blockers and continuous naso-gastric feeding (common practice in neonatal care) increase gastric pH thus decreasing bacterial destruction and increasing the risk of infection.<sup>24</sup>

Apart from immunity acquired passively through the placenta there are two defence systems working conjointly that respond to

pathogen/s; 1) the innate immune system and 2) specific or the adaptive immune system. The innate immune system provides the initial immunological response and is responsible for induction of the secondary specific/adaptive immune response. Immune system in mammals develops from cells developed in the yolk sac, fetal liver and bone marrow. These cells then differentiate and proliferate to form components of the innate and adaptive/specific immune system.

### **Innate Immune System**

Role of the innate response is to provide for a smooth transition from the normally sterile intra-uterine environment to the antigen rich extra-uterine environment. Nearly all the cells of the haemopoietic system {granulocytes, macrophage, monocyte, dendritic cell and the natural killer (NK) lymphocyte} along with complement, cytokines and acute phase proteins are involved in innate immunity. This system is characterised by its immediate response, limited diversity, non-specificity and lack of immunologic memory. Pathogen recognition is dependent on pattern recognition through toll-like receptor (TLRs) found on cell surface. TLRs play a central role in recognising and helping the cell to engulf pathogen through 'pattern recognition', and activating other elements of the innate immune system. A number of TLR's have been identified that are specific for recognising bacteria, fungi and viruses.

#### *1a) Cellular Components of the Innate Immune System*

1) Macrophage is perhaps the most important cell in the innate immune system. It is derived from blood borne monocytes that first appear in foetal liver and blood during the 5<sup>th</sup> and 6<sup>th</sup> week of gestation and in lymph nodes around 12-14 weeks of gestation. Macrophage can discriminate between 'foreign' and 'self' molecules thus are ideal cells for surveillance and scavenging pathogens. Along with neutrophils, macrophages have receptors for antibodies and complement that enhance their

opsonisation and phagocytic ability. This later ability is deficient in the VLBW preterm infants.

- 2) Alongside activated macrophage interdigitating dendritic cells behave as soluble antigen-presenting cells that up regulate CD80 and CD86 on their surface, induce proliferation of T lymphocytes by secretion of cytokines and endocytose extra-cellular antigens. In neonates data indicates significant deficiencies in this process thus reducing the production of appropriate cytokines<sup>25,26</sup> in response to infection.
- 3) Neutrophils are essential for immediate response; they appear in foetal circulation from 10-16 weeks of gestation. In the VLBW infant though they are large in number in the circulating pool (peripheral blood) but the bone marrow storage pool is only 20% of that a term infant.<sup>27</sup> While the neonate can rapidly increase the number of neutrophils in circulation following an infectious stimulus from its bone marrow storage pool it also equally rapidly depletes it, often totally consuming it in severe sepsis (causing severe neutropenia).
- 4) For neutrophils to get to the site of infection they need to stop rolling along the vascular wall and adhere to the vascular endothelium, deform and pass between endothelial cells. Decreased expression of beta-2-integrins on the neonatal vascular surface leads to diminished adhesion and immobility of neutrophils. For passing through the endothelial cells neutrophils need to deform by formation of actin filaments, this ability is significantly reduced in the neutrophils of VLBW preterm infants, added to this the increased fluidity of their cell membrane results in reduced plasticity/deformability thus delaying transmigration of neutrophils through the endothelial cells.<sup>28,29</sup> Once outside the vascular compartment, neutrophils move towards the site of infection guided by various chemotactic factors. These chemotactic

factors are also reduced in preterm infants leading to decreased accumulation of neutrophils at the site of inflammation. At the site of inflammation neutrophils ingest and destroy the opsonised pathogen by action of anti microbial proteins and hydrolytic enzymes<sup>28</sup> producing a 'respiratory burst' i.e. a sudden increase in cellular metabolism of oxygen, leading to production of toxic oxygen metabolites that have bactericidal activity. The capacity to generate 'respiratory burst' and activate chemiluminescence is significantly reduced in neutrophils of the preterm infant.<sup>30</sup>

- 5) *Other cells* Unlike neutrophils and macrophages, eosinophils and basophils have only weak phagocytic activity. Natural killer (NK) cells which are large granular lymphocytes destroy infected cells by linking to antibody coated target cells and cytotoxicity are present in adequate numbers. The number of NK cells increases with gestational age reaching adult levels at term, but their capacity for cytotoxicity is much less in the newborn due to phenotypical and functional differences from adult NK cells.<sup>31</sup>
- 6) Role of erythrocytes and platelets is often over looked when discussing sepsis but as they also have complement receptors, they play an important role in clearance of antigen-antibody complexes. Erythrocytes due to their nitric oxide carrying capacity have an important role in maintaining blood flow improving tissue perfusion and oxygen delivery so often compromised in sepsis.

#### *1b) Soluble Factors (Complement, Acute-Phase Proteins and Cytokines)*

- 1) Complement system consists of around 20 proteins produced mainly by the liver of the foetus and the newborn. They first appear in the foetal liver around the 10<sup>th</sup> week of gestation. Compliment system can be activated in three ways; i) classic

pathway activated at C1 level by antigen-antibody complexes, ii) alternate pathway by products of microbial cell wall and iii) the lectin pathway by the interaction of microbial carbohydrate with mannose-binding protein in plasma. Complement activation generates immunologically active substances that enhance opsonisation, phagocytosis and release of inflammatory and chemotactic mediators. They form a 'membrane attack complex' which perforates the cell membrane of the pathogen causing its death. Newborns in particular preterm VLBW infants have only 10% or less of maternal levels of the terminal cytotoxic components like C3 and C3b that lead to killing of the organism, thus significantly compromising their ability to kill the pathogen. More importantly the VLBW preterm infants have difficulty in activating the rapidly responsive alternate or the mannose binding lectin pathway<sup>32,33</sup> compromising chemotaxis, localisation, opsonisation, phagocytosis and killing of the pathogen---- all elements important in the fight against infection.

- 2) Molecules collectively called acute-phase proteins like C - reactive protein (CRP), proteinase inhibitors, amyloid A protein and various coagulation proteins function to enhance resistance to infection and promote repair. These are deficient both quantitatively and qualitatively in the preterm VLBW infant.<sup>34</sup>
- 3) Cytokines are a group of soluble mediators that act as messengers between cells of the immune system and between the cells of the immune system and other systems through an integrated network to regulate host immune response.<sup>35</sup> Cytokine response in the newborn infant is related to both gestational age and the environmental milieu. Pro-inflammatory cytokines develop gradually with increasing gestational age while anti-inflammatory cytokines are regulated on an individual basis influenced by the intra-uterine cytokine environment.<sup>36</sup>

### Adaptive/Specific Immune System

Specific/adaptive immune system is dependent on T and B cells and their products like antibodies and cytokines. Specialised T and B lymphocytes are responsible for the very large diversity of this system. This system not only responds to microbial and non-microbial antigens but unlike the innate immune system has the ability to lay down 'memory' which enables a quantitatively and qualitatively superior immune response to be mounted on reexposure.

- 1) T Lymphocytes are specialised cells activated either by directly recognising antigen or being stimulated by antigen-presenting cells. They are capable of producing over a thousand T-cell receptor variable regions as transmembrane molecules responsible for expressing or producing cytokines that regulate the immune system.<sup>37,38</sup> T lymphocytes that are important for adaptive immunity are CD4+ or the helper Th1 cells whose function is to activate macrophage through interferon gamma (INF $\gamma$ ) and to encourage B lymphocytes for production of antibodies. Generation of these T lymphocytes is delayed in neo-nates particularly the VLBW infant. Other important T lymphocyte is the CD8+ or Th2 cytotoxic cell which along with NK cells mediates lysis and eradication of pathogen.<sup>39</sup> In the preterm VLBW infant both Th1 and Th2 lymphocytes are markedly reduced, exhibiting a slow proliferative response, decreased cytotoxic and cytolytic activity and reduced production of appropriate cytokines.<sup>39</sup>
- 2) B lymphocytes are responsible for production of immunoglobulin's/antibodies. Initial response to an antigen challenge is production of IgM. However the capacity to do so in the neonate is only around 10% of that of an adult.<sup>39</sup>
- 3) Similarly, synthesis, memory and capacity to respond by immunoglobulins like IgA and IgG is limited in the neonate.<sup>39</sup>

### Passive (Transplacental) Immunity

Transplacental transfer of immunoglobulin's starts around 12 weeks of gestation, increasing in a direct linear correlation with gestational age. Initially transplacental transfer is slow and selective, for example, IgG1 and IgG3 (*more effective against viral infection*) are transferred more efficiently than IgG2 and IgG4 (*more effective against encapsulated organisms*). IgG2 and IgG4 only reach 50-60% of maternal levels at term though the total level of IgG in infant at term is the same or higher than the maternal levels. We<sup>40</sup> have shown that a serum level of 400 mg/dl of total IgG appears to be critical to prevent the newborn from infection as none of the infants in our cohort who attained level above 400 mg/dl died from infection whilst all the infants who died from sepsis had levels below 400 mg/dl. The foetus normally achieves this level of total IgG around 32 weeks of gestation and it is not surprising that infection is highest before 32 weeks of gestation.

Human milk provides several protective elements like sIgA and lactoferrin (main protein content of mature breast milk) both have antimicrobial and immunostimulatory properties. Oligosaccharides present in breast milk help in development of 'friendly' intestinal flora that are essential for reducing the growth of pathogenic bacteria in the gut.

### Genetic Influence

It is increasingly recognised that an individual neonate's response to pathogen depends on its genetic makeup and polymorphisms of its gene coding for proteins involved in recognising and responding to pathogen.<sup>41</sup> Though knowledge concerning genetic polymorphisms is still quite limited, it is known that polymorphisms in TNF locus (TNF $\alpha$ -308 and TNF $\beta$ -252) for example, correlates with immune dysfunction and increased susceptibility of the host to infection. Lipopolysaccharide (LPS) elicits its response by binding to cell surface through TLR4, due to genetic polymorphism impaired TLR4 pathogen processing leads some neonates to respond poorly to an LPS challenge. The same is true for many other

elements responsible in infection cascade e.g. tumour necrosis factor (TNF), Interleukin-10 (IL-10) and mannose binding lectin (MBL).<sup>42</sup>

Thus, in summary: In the preterm VLBW infant, though all molecular and cellular elements necessary for adequate host defence are present; their number/capacity or function is reduced (*newborn's immune naivety*) accounting for decreased magnitude of immune response. This *immune naivety* is made worse by sepsis. Unless this is adequately addressed in the management package along with killing of the pathogen/s it is unlikely that mortality rates from sepsis will come down.

#### **Pathophysiology: The Sepsis Cascade**

Sepsis disturbs the harmonious balance that exists in healthy state between pro and anti-inflammatory cytokines, coagulant and anti-coagulant elements, and between endothelial integrity and circulating cells. Infection by a pathogen disturbs this balance. Body deals with infection by activating many of host defence systems simultaneously to regain the balance. If the balance is regained then outcome is recovery, but if this balance is either not restored or accentuated then the outcome is poor.

During the inflammatory process, cells of the haemopoetic system and immune modulating mediators are activated to move towards the affected site for destroying the pathogen. Activation of the inflammatory response is initiated by release of endotoxin (LPS) from Gram-negative or exotoxins (peptoglycans) from Gram-positive organism and other cellular antigenic components of the pathogen/s. From then on initiation and maintenance of inflammatory cascade result from a complex array of interactions between pathogen and host defence systems.<sup>4,7</sup> Leukocyte activation in particular that of macrophage and mononuclear cells brings about transcriptional changes related to immune activation and signal transduction dependent on genetic predisposition and bacterial characteristics.<sup>43</sup>

Transcription factors up-regulate the production of pro-inflammatory cytokines such as TNF- $\alpha$ , INF $\gamma$ , IL-6 and anti-inflammatory cytokines IL-10, IL-18.<sup>44</sup> Activation of complement pathway leads to generating C3b that coats the pathogen (opsonisation), production of C5a and chemotactic neutrophils factors along with C3a and C4a that degranulate mast cells causing contraction of smooth muscle increasing permeability of vascular endothelium allowing activated cells to move out of the vessels. Substances released from pathogens and damaged tissues up regulate adhesion molecules on the vascular endothelium arresting and activating rolling neutrophils on to the vascular wall. Activated neutrophils change shape to pass through the vessel wall and move to the site of infection where they phagocytose C3b coated organisms. Mediators like complement, chemokines, products of prostaglandin metabolism, and leukotrienes all contribute towards recruitment of inflammatory cells to the site of infection. As described earlier preterm VLBW infants are either deficient or inefficient in generating these responses in an adequate manner. In particular, poor transmigration of neutrophils and chemotaxis results in lack of localisation of infection hence the neonate is prone to more frequent generalised blood stream infections.

The process of activated inflammatory cells producing range of pro-inflammatory mediators like TNF- $\alpha$ , IL-1, IL-6, and IL-8, platelet activating factor (PAF), leukotrienes and thromboxane A<sub>2</sub> accentuate endothelial damage.<sup>45</sup> Leak of granulocytes and other mediators through the injured endothelium cause the clinical effects seen in sepsis which can be enumerated by the synonym CHAOS;

- C = Cardiovascular; changes in the micro and macro-circulation, decrease vascular tone, poor tissue perfusion, hypotension and organ failure.
- H = Haemopoetic; anaemia, neutropenia, disseminated intra-vascular coagulation (DIC).

- A = Apoptosis; increase in planned cell death.
- O = Organ dysfunction; renal, hepatic and cardiovascular system failure.
- S = Suppression of the immune system; immune paralysis (usually transitory).

The process of CHAOS take place with varying degree of severity in every infant with sepsis and correction of CHAOS, the imbalance between pro-inflammatory and anti-inflammatory cytokines, hypercoagulation and fibrinolysis apart from killing the pathogen is required for adequate management of sepsis.<sup>7</sup>

Inflammation and coagulation are closely linked in sepsis for example TNF- $\alpha$ , IL-1 and IL-6 activate monocytes that express tissue factors which in turn stimulate the extrinsic coagulation pathway leading to the formation of fibrin clots. Thrombin that normally maintains a balance between coagulation and fibrinolysis also has a pro-inflammatory effect on cells of the endothelium (making them sticky) in addition to making macrophage and monocytes release inflammatory mediators. In sepsis, thrombin generation becomes un-regulated leading to an initial hypercoaguable phase followed by the septic process impairing normal fibrinolysis, therefore, the body becomes less able to remove the microthrombi causing DIC often seen early in neonatal sepsis. During this initial hypercoaguable phase coagulation factors are consumed rapidly leading to fibrinolysis and bleeding also seen in infants with severe sepsis.

Relationship between infection, brain (white matter) injury and neuro-developmental impairment though now established;<sup>5, 8-11</sup> its pathogenesis is only now being gradually understood. White matter injury due to infection is likely to be the result of multifactorial events involving direct toxin insult, cytotoxic injury and vascular compromise associated with hypoxic/ischemic events. It is also now recognised that hypoxic ischemic brain injury is

accentuated in presence of infection and vice versa.<sup>46</sup> The presence of inflammatory cytokines<sup>47</sup> in the brain is known to inhibit proliferation of neuronal precursor cells, activate astrogliosis and stimulate oligodendrocyte death all of which increase white matter injury<sup>48</sup> and hamper recovery.

Thus, it is important to appreciate that whilst micro-organisms may initiate the sepsis process, it is our response to their presence that make the disease. We are as much in danger of injury from the bacteria as we are from our own response or lack of it to their presence.

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