

REVIEW

Bench-to-bedside review: Neonatal sepsis - redox processes in pathogenesis

Ivan Spasojević^{1*}, Budimir Obradović² and Snežana Spasić³**Abstract**

The present review is aimed at elucidating the neonatal 'sepsis redox cycle' - the cascade of inflammatory and redox events involved in the pathogenesis of sepsis in neonates. While adult and neonatal sepsis share some common features, there are some substantial differences: higher mortality rates occur in adult sepsis and worse long-term effects are evident in neonatal sepsis survivors. Such epidemiological data may be explained by the lower ability of IL6 and IL8 to activate NF-κB-regulated transcription in neonatal sepsis in comparison to TNF-α, which is involved in the mechanisms of adult sepsis. The activation of NF-κB in neonatal sepsis is further promoted by hydrogen peroxide and results in mitochondrial dysfunction and energy failure as septic neonates experience decreased O₂ consumption as well as lower heat production and body temperature in comparison to healthy peers. In neonates, specific organs that are still under development are vulnerable to sepsis-provoked stress, which may lead to brain, lung, and heart injury, as well as vision and hearing impairments. In the light of the processes integrated here, it is clear that therapeutic approaches should also target specific steps in the neonatal 'sepsis redox cycle' in addition to the current therapeutic approach that is mainly focused on pathogen eradication.

Introduction

Sepsis is a devastating health problem taking millions of lives every year in neonatal ICUs (NICUs) all around the world [1,2]. The original hypothesis addressing the pathogenesis of sepsis that blamed aggressive immune activity for sepsis-related health problems and death was

countered by new facts showing that sepsis is best explained by generally reversible mitochondrial and cellular dysfunction [3]. Taking into account that an activated immune system and dysfunctional mitochondria represent the two most potent sources of reactive molecular species and that many reports imply an important role of reactive oxygen and nitrogen species (ROS and RNS) in the pathogenesis of sepsis, we recently outlined the main redox events that are interconnected in a self-sustaining and self-promoting pathological process we term the 'sepsis redox cycle', which may result in the total loss of cellular and organ function [3]. This review is aimed at elucidating the 'sepsis redox cycle' in neonatal sepsis (the neonatal 'sepsis redox cycle'), and represents a logical extension of our previous review, which was based on the available data addressing sepsis in adults. A complete picture of neonatal sepsis and therapy potentials requires a thorough understanding of the developmental differences that separate the pathogenesis of adult and neonatal sepsis. While adult and neonatal sepsis share some common features, there are some substantial differences: higher incidence and mortality rates are observed for adult sepsis, while long-term effects are worse in neonatal sepsis survivors. Fortunately, in developed countries neonatal sepsis is rare (up to 9 cases per 1,000 newborns). An epidemiological study performed in the US has illustrated that the incidence of sepsis is age-related, being highest in people over 65 years of age (26.2/1,000), while in infants under 1 year of age it was 5.3/1,000 [4]. In a population of sepsis patients admitted to ICUs and given both antibiotics and supportive care, neonatal sepsis is substantially less lethal (3 to 10% mortality rate in developed countries) [5-7] compared to sepsis in adults (mortality rate of around 35%) according to the latest Surviving Sepsis Campaign report for 2010 [8]. This is somewhat surprising bearing in mind that neonatal sepsis has been a subject of significantly less research. We have undertaken a brief systematic search of PubMed (electronic database of the US National Library of Medicine) looking for articles that contain: (i) the term 'neonatal sepsis' or a combination of the words sepsis and neonatal, neonate, newborn or baby in the title/abstract section; and (ii) the word sepsis but

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neither of the previous terms in the same section. While the first search returned some 4,000 results, the second search returned around 50,000 papers, implying that comparatively less is known about neonatal sepsis. Therefore, significantly lower mortality rates in NICUs do not seem to be related to more developed therapeutic approaches and finely tuned care in comparison to ICUs, but to specific differences between neonatal and adult sepsis pathogenesis, making the former less life-threatening. On the other hand, it seems that those who survive sepsis are more likely to develop different morbidities later in life if sepsis episode(s) took place during the first 4 weeks of life (neonatal period). It should be stressed that the long-term effects of sepsis have not been well documented, and there are not many studies on this issue. Nevertheless, two cohort studies on extremely low birth weight neonates reported a significantly increased incidence of a number of different morbidities at the age of 18 to 22 months in the population of neonatal sepsis survivors in comparison to age- and birth-weight-matched controls; these include respiratory distress syndrome, bronchopulmonary dysplasia, periventricular leukomalacia (PVL), severe intraventricular hemorrhage, cerebral palsy, and vision and hearing impairments [9,10]. A retrospective cohort study documented that only 28% of neonatal septic shock survivors were alive and were considered normal 18 months after the septic shock episode(s) [11]. In contrast, adult severe sepsis survivors generally show recovery of baseline or near-normal values of general health and most of the other 'quality of life' parameters (only) 6 months after the sepsis episode [12]. Although different neurocognitive impairments have been reported in adult sepsis survivors, a consistent finding across investigations is that no associations exist between the indicators of severity and the development of unfavourable neurocognitive outcomes in survivors of critical illness [13]. Adult sepsis studies examining morbidities other than these are not available, but there are data on outcomes in an acute respiratory distress syndrome cohort and in a general population of ICU survivors. These surveys showed that nearly all acute respiratory distress syndrome patients fully recover lung function within 1 year [14], while ICU patients that survived renal failure almost always experience a complete recovery of renal function [15]. Such disparity in long-term effects further points out that there are significant differences between the mechanisms of neonatal and adult sepsis. Therefore, to come to new conclusions and the mechanism of neonatal sepsis pathogenesis, we will compare neonatal and adult sepsis step-by-step, from initial events all the way down to cellular dysfunction, focusing on redox processes but not underestimating other components, such as immune system activity. It should

be stressed here that data available on neonatal sepsis are rather limited, as illustrated by the number of published papers. This may represent the reason why some previous reviews addressing mechanisms of neonatal sepsis failed to resist the temptation to combine data from neonatal with those from adult sepsis studies. This is not the case with the present review, as we have carefully separated neonatal from adult sepsis, underlining the caveats in the state-of-the-art knowledge on the former.

Redox mechanisms in neonatal sepsis

Pathogen-provoked events in the plasma

Sepsis is a process that is initiated by pathogens, followed by increased immune system activity that activates a redox cascade in the intracellular compartment, and ends in cell and organ dysfunction [3]. The fact that pathogens are the initiators of a process that is thereafter principally independent of their presence is substantiated by the fact that a large percentage of septic adults (10 to 40% [16,17]) and neonates (over 50% in some studies [18,19]) show negative blood cultures at some points during the disease course. Inflammatory responses related to tachycardia, tachypnea, hyperthermia or hypothermia and leukocytosis most commonly triggered by infection could also be present following trauma, burn injury and various other pathogen-unrelated insults [20]. Finally, the fact that neonates are comparatively more susceptible to infections but less to sepsis than adults [21] implies that pathogens do not play a central role in sepsis development. However, pathogens do induce an innate immune system response, which represents the second step in sepsis pathogenesis.

There are several key developmental differences in the host response to infection that clearly delineate neonatal sepsis as a separate entity from adult sepsis. The most obvious dissimilarity lays in the activity of the innate immune system. In comparison to the innate immune system and inflammatory response in adults, the neonatal system under septic conditions has: (i) a lower capacity to generate ROS and RNS; (ii) a different cytokine profile; (iii) a low neutrophil pool and a reduced capacity for increasing progenitor cell proliferation; (iv) neutrophil granulocytes exhibiting quantitative and qualitative abnormalities; (v) and neutrophils showing reduced function and an impaired capacity for migration, chemotaxis, endothelial adherence, and phagocytosis [22-24]. The first two points are particularly important here and require further explanation.

Neutrophils, macrophages and endothelial cells represent the first line of defence against pathogens and for this purpose they are equipped with different ROS and RNS that provoke oxidative damage and kill the invaders [3]. However, some of the reactive species produced, such as hydrogen peroxide (H_2O_2) and nitric oxide ($\cdot NO$) are

Table 1. The capacity of neonatal versus adult immune system cells to generate reactive oxygen species

Cell type	Stimulus	Parameter	Group		Reference
			Neonate	Adult	
Bovine polymorphonuclear leukocytes	PMA	$\cdot\text{O}_2^-/10^6$ cells/5 minutes (nmol)	5.7 ± 0.8	9.6 ± 2.1 ($P < 0.01$)	[93]
Human neutrophils	fMPL	Relative production of $\cdot\text{O}_2^-$ per minute	8.0 ± 3.6	10.6 ± 2.1 ($P < 0.05$)	[94] ^a
Human neutrophils	PMA	Relative production of $\cdot\text{O}_2^-$ per minute	15.3 ± 6.8	27.5 ± 4.8 ($P < 0.01$)	[94] ^a
Human granulocytes	fMPL	Maximal ROS production in arbitrary units	24 ± 6	57 ± 8 ($P < 0.01$)	[95]
Human alveolar macrophages	PMA	Intracellular $\cdot\text{O}_2^-$ production (pmol/ 3×10^5 cells)	26 ± 6	94 ± 22 ($P < 0.05$)	[96]
Human alveolar macrophages	Oposonized zymosan	Intracellular $\cdot\text{O}_2^-$ production (pmol/ 3×10^5 cells)	50 ± 16	164 ± 22 ($P < 0.05$)	[96]
Human mononuclear phagocytes	IFN- γ	$\cdot\text{O}_2^-$ release (nmol/ 10^6 cells)	20 ± 4	31 ± 5 ($P < 0.01$)	[97]

^aWe extracted and pooled the results provided in the manuscript and performed statistical analysis using Statistica 6.0 (StatSoft, Inc., Tulsa, OK, USA); statistical significance was determined by the means of non-parametric two-tailed Mann-Whitney test. fMPL, N-formyl-methionyl-leucyl-phenylalanin (degradation product of bacterial proteins); IFN, interferon; $\cdot\text{O}_2^-$, superoxide; PMA, phorbol 12-myristate 13-acetate; ROS, reactive oxygen species.

capable of crossing the cellular membrane to enter the intracellular compartment, where they may initiate and participate in the 'sepsis redox cycle' [3]. While this is true for adult sepsis, data show that when challenged by pathogens or experimental inducers, the oxidative burst performed by the neonatal immune system is significantly less pronounced than in adult sepsis (Table 1). As a result of lower ROS-generating activity of the innate immune system, neonatal plasma generally does not show positive markers of oxidative stress, which is in strong contrast to the results obtained in adults [3]. For example, Cherian and colleagues [25] reported that there were no significant changes in the levels of ascorbate, glutathione (GSH), and oxidative stress biomarkers in the blood of neonates and babies with sepsis when compared to age-matched controls. Another study showed merely a slight increase in the level of lipid peroxidation products in the serum of septic neonates in comparison to controls [26]. A transient increase of total hydroperoxide level was reported in the blood of septic newborn piglets, while biological antioxidant potential was even increased at some time points during the 6 hour monitoring period [27]. Hydrogen peroxide has a central place in initiation of the 'sepsis redox cycle', so lower prooxidative activity of the neonatal immune system may account for the low incidence of sepsis in neonates. It is noteworthy that one Cochrane study showed that the supplementation of vitamin E, which is involved in free radical scavenging in the blood, significantly increases the risk of sepsis in neonates [28]. This may be attributed to vitamin E-mediated suppression of the already weak oxidative activity of the neonatal immune system, resulting in decreased bactericidal capacity.

While many cytokines are present at similar levels in the blood of neonatal and adult septic patients, some show substantial differences. Table 2 lists results from a series of studies documenting notably higher production of IL6 and IL8 and generally lower production of TNF- α

in neonatal sepsis. In addition, IL6 and IL8 are significantly increased in the serum of septic neonates in comparison to uninfected peers, and probably represent the best early diagnostic markers for neonatal sepsis among the components of the immune system [29,30]. For example, Küster and co-workers [31] showed that the level of IL6 in the neonatal plasma increases approximately ten-fold two days before clinical diagnosis of sepsis. Other groups showed levels of IL6 and IL8 increased in septic neonates by approximately 20- and 8-fold, respectively [32], and 200 and 15 times, respectively, in comparison to healthy controls [33]. It is important to note here that plasma concentrations reflect only a small portion of the IL8 blood pool (approximately 10%; most of IL8 is cell associated) [34]. This is also likely to be the case for IL6. Altogether, these data imply that while TNF- α represents the central mediator of sepsis in adults [35], this role is played by IL6 and IL8 in the pathogenesis of neonatal sepsis.

Intracellular redox changes in neonatal sepsis

Pro-oxidative and pro-inflammatory events in the plasma may have a strong impact on the intracellular milieu. In adult sepsis, H_2O_2 and TNF- α activate NF- κB , which has a special place in sepsis development [3]. Its activity is significantly higher in septic non-survivors in comparison to controls and survivors and may predict sepsis-related mortality [36,37]. In spite of different redox settings and cytokine profiles, NF- κB is also activated in neonatal sepsis. Several studies showed that the stimulation of different neonatal cell types by lipopolysaccharide (LPS) results in the activation of NF- κB , which was similar to or even higher than in adult systems [38-42]. Kenzel and colleagues [43] showed using a model of neonatal sepsis and two different bacterial species that NF- κB -dependent expression increases several fold in the presence of pathogens, while an *in vivo* investigation on newborn septic rats showed that NF- κB was activated in the lungs,

Table 2. Levels of IL6, IL8 and TNF-α in neonatal versus adult sepsis

Sample	Stimulus	Cytokine	Group		Other cytokines showing no difference	Reference
			Neonate	Adult		
Human blood	GBS	IL6 (pg/ml)	100 ± 105	14 ± 13 (<i>P</i> = 0.003)	IL-1β	[98]
		IL8	3,355 ± 1,762	1,109 ± 452 (<i>P</i> = 0.01)		
		TNF-α	592 ± 349	481 ± 261 (NS)		
Human blood	<i>E. coli</i>	IL6 (pg/ml)	1,000 ± 0	783 ± 84 (<i>P</i> = 0.02)	IL-1β	[98]
		IL8	7,120 ± 751	4,995 ± 472 (<i>P</i> = 0.003)		
		TNF-α	952 ± 167	908 ± 62 (NS)		
Human blood	HSV-1	IL6 (pg/ml)	3,920 ± 3750	360 ± 190 (<i>P</i> = 0.033)	-	[99] ^a
		IL8 (ng/ml)	32 ± 38	6.5 ± 1.7 (<i>P</i> = 0.066)		
Human mononuclear cells	11 bacterial species ^b	IL6 (ng/ml)	104 ± 36	59 ± 20 (<i>P</i> < 0.01)	IL10 IL12	[100] ^a
		TNF-α	16 ± 14	17 ± 15 (NS)		
Human monocytes	LPS	TNF-α (pg/ml)	610	2,230 (<i>P</i> < 0.05)	-	[101]
Human monocytes	LPS	IL6 (ng/ml)	3.7 ± 1.1	1 ± 0.3 (<i>P</i> < 0.05)	-	[102]
		TNF-α	0.6 ± 0.2	3.3 ± 1.3 (<i>P</i> < 0.05)		
Human blood	LPS	TNF-α (ng/ml)	1.47 ± 1.03	3.89 ± 1.94 (<i>P</i> < 0.05)	IL2 IL4 IFN-γ	[38]

^aWe extracted and pooled the results provided in the manuscripts and performed statistical analysis. ^bEleven different bacterial species from intestinal flora, each being studied separately. GBS, Group B streptococcus; HSV-1, herpes simplex virus type-1; IFN, interferon; NS, not significant.

liver, and spleen [44]. Recent studies shine a new light on NF-κB activation in neonatal sepsis. Manna and co-workers [45,46] have shown that IL8 represents a NF-κB activator in different cell types. IL8 followed a time- and dose-dependent pattern of NF-κB activation that was similar to TNF-α. However, IL8 is approximately two orders of magnitude less effective as an NF-κB activator in comparison to TNF-α - that is, similar levels of NF-κB-regulated expression have been observed with IL8 at a concentration of 1 nM as with TNF-α at 10 pM [45,46]. IL6 also represents an activator of NF-κB-regulated expression, and seems to be less efficient in comparison to TNF-α [47]. It is important to note here that IL6 binds to trans-membrane IL6 receptors, or forms a complex with soluble IL6 receptors, which associates with two molecules of the signal transducing protein gp130, thereby initiating intracellular signalling and NF-κB activation [48]. The lesser ability of IL6 and IL8 to activate NF-κB-regulated transcription in comparison to TNF-α should be considered a possible reason for the lower incidence and mortality rates in neonatal sepsis. The levels of IL6 and IL8 increase during the first 12 to 24 hours of neonatal sepsis development, following which they generally decline in the blood to normal values characteristic of infection-free neonates [29]. This is in line with their role as initiators of a cascade of events that is independent of inflammatory processes thereafter.

NF-κB binds to DNA to enable the initiation of the transcription process of a number of genes, two of them encoding redox-active enzymes: inducible nitric oxide (•NO) synthase (iNOS) and cyclooxygenase-2 (COX-2; which generates superoxide (•O₂⁻) as a by-product) [3].

Pertinent to the role of IL8 and IL6 in neonatal sepsis, it has been shown that the exposure of cells to these cytokines results in the expression/up-regulation of iNOS and COX-2 [45,49]. The increased expression and activity of iNOS and COX-2 have been documented in various tissues (brain, skeletal muscle, lung, and cardiac tissue) of rodent and porcine models of neonatal sepsis when initiated using *Escherichia coli*, GBS or LPS [41,50-57]. The importance of the activation of iNOS expression in sepsis pathogenesis is substantiated by the findings of Mittal and co-workers [50], who showed that iNOS^{-/-} newborn mice infected with *E. coli* display no disruption of the blood-brain barrier, a reduced inflammatory response and normal brain physiology. Generally, iNOS is absent in resting neonatal cells and is triggered by pathogens or cytokines, leading to the production of •NO in the micromolar range [52]. This is much higher in comparison to the capacity of constitutively expressed endothelial nitric oxide synthase, which produces local •NO concentrations in the nanomolar range [50]. Significantly increased •NO production in septic neonates and neonatal sepsis models has been verified in a number of studies [50,58-60]. •NO is known to provoke the inhibition of the electron transport chain in mitochondria in adult sepsis [61].

In addition to COX-2-mediated •O₂⁻ production, this radical is produced in neonatal sepsis by NADPH oxidase and in mitochondria showing inhibited respiration. It has been shown that LPS treatment of rat neonatal cardiomyocytes leads to two-fold increased NADPH oxidase expression and •O₂⁻ generation [40]. IL6 may promote NADPH oxidase •O₂⁻-producing activity [62], while

Miyoshi and colleagues [63] have demonstrated using endothelial cells from umbilical vein that IL8 is directly involved in the activation of NADPH oxidase in sepsis. Investigations of mitochondrial function in neonatal sepsis are not very extensive, whereas data on $\cdot\text{O}_2^-$ production in mitochondria under such settings are missing. Nevertheless, it has been shown using cytokine-treated cardiac myocytes and hepatocytes, both isolated from rat neonates, that $\cdot\text{NO}$ inhibits the electron transport chain and normal mitochondrial functioning [64-66]. A study on hepatocytes from suckling rats with LPS-induced sepsis showed that intra-mitochondrial O_2 consumption was decreased two-fold in comparison to controls, and that the mitochondria exhibited altered morphology, being swollen with indistinct cristae, disrupted membranes, and outer membrane fusion [67]. The dysfunction of mitochondria and energy failure in neonatal sepsis are also implicated by the fact that septic neonates experience rapidly decreased O_2 consumption, as well as lower heat production and body temperature in comparison to healthy peers [68]. However, in contrast to adult sepsis, where ATP depletion has been well documented [3], the changes in ATP level have not been amply investigated in neonates. Only two studies have been performed on hepatocytes obtained from rat neonates very early in sepsis (2 hours after LPS injection), showing that there is no significant decrease in ATP levels [67,69]. This may be due to the ability of neonatal cells to compensate for mitochondrial dysfunction by extra-mitochondrial ATP production [67]. The compensation leads to excessive consumption of glucose and increased extra-mitochondrial O_2 consumption, which have been documented in these studies [67,69]. Such production, however, yields only small amounts of ATP, which may maintain energy metabolism in balance for a short time, but with non-functioning mitochondria, glycolysis cannot prevent ATP depletion and cellular dysfunction in the long run. This remains to be substantiated by evidence on levels of ATP later in the course of neonatal sepsis development.

Superoxide reacts with $\cdot\text{NO}$ to produce peroxynitrite ($\text{ONOO}\cdot$), but there are no direct data showing the production and role of $\text{ONOO}\cdot$ in neonatal sepsis. However, the formation of $\text{ONOO}\cdot$ represents a simple chemical consequence of the co-existence of $\cdot\text{O}_2^-$ and $\cdot\text{NO}$ [70], which most likely does not depend on cell age or type. Arstall and co-workers [71] showed that in neonatal rat ventricular myocytes exposed to cytokines, a sequence of events develops involving activation of iNOS and increased $\cdot\text{O}_2^-$ and $\text{ONOO}\cdot$ production. Mitochondria are specifically targeted by highly reactive products of $\text{ONOO}\cdot$ decomposition - $\cdot\text{OH}$ and $\cdot\text{NO}_2$ [3]. The first is notoriously reactive and provokes damage to membranes, proteins and DNA while $\cdot\text{NO}_2$ binds to proteins leading to increased susceptibility to protease-mediated degradation

[3]. Pertinent to this, Fukumoto and co-workers [66] have shown that $\text{ONOO}\cdot$ drastically affects the functioning of mitochondria isolated from the hearts of rat neonates.

The main consequence for $\cdot\text{O}_2^-$ is to be dismutated to H_2O_2 in mitochondria by Mn superoxide dismutase (MnSOD) or in the cytoplasm by CuZnSOD. Hydrogen peroxide provokes further NF- κ B activation [72], thus closing the redox loop. Pertinent to this, it has been reported that the expression of COX-2 in LPS-treated neonatal rat cardiomyocytes can be prevented by the inhibition of $\cdot\text{O}_2^-$ production. Peng and colleagues [40] also showed that LPS-induced NF- κ B activation is dependent on NADPH oxidase-mediated activity, which leads to increased levels of H_2O_2 . These facts imply that extracellular stimuli (IL6, IL8, LPS) only push the cascade of events by activating NF- κ B-regulated expression, and the cascade then reaches maximum potential through H_2O_2 -mediated activation, most likely representing a critical step in the development of neonatal sepsis. It is noteworthy that CuZnSOD over-expression is not beneficial in neonatal mouse brain cells showing mitochondrial dysfunction, implying the negative role of its product - H_2O_2 . In contrast, over-expression of the H_2O_2 -removing enzyme GSH peroxidase (GPx) was shown to be brain-protective [73]. In line with this, a Cochrane systematic review showed that the supplementation of selenium, which is necessary for GPx synthesis, was associated with a significant reduction in neonatal sepsis incidence [74]. It should be stressed that mitochondria base their defence against H_2O_2 on GPx activity [75]. Clearly, under conditions in which cellular respiration is obstructed, such as neonatal sepsis, the main problem comes from H_2O_2 , which may leak from mitochondria or is produced by CuZnSOD in the cytoplasm. Hence, the positive effects of GPx in neonatal sepsis may be attributed to its ability to stop the redox loop.

Some other processes that have been described in adult sepsis still remain inconclusive in septic neonates. For example, the sequence of events involving $\text{ONOO}\cdot$ -mediated activation of poly(ADP-ribose) polymerase that leads to augmented $\cdot\text{O}_2^-$ production on mitochondrial complex I in adult sepsis [3] has not been studied in neonatal sepsis. In adult sepsis, $\cdot\text{NO}$ is known to leak from cells into the blood, leading to methaemoglobin formation, hemolysis and increased iron availability, thus boosting pathogen proliferation [3]. Pertinent to this, there is only one obscure report showing higher methaemoglobin level in septic neonates in comparison to healthy controls [76].

Figure 1 amalgamates the key redox events in neonatal sepsis into a self-sustaining and self-promoting neonatal 'sepsis redox cycle'. It is important to note that we have presented only those steps in the pathogenesis of neonatal sepsis that have been substantially documented,

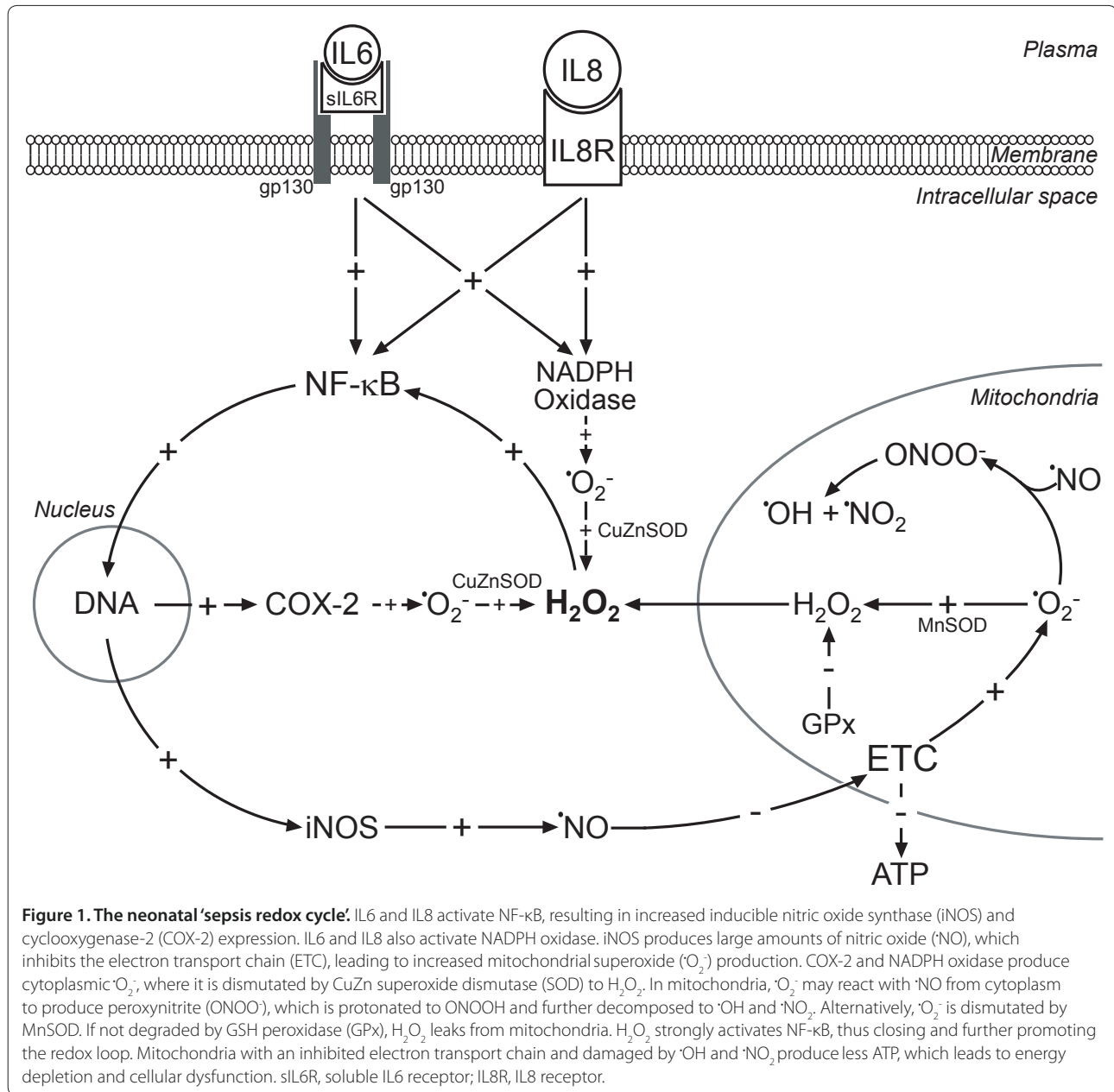


Figure 1. The neonatal 'sepsis redox cycle'. IL6 and IL8 activate NF-κB, resulting in increased inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression. IL6 and IL8 also activate NADPH oxidase. iNOS produces large amounts of nitric oxide ($\cdot\text{NO}$), which inhibits the electron transport chain (ETC), leading to increased mitochondrial superoxide ($\cdot\text{O}_2^-$) production. COX-2 and NADPH oxidase produce cytoplasmic $\cdot\text{O}_2^-$, where it is dismutated by CuZn superoxide dismutase (SOD) to H_2O_2 . In mitochondria, $\cdot\text{O}_2^-$ may react with $\cdot\text{NO}$ from cytoplasm to produce peroxynitrite (ONOO^-), which is protonated to ONOOH and further decomposed to $\cdot\text{OH}$ and $\cdot\text{NO}_2$. Alternatively, $\cdot\text{O}_2^-$ is dismutated by MnSOD. If not degraded by GSH peroxidase (GPx), H_2O_2 leaks from mitochondria. H_2O_2 strongly activates NF-κB, thus closing and further promoting the redox loop. Mitochondria with an inhibited electron transport chain and damaged by $\cdot\text{OH}$ and $\cdot\text{NO}_2$ produce less ATP, which leads to energy depletion and cellular dysfunction. sIL6R, soluble IL6 receptor; IL8R, IL8 receptor.

while some others remain to be further investigated. Instead of shutting down upon pathogen eradication or in the immune hypoactive phase, the neonatal 'sepsis redox cycle' continues to drain energy and prevents normal function to be re-established due to a positive feedback loop. The pathophysiological redox profile of one cell can spill over to surrounding tissue due to the ability of H_2O_2 and $\cdot\text{NO}$ to cross membranes, thus leading to organ failure.

The outcome

While in adults sepsis-related cellular dysfunction is generally reversible [3], in neonates this seems to be far from the truth. In this fragile population, nervous,

respiratory, and cardiovascular systems that are still developing are vulnerable to sepsis-provoked stress, which may lead to brain (PVL, intraventricular hemorrhage, cerebral palsy), lung (respiratory distress syndrome and bronchopulmonary dysplasia), and heart injury (patent ductus arteriosus), as well as vision and hearing impairments [10,77-79].

Together, a fall in ATP concentration and oxidative stress exerted on mitochondria and other compartments, both resulting from the neonatal 'sepsis redox cycle', may lead to mitochondrial permeability transition pore opening with eventual organelle swelling and cytochrome c release [80]. Once in the cytoplasm, cytochrome c can

bind to apoptotic protease activating factor 1 (APAF-1) and thus activate caspase-9, which in turn activates caspases-3 and -7, culminating in apoptosis [81]. Proliferating cells in neonatal patients may be particularly susceptible to apoptosis, taking into account increased demands for energy in such cells. In addition, APAF-1, caspase-3 and -9, and the pro-apoptosis Bcl-2 family member Bim are present in higher concentrations in developing neonatal brain in comparison to adult brain tissue [82,83]. Bacteraemia is known to further promote caspase-3 gene expression in neonates [51], while the changes in mitochondrial morphology characteristic of apoptosis have been documented to develop in a neonatal sepsis model [67]. In contrast, immunohistochemical analysis has shown that apoptosis generally does not develop in adult sepsis [3].

Particularly vulnerable to oxidative injury and susceptible to apoptosis are oligodendrocyte progenitors and subplate neonatal neurons, which represent the major cellular targets in the pathogenesis of white matter injury/PVL in neonatal sepsis [84-86]. Hence, brain-related morbidities in neonatal sepsis survivors may be explained by neonatal 'sepsis redox cycle'-provoked apoptosis in these specific cell types. Pertinent to this, the levels of IL6 and IL8 in the blood of septic neonates showed positive correlation with poor mental and psychomotor characteristics at the age of 2 [87]. The increased odds of developing visual impairments in neonatal sepsis survivors may be explained by the increased susceptibility of oligodendrocytes in the developing optic nerve to apoptosis [88], as well as by the fact that subplate neurons, which may be affected in sepsis, are required for normal visual cortical development [85]. Respiratory morbidities may be related to the fact that during early postnatal alveolar formation, the lung tissue undergoes a physiological remodelling involving apoptosis of distal lung cells [89]. For example, autopsy analysis of lungs of neonates who have died of fatal respiratory failure showed an elevated number of apoptotic cells in comparison to autopsy samples obtained from controls with no lung disease [90,91]. Finally, cardiovascular morbidities may be explained by a lower resistance of neonatal cardiomyocytes and cardiomyoblasts to apoptosis in comparison to adult cardiomyocytes. Activation of caspase-9 and -3, and cell death occur earlier and are more pronounced, while the levels of expression of the mitochondrial pro-apoptotic protein APAF-1 were significantly higher in neonatal compared to adult cells exposed to oxidative stress [92]. In summary, while the neonatal 'sepsis redox cycle' in most cells types may lead to reversible dysfunction, in others that are proliferating and sensitive to oxidative stress, it may initiate apoptosis, which seems to account for most morbidities found following a neonatal sepsis episode.

Conclusion

Although sharing many features with adult sepsis, neonatal sepsis exhibits its own hallmarks. The neonatal 'sepsis redox cycle' is initiated by IL6 and IL8, and further promoted by intracellular H₂O₂ production, while in adult sepsis TNF- α and extracellular H₂O₂ represent the initiators of the intracellular chain of redox events. The fact that the latter two are more effective NF- κ B activators may explain why adult sepsis is more frequent and more deadly in comparison to neonatal sepsis. On the other hand, a higher susceptibility of developing cells to apoptosis may explain the more frequent and wider spectrum of morbidities found in neonatal sepsis survivors. Current strategies in neonatal sepsis treatment are focused on pathogen eradication by an early application of antibiotics, which is no surprise since neonatal sepsis represents one of the most rapidly fulminating clinical diseases in NICUs. However, the increased incidence of fungal and coagulase-negative staphylococci-provoked sepsis, potentially increased antibiotic resistance, and sporadic outburst of resistant strains in NICUs require an additive (early and safe) therapeutic approach that is beneficial independently of the pathogen that initiated the process. In light of the integrated processes described here, it is clear that such approaches should target specific steps in the neonatal 'sepsis redox cycle'.

Abbreviations

APAF-1, apoptotic protease activating factor 1; COX-2, cyclooxygenase-2; GSH, glutathione; GPx, GSH peroxidase; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; NF, nuclear factor; NICU, neonatal ICU; NO, nitric oxide; PVL, periventricular leukomalacia; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF, tumour necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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