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CRITICAL CARE

REVIEW

Soluble adhesion molecules as markers for sepsis and the potential pathophysiological discrepancy in neonates, children and adults

Rens Zonneveld[1,2,3], Roberta Martinelli[2], Nathan I Shapiro[4], Taco W Kuijpers[3], Frans B Plötz[1] and Christopher V Carman[2*]

Abstract

Sepsis is a severe and life-threatening systemic inflammatory response to infection that affects all populations and age groups. The pathophysiology of sepsis is associated with aberrant interaction between leukocytes and the vascular endothelium. As inflammation progresses, the adhesion molecules that mediate these interactions become shed from cell surfaces and accumulate in the blood as soluble isoforms that are being explored as potential prognostic disease biomarkers. We critically review the studies that have tested the predictive value of soluble adhesion molecules in sepsis pathophysiology with emphasis on age, as well as the underlying mechanisms and potential roles for inflammatory shedding. Five soluble adhesion molecules are associated with sepsis, specifically, E-selectin, L-selectin and P-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1. While increased levels of these soluble adhesion molecules generally correlate well with the presence of sepsis, their degree of elevation is still poorly predictive of sepsis severity scores, outcome and mortality. Separate analyses of neonates, children and adults demonstrate significant age-dependent discrepancies in both basal and septic levels of circulating soluble adhesion molecules. Additionally, a range of both clinical and experimental studies suggests protective roles for adhesion molecule shedding that raise important questions about whether these should positively or negatively correlate with mortality. In conclusion, while predictive properties of soluble adhesion molecules have been researched intensively, their levels are still poorly predictive of sepsis outcome and mortality. We propose two novel directions for improving clinical utility of soluble adhesion molecules: the combined simultaneous analysis of levels of adhesion molecules and their sheddases; and taking age-related discrepancies into account. Further attention to these issues may provide better understanding of sepsis pathophysiology and increase the usefulness of soluble adhesion molecules as diagnostic and predictive biomarkers.

Introduction

Sepsis [1], due to its detrimental sequelae and limited therapeutic options, continues to be responsible for many deaths amongst all age groups [2-4]. Growing evidence indicates that aberrant leukocyte activation and recruitment into host tissues plays a pivotal role in causing breakdown of the vascular endothelium [5], which in turn leads to organ failure and death [6]. Inflammatory leukocyte recruitment is initiated by soluble mediators (for example, cytokines or bacterial-derived lipopolysaccharide (endotoxin)), which upregulate adhesion molecule expression on both leukocytes and the endothelium. This upregulation results in a multistep adhesion cascade whereby circulating immune cells sequentially roll on, firmly adhere to, and transmigrate across the endothelium [7-9]. During the progression of inflammatory responses, soluble isoforms of the leukocyte recruitment adhesion molecules are shed from cell surfaces and accumulate within the circulating blood plasma [10]. These soluble isoforms have been considered promising prognostic biomarkers of severity of inflammation but the clinical utility of monitoring such changes remains poor [11].

One reason for the thus far limited clinical utility of these soluble isoforms is the fact that shedding in

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general is neither a passive nor an inevitable consequence of upregulated expression/cell activation. Most shedding is an active process, which is discretely regulated by diverse proteolytic enzymes, although cell damage can also variably contribute to soluble adhesion molecule levels [10]. Although still a matter of controversy, there is increasing evidence that shedding serves regulatory roles to dampen inflammation (and specifically to reduce leukocyte–endothelial interactions) and protect the host from excessive collateral damage [10,12]. Furthermore, age-related differences in both levels of soluble adhesion molecules and the enzymes that mediate shedding have been observed in both healthy and septic patients (as discussed in detail below). The relationship between soluble adhesion molecule levels, underlying inflammatory and shedding activities and clinical outcomes may thus be more complex than once thought.

The goals of this review are therefore to summarize existing knowledge regarding the mechanisms and putative functions for shedding of cell surface adhesion molecules/generation of soluble isoforms, unequivocally identified to exist at elevated levels in the blood of septic patients, and to investigate how these levels and their shedding differ amongst healthy and septic neonates, children and adults to improve our understanding and clinical utility of soluble adhesion molecules.

Literature search

We performed a comprehensive literature search in MEDLINE using medical subject headings and text words, supplemented by scanning the bibliographies of the recovered articles. We combined 'endothelium' and 'leukocytes' using the term 'OR'. This search was subsequently combined with 'sepsis' using the Boolean operator 'AND'. We used a similar search strategy, using the terms 'soluble' and 'circulating adhesion molecules'. We combined these results with the terms 'sepsis', 'septic shock', 'endothelium', 'leukocytes', 'monocytes', 'granulocytes', 'macrophages', 'neutrophils', 'lymphocytes' and 'inflammation'. We then combined these results with the terms 'children', 'neonates', 'adults' and 'age'.

Soluble adhesion molecules: from cell surface to circulation

Five soluble adhesion molecules were associated with sepsis and their main characteristics are summarized in Table 1. Three adhesion molecules (E-selectin, L-selectin and P-selectin) belong to the selectin superfamily and function in leukocyte rolling (Figure 1). Two adhesion molecules (intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1)) belong to the immunoglobin domain superfamily cell adhesion molecules that are important for firm adhesion and transendothelial migration [13]. In all cases, inflammatory mediators (for example, cytokines, thrombin, lipopolysaccharide) first increase cell surface expression of these molecules followed by the later appearance of shed, soluble isoforms (Table 1 and Figure 2).

E-selectin

Soluble isoforms of E-selectin can be found in the supernatant of endothelial cells cultured *in vitro* within 24 hours of cytokine activation and are generated through a largely caspase-dependent shedding process [10,14-16]. In healthy individuals low levels of soluble E-selectin (sE-selectin) are found in serum, but these levels are greatly elevated in septic patients [16,17]. Importantly, shed sE-selectin from sera of septic patients retained the ability to adhere to granulocytes *in vitro* [16]. Shedding of E-selectin has thus been proposed to limit leukocyte–endothelial interactions both by decreasing the cell surface density on the endothelium and by generating an intravascular competitive inhibitor or decoy ligand (that is, sE-selectin) for leukocytes, thereby reducing collateral damage in the host [18]. Indeed, one clinical study found that while sE-selectin was elevated in septic children, those with the highest levels exhibited the best outcomes and survival rates [19].

Table 1 Characteristics of adhesion molecules involved in sepsis

Adhesion molecule	Expression	Ligands	Inflammatory mediators	Mode of expression	Specific function	Sheddase
E-selectin	Endothelial cells	ESLG-1, PSGL-1	TNFα, LPS, IL-1	Inducible	Rolling	Caspase
L-selectin	Leukocytes	GlyCAM-1, MAdCAM-1	TNFα, LPS, IL-1, IL-6	Constitutive, inducible	Rolling	ADAM-17
P-selectin	Endothelial cells, platelets	PSGL-1	TNFα, IL-4, IL-13, histamine, thrombin	Constitutive	Rolling	MMP
ICAM-1	Endothelial cells	Mac-1, LFA-1	TNFα, LPS, IL-1	Constitutive, inducible	Firm adhesion, TEM	ADAM-17, NE
VCAM-1	Endothelial cells	VLA-4	TNFα, LPS, IL-1	Constitutive, inducible	Firm adhesion, TEM	ADAM-17, NE

ADAM, a disintegrin and metalloproteinase; *ESGL-1*, endothelial selectin glycoprotein ligand; *GlyCAM-1*, glycosylation dependent cell adhesion molecule; *ICAM-1*, intercellular adhesion molecule-1; *IL*, interleukin; *LFA*, leukocyte function antigen; *LPS*, lipopolysaccharide; Mac, macrophage antigen; *MAdCAM*, mucosal vascular addressin cell adhesion molecule; *MMP*, matrix metalloproteinase; *NE*, neutrophil elastase; *PSGL*, platelet selectin glycoprotein ligand; *TEM*, transendothelial migration; *TNF*, tumor necrosis factor; *VCAM-1*, vascular cell adhesion molecule-1; *VLA*, very late antigen.

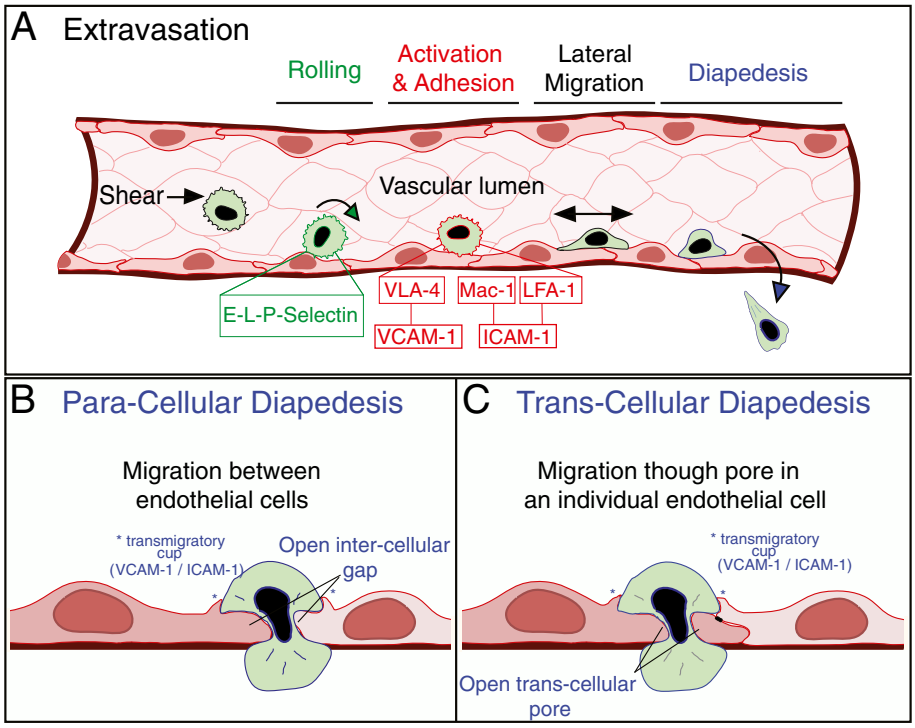


Figure 1 Stages of extravasation of a leukocyte. (A) Leukocytes first undergo tethering and rolling on the endothelium, mediated by E-selectin, L-selectin, and P-selectin and their carbohydrate ligands. Activation and adhesion: leukocyte rolling facilitates interaction with chemoattractants present on endothelial surfaces, which in turn causes leukocyte activation that triggers firm adhesion and arrest, mediated by the integrins macrophage-1 (Mac-1), leukocyte function antigen-1 (LFA-1) and very late antigen-4 (VLA-4) binding to their endothelial ligands intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Subsequently, leukocytes engage in lateral migration over the endothelial wall in search of a site to transmigrate, guided by VCAM-1/ICAM-1-enriched transmigratory cups (asterisks in **(B)** and **(C)**), present on endothelial cells. The last step in this cascade is transendothelial migration or diapedesis, whereby the leukocytes cross the endothelial barrier, either **(B)** paracellular, through the interendothelial junctions, or **(C)** transcellular, via the formation of a transcellular pore. See [7-9,13] for additional details.

L-selectin

Within approximately 10 to 15 minutes of leukocyte activation by cytokines (for example, tumor necrosis factor alpha) or lipopolysaccharide, soluble L-selectin (sL-selectin) is measurable in the blood plasma as a result of cleavage by a disintegrin and metalloproteinase (ADAM)-17 [10,20,21]. Clinical studies show that L-selectin is shed and detected at elevated levels in the plasma during the systemic inflammatory response [22]. Interestingly, Seidelin and colleagues [22] found that the greatest survival was among septic adults that presented with the highest levels of sL-selectin, and similar findings were made in another study focused on children [19]. Additionally, in an *in vitro* fluid shear flow model, exogenously added sL-selectin inhibited leukocyte rolling and firm adhesion to the endothelium in a dose-dependent manner, presumably by competing with cell surface L-selectin for binding of endothelial ligands [23]. Moreover, Ferri and colleagues have demonstrated that systemic administration of exogenous sL-selectin to mice *in vivo* reduced intravascular leukocyte rolling and adhesion, and as a consequence decreased vascular leak in models of both local inflammation and sepsis [24-26]. Alternatively, addition of a small molecule inhibitor of shedding increased leukocyte adhesion and vascular leak in the same settings [26]. The authors thus propose a significant protective role for L-selectin shedding in sepsis.

P-selectin

P-selectin is found within both endothelial cells and platelets [27,28]. As with the other selectins, P-selectin can be measured in its soluble form in cell culture supernatants and in blood plasma, with greater levels found in septic patient plasma [29]. Mechanisms for P-selectin shedding remain poorly characterized, although some experimental data show that shedding of P-selectin might occur through cleavage by matrix metalloproteinase in patients with cardiovascular disease or hypertension [30,31]. The degree to which plasma soluble P-selectin (sP-selectin) is derived from endothelial cells versus platelets remains unclear. However, one study found a strong positive correlation between coagulation (disseminated intravascular coagulation, fibrinogen consumption and thrombin activation markers) and sP-selectin in septic patients, indicating a significant

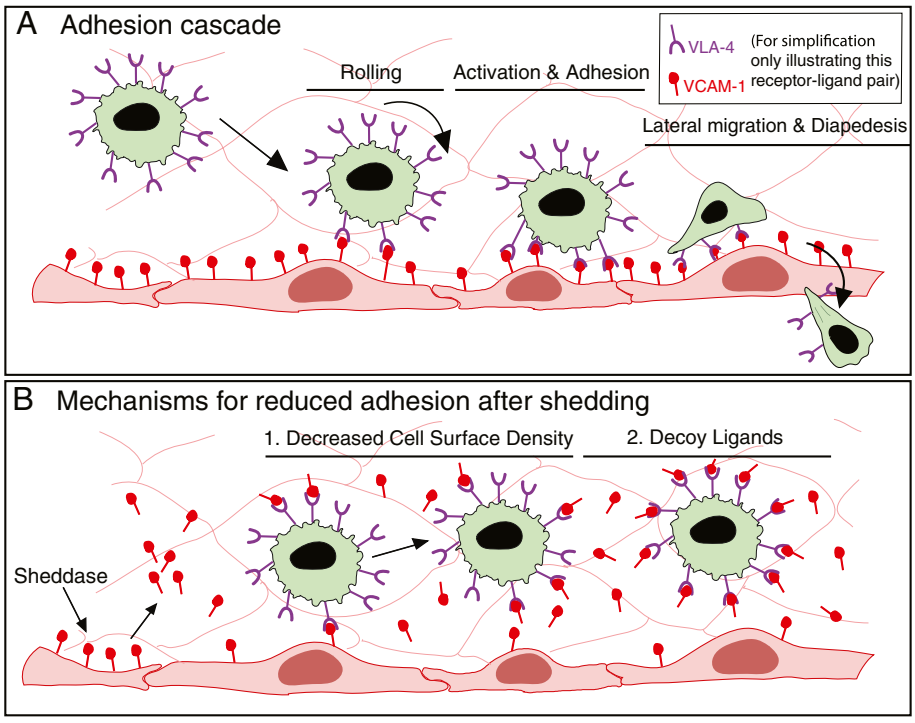


Figure 2 Shedding of selectin and immunoglobulin superfamily adhesion molecules and its functional implications. For simplification, only one example receptor ligand pair (very late antigen-4 (VLA-4)/vascular cell adhesion molecule-1 (VCAM-1)) is illustrated. **(A)** Interactions of cell surface integrin VLA-4, present on leukocytes, with endothelial cell surface VCAM-1 during different steps in the leukocyte adhesion cascade. **(B)** Ectodomain shedding of cell surface VCAM-1 (thereby generating the soluble isoform sVCAM-1) by sheddases might reduce leukocyte adhesion to the endothelium on two complementary levels: reduction of cell surface density of adhesion molecules (for example, decreased endothelial cell surface VCAM-1, in this example); and binding of the resulting soluble isoforms to cell surface ligands (that is, binding of sVCAM-1 to leukocyte cell surface VLA-4 in this example), thereby serving as competitive antagonists (or decoy ligands) for the remaining cell-surface adhesion receptors. See [10] and the text for more details on functional implications of shedding.

role for platelet shedding of P-selectin [32]. Independently of its sources, sP-selectin could negatively modulate direct leukocyte–endothelial interactions and/or indirect platelet-mediated secondary capture of leukocytes on the endothelium (both of which are dependent on P-selectin–platelet selectin glycoprotein ligand-1 adhesion), although this remains to be tested directly [28].

Intercellular adhesion molecule-1

In vitro 1 to 6 hours after activation of endothelial cells by cytokines, soluble ICAM-1 (sICAM-1) can be measured in culture supernatants, after shedding mediated by neutrophil elastase-dependent, ADAM-17-dependent and matrix metalloproteinase-9-dependent shedding [10,33-35]. Shedding of ICAM-1 is thought to promote detachment of leukocytes from the endothelium, thus limiting local inflammation [10]. Indeed, addition of exogenous neutrophil elastase was shown to be highly effective at cleaving surface-bound human ICAM-1 *in vitro*, which in turn abrogated Mac-1-dependent leukocyte adhesion [36]. Evidence supports a potentially protective role for ICAM-1 shedding during sepsis. Elevated levels of sICAM-1 are well documented in human sepsis [5,6,11], and studies performed in both humans and mice demonstrate that this is induced within ~4 hours of endotoxin challenge [37-39]. Significantly, septic children with the highest levels of sICAM-1 had better outcomes/survival rates [19], suggesting that shedding and loss of cell surface ICAM-1 from the endothelium may serve a protective function. Interestingly, in a cecal ligation puncture model of sepsis, ICAM-1-knockout mice – whereby cell-surface ICAM-1 is completely abolished – exhibited a significant decrease in leukocyte tissue invasion, organ damage and mortality compared with wild-type mice [37].

Vascular cell adhesion molecule-1

In vitro 1 to 6 hours after cytokine activation, VCAM-1 is measurable in its soluble form (sVCAM-1) in endothelial cell supernatant through shedding mediated by ADAM-17, cathepsin G and neutrophil elastase [10]. Singh and colleagues demonstrate that this may be achieved, at least in part, through the cytokine-mediated (that is, interleukin-1β-mediated and tumor necrosis

factor alpha-mediated) downregulation of tissue inhibitor metalloproteinase-3, which they showed to function as a tonic suppressor of ADAM-17-mediated VCAM-1 shedding [40]. In response to endotoxin, sVCAM-1 was observed to be markedly elevated in mice [38] and humans [39]. Furthermore, increased levels of sVCAM-1 are reported in human sepsis, and higher levels seem to be associated with increased severity of disease and non-survival [5,6]. Shedding of VCAM-1 is implicated to counteract the pro-adhesive state of leukocytes to the endothelium both by lowering endothelial receptor density [10] and by forming sVCAM-1 to act as a competitive inhibitor (or decoy receptor) of leukocyte very late antigen-4 [40,41] (Figure 2). Interestingly, prednisolone – a synthetic glucocorticoid shown to be beneficial in the treatment of sepsis – was shown to enhance sVCAM-1 levels, suggesting the intriguing possibility that its mechanism of action may be at least partially related to potentiation of VCAM-1 shedding [39].

Levels of soluble adhesion molecules: impact of age

Neonates

Basal levels of all soluble adhesion molecules of healthy neonates are comparable with (sICAM-1) or higher than

Table 2 Levels of soluble E-selectin in neonates, children and adults

Study (reference)	Mean age	Sepsis criteria	Healthy (μg/ml)[a]	Number of patients (healthy)	Sepsis (μg/ml)[a]	Number of patients (sepsis)
Neonates						
Dollner and colleagues [52]	0 to 7 days	Clinical	91.4 (2 to 217.8)	24	151.7 (37 to 362.2)	18
Austgulen and colleagues [45]	Pre/at term	Clinical	134.1 (69.5 to 280)	168	187.7 (118.4 to 262.2)	24
Edgar and colleagues [57]	0 to 7 days	Clinical	71 (51 to 118)	27	135 (94 to 192)	192
Giannaki and colleagues [47]	At term	Clinical	139 ± 48	40		
Edgar and colleagues [55]	At term	Clinical	71 (51 to 118)	46	158 (94 to 207)	46
Children						
Andrys and colleagues [60]	6 to 10		57.6 (36.7 to 152.2)	68		
	11 to 15		42.1 (29.9 to 114.1)	90		
Paize and colleagues [61]	2 to 16	PRISM	100 (90 to 110)	40	230 (100 to 380)	20
Krueger and colleagues [62]	3.5 (0.2 to 16)	ACCP/SCCM	68 (49 to 105)	22	131 (112 to 146)	22
Whalen and colleagues [63]	1 day to 17 years	Criteria of Doughty and colleagues[b]	46 ± 6	14	230	77
Nash and colleagues [64]	9		70 (35 to 121)	81		
	15		59 (25 to 119)			
Briassoulis and colleagues [19]	6.5 (2.8)	PRISM	161 ± 43	10	936 ± 399	10
Adults						
Presterl and colleagues [65]	51 (30 to 67)	APACHE II	48.9 (14.3 to 89.9)	20	130 (40 to 570)	20
Weigand and colleagues [66]	58.7 (4.4)	ACCP/SCCM	29 (14.3 to 89.9)	7	85	14
Hynninen and colleagues [67]	49 (17.2)	APACHE II			73 (62 to 89)	11
Knapp and colleagues [68]	51 (21 to 96)	APACHE III	43.7 ± 20.3	15	94.5 ± 54	28
Osmanovic and colleagues [69]	Adult		28.5 ± 14.3	18	118 ± 84	9
Soderquist and colleagues [70]	71 (10 to 91)	Unknown	48 (20 to 97)	15	80 (22 to 200)	41
Takala and colleagues [71]	44 to 59 (17 to 86)	APACHE II	45 (10 to 100)	Unknown	154 (61 to 394)	20
Geppert and colleagues [72]	59 (35 to 85)	SIRS	42.8 ± 19.4	7	96.2 ± 47.3	27
De Pablo and colleagues [73]	61.2 (3.2)	APACHE II	48	36	98	52
Kayal and colleagues [74]	57.2 (3.9)	ACCP/SCCM	40.5 ± 4.5	9	231 ± 41.8	25
Shapiro and colleagues [6]	57 (19)	APACHE III	49	207	95	13
Andrys and colleagues [60]	46		54.3 (8.3 to 116.9)	68		
Giannaki and colleagues [47]	Adult		48 ± 13	40		

ACCP/SCCM, American college of chest physicians/society of critical care medicine; *APACHE*, acute physiology and chronic health evaluation; *PRISM*, pediatric risk of mortality; *SIRS*, systemic inflammatory response syndrome. [a]Data presented as mean (range) or mean ± standard deviation. [b]Criteria from [75]. Ages expressed in years unless otherwise stated.

Table 3 Levels of soluble L-selectin in neonates, children and adults

Study (reference)	Mean age	Sepsis criteria	Healthy (μg/ml)[a]	Number of patients (healthy)	Sepsis (μg/ml)[a]	Number of patients (sepsis)
Neonates						
Figueras-Aloy and colleagues [49]	0 to 14 days	SNAP-II	580 (523 to 717)	12	681 (541 to 757)	15
Kourtis and colleagues [50]	0 to 2 days	Clinical	1,155	75	1,331 (1,123 to 1,427)	14
Giannaki and colleagues [47]	At term		674 ± 223	40		
Rebuck and colleagues [43]	At term		463 (338 to 557)	22		
Koenig and colleagues [42]	0 to 7 days		324 ± 24	10		
Children						
Kourtis and colleagues [59]	Children		3,356 (2,818 to 3,894)	100		
Briassoulis and colleagues [19]	6.5 (2.8)	PRISM	3,750 ± 321	10	6,263 ± 3,813	10
Adults						
Weigand and colleagues [66]	58.7 (4.4)	ACCP/SCCM	460	7	400	14
Kourtis and colleagues [50]	Adult		950 (700 to 1,220)	75		
Schleiffenbaum and colleagues [23]	Adult		1,600 ± 800	63		
Giannaki and colleagues [47]	Adult		938 ± 181	40		
Rebuck and colleagues [43]	Adult		717 (410 to 822)	22		
Koenig and colleagues [42]	Adult		537 ± 28	9		

ACCP/SCCM, American college of chest physicians/society of critical care medicine; *PRISM*, pediatric risk of mortality; *SNAP*, score for neonatal acute physiology. [a]Data presented as mean (range) or mean ± standard deviation. Ages expressed in years unless otherwise stated.

(sE-selectin, sP-selectin and sVCAM-1) basal levels in children or adults (Tables 2, 3, 4, 5 and 6 and Figure 3). Only the levels of sL-selectin are lower in neonates than in children or adults. Importantly, in neonatal sepsis, levels of all soluble molecules are increased, but both the relative and absolute extent of increase is remarkably lower compared with adults or children (Tables 2, 3, 4, 5 and 6 and Figure 3). This raises the important question of whether neonates are less effective at shedding or less avidly upregulate adhesion molecules in the first place. Indeed, some studies have been conducted to directly address this issue, which suggests contributions from both of these mechanisms. Cell surface levels of L-selectin on neutrophils and sL-selectin levels from cord blood were both lower than the cell surface and the circulating form of L-selectin found in adult blood [42-44]. Interestingly,

Table 4 Levels of soluble P-selectin in neonates, children and adults

Study (reference)	Mean age	Sepsis criteria	Healthy (μg/ml)[a]	Number of patients (healthy)	Sepsis (μg/ml)[a]	Number of patients (sepsis)
Neonates						
Figueras-Aloy and colleagues [49]	0 to 14 days	SNAP-II	272 (152 to 288)	12	244 (170 to 324)	15
Sitaru and colleagues [48]	0 days	Clinical	104 ± 71	10	222 ± 128	9
Children						
Paize and colleagues [61]	2 to 16	PRISM	50 (44 to 60)	40	61 (47 to 119)	20
Adults						
Mosad and colleagues [32]	3	SIRS/SOFA	28.6 ± 6		63 ± 9	176
Fijnheer and colleagues [29]	Adult	SIRS	122 ± 38	10	398 ± 203	26
Weigand and colleagues [66]	58.7 (4.4)	ACCP/SCCM	32.1 ± 5.1	7	296 ±56	14
Osmanovic and colleagues [69]	Adult	Unknown	181 ± 44	18	305 ± 158	9
Geppert and colleagues [72]	59 (35 to 85)	SIRS	116.9 ± 33.4	7	291 ± 227.4	27
Leone and colleagues [76]	45 to 47 (16 to 21)	SIRS	62 ± 20	26	129 ± 98	11

ACCP/SCCM, American college of chest physicians/society of critical care medicine; *PRISM*, pediatric risk of mortality; *SIRS*, systemic inflammatory response syndrome; *SNAP*, score for neonatal acute physiology; *SOFA*, sequential organ failure assessment. [a]Data presented as mean (range) or mean ± standard deviation. Ages expressed in years unless otherwise stated.

Table 5 Levels of soluble intercellular adhesion molecule-1 in neonates, children and adults

Study (reference)	Mean age	Sepsis criteria	Healthy (μg/ml)[a]	Number of patients (healthy)	Sepsis (μg/ml)[a]	Number of patients (sepsis)
Neonates						
Figueras-Aloy and colleagues [49]	0 to 14 days	SNAP-II	215 (156 to 274)	12	426 (394 to 458)	15
Apostolou and colleagues [58]	At term	Clinical	358.4 ± 28.9	10	710.7 ± 56.6	10
Dollner and colleagues [52]	0 to 7 days	Clinical	244 (95.2 to 500)	24	413 (255.6 to 500)	18
Austgulen and colleagues [45]	Pre/at term	Clinical	258.8 (94 to 500)	168	394.2 (197.5 to 500)	24
Berner and colleagues [51]	0 to 3 days	Clinical	421 (291 to 459)	35	446 (171 to 534)	136
Edgar and colleagues [57]	0 to 7 days	Clinical	165 (130 to 290)	27	341 (236 to 554)	192
Edgar and colleagues [56]	0 to 7 days	Clinical	205	46	406	46
Children						
Andrys and colleagues [60]	6 to 10		346.8 (206.8 to 486.8)	68		
	11 to 15		269 (184.1 to 354)	90		
Paize and colleagues [61]	2 to 16	PRISM	260 (240 to 300)	40	705 (400 to 850)	20
Whalen and colleagues [63]	1 day to 17 years	Criteria of Doughty and colleagues[b]	205 ± 29	14	595	77
Nash and colleagues [64]	9		310 (280 to 410)	81		
	15		300 (270 to 390)			
Briassoulis and colleagues [19]	6.5 (2.8)	PRISM	199 ± 98	10	172 ± 93	10
Adults						
Weigand and colleagues [66]	58.7 (4.4)	ACCP/SCCM	190	7	1,100	14
Soderquist and colleagues [70]	71 (10 to 91)	Unknown	202 (62 to 392)	15	451 (216 to 1,030)	41
Scherpereel and colleagues [77]	58.9 (14.9)	SAPS II			2,130	63
Hofer and colleagues [78]	65.9 (12.4)	APACHE II	219.6 (195.2 to 285.1)	108	444.7 (330 to 665.5)	18
De Pablo and colleagues [73]	61.2 (3.2)	APACHE II	480	36	1100	52
Kayal and colleagues [74]	57.2 (3.9)	ACCP/SCCM	208 ± 20.5	9	868 ± 131	25
Shapiro and colleagues [6]	57 (19)	APACHE III	185	207	240	13
Andrys and colleagues [60]	46		140 (60.2 to 218.4)	68		
Leone and colleagues [76]	45 to 47 (16 to 21)	SIRS	151	26	824	11

ACCP/SCCM, American college of chest physicians/ society of critical care medicine; *APACHE*, acute physiology and chronic health evaluation; *PRISM*, pediatric risk of mortality; *SAPS*, simplified acute physiology score; *SIRS*, systemic inflammatory response syndrome; *SNAP*, score for neonatal acute physiology. [a]Data presented as mean (range) or mean ± standard deviation. [b]Criteria from [75]. Ages expressed in years unless otherwise stated.

when challenged with neutrophil-activating chemoattractants, neonatal neutrophils exhibited a significantly lower shedding response compared with adult neutrophils [42,43]. Austgulen and colleagues suggest that these differences may be a reflection of a developing immune system [45] that shows features of hyporesponsiveness [46]. Since neonatal sepsis/infection is particularly difficult to diagnose and no dependable predictors exist, sE-selectin [45,47,48], sL-selectin [49,50] and sP-selectin [48,49] as well as sICAM-1 [50-59] and sVCAM-1 [49] were evaluated as markers for the presence of infection in neonates. However, none of these soluble isoforms were introduced in a clinical setting because they did not reach predictive ability. The above discussion (and additional elaborations below) points toward complexities that need to be resolved before meaningful interpretations can be made.

Children

Generally speaking, the basal levels of soluble adhesion molecules in healthy children are similar to or lower than those of adults and neonates. However, both the relative amount and the absolute amount of sE-selectin and sL-selectin during sepsis seem much higher, whereas sP-selectin levels remain low. On the other hand, sICAM-1 and sVCAM-1 have similar basal levels and sepsis generates comparable or higher levels versus adults (Tables 2, 3, 4, 5 and 6 and Figure 3). Three studies assessed age-dependent differences in levels of selectins in healthy children [59,60,64]. Interestingly, infants

Table 6 Levels of soluble vascular cell adhesion molecule-1 in neonates, children and adults

Study (reference)	Mean age	Sepsis criteria	Healthy (μg/ml)[a]	Number of patients (healthy)	Sepsis (μg/ml)[a]	Number of patients (sepsis)
Neonates						
Figueras-Aloy and colleagues [49]	0 to 14 days	SNAP-II	928 (856 to 1,005)	12	1,112 (1,072 to 1,153)	15
Austgulen and colleagues [45]	0 to 7 days	Clinical	1,940 (1,100 to 3,500)	168	1,950 (1,190 to 3,495)	24
Children						
Andrys and colleagues [60]	6 to 15 years		590.8 (359.6 to 822.0)	68		
Paize and colleagues [61]	2.16	PRISM	600 (390 to 790)	40	1,550 (1,360 to 1,910)	20
Krueger and colleagues [62]	3.5 (0.2 to 16)	ACCP/SCCM	766 (644 to 915)	22	1,239 (928 to 1,615)	22
Whalen and colleagues [63]	1 day to 17 years	Criteria of Doughty and colleagues[b]	231 ± 46	14	600	77
Nash and colleagues [64]	9 years		790 (580 to 1,060)	81		
	15 years		780 (420 to 1,000)			
Adults						
Presterl and colleagues [65]	51	APACHE II	545 (374 to 829)	20	2633	20
Knapp and colleagues [68]	51 to 55 (21 to 96)	APACHE III	569 ± 98	15	1,395 ± 801	28
Soderquist and colleagues [70]	71 (10 to 91)	Unknown	533 (354 to 1,018)	15	1,173 (525 to 3,500)	41
Hofer and colleagues [78]	65.9 (12.4)	APACHE II	1,524.7 (991.2 to 2,038)	108	1,147.9 (883.5 to 2,074.4)	18
De Pablo and colleagues [73]	61.2 (3.2)	APACHE II	890	48	1,600	52
Shapiro and colleagues [6]	57 (19)	APACHE III	1,050	49	1,550	95
Andrys and colleagues [60]	46		743 (338 to 1,148)	68		
Leone and colleagues [76]	45 to 47 (16 to 21)	SIRS	458 ± 123	26	1,604 ± 940	11

ACCP/SCCM, American college of chest physicians/ society of critical care medicine; *APACHE*, acute physiology and chronic health evaluation; *PRISM*, pediatric risk of mortality; *SIRS*, systemic inflammatory response syndrome; *SNAP*, score for neonatal acute physiology. [a]Data presented as mean (range) or mean ± standard deviation. [b]Criteria from [75]. Ages expressed in years unless otherwise stated.

had significantly lower levels of sL-selectin when compared with toddlers (average age 2 years) [59]. Additionally, healthy children (age 9 to 15.5 years) were found to have significantly decreasing sE-selectin levels with increasing age [64]. The authors of all three studies suggest that potential developmental changes exist in both expression and shedding of selectins, but that the physiological relevance of these observations remains to be determined.

During sepsis in children, studies show a significant increase in levels of soluble adhesion molecules [19,61-63]. Interestingly, Briassoulis and colleagues show significant increase of sE-selectin, as well as sL-selectin and ICAM-1, especially amongst survivors [19]. The authors conclude that inadequate or suppressed shedding during sepsis might be associated with increased mortality, and they hypothesize that the shedding process is indeed protective for the host. Similarly, in a large pediatric ICU study on microcirculatory dysfunction in meningococcal sepsis in children, levels of sE-selectin, sVCAM-1 and sICAM-1, but not sP-selectin, were significantly increased in septic patients but negatively correlated with the degree of microcirculatory dysfunction (a measure of sepsis severity), as assessed by sublingual imaging [61].

Adults

Generally, basal levels of soluble adhesion molecules in adults are similar to or somewhat lower than those of neonates and children (Tables 2, 3, 4, 5 and 6 and Figure 3). All molecules show increase during sepsis, with sICAM-1 and sP-selectin exhibiting the greatest increases compared with neonates and children. Age group stratification in levels of soluble adhesion molecules in adults is limited. Rudloff and colleagues determined sICAM-1 levels in healthy adults between 18 and 65 years old and reported no age-dependent differences [79].

As discussed above, in a large number of clinical sepsis studies in adults, higher levels of soluble adhesion molecules were generally related to severity of disease and mortality, although statistically significant correlations could not be made [5,6,15-17,37,65-74,76-82]. Some studies imply an alternate interpretation of these levels. For example, clinical studies have demonstrated that septic adults with modest levels of soluble adhesion molecules (putatively reflecting inadequate/aberrant shedding) had poorer outcome and higher mortality than those with the highest levels [22,83]. Donnelly and colleagues found that critically

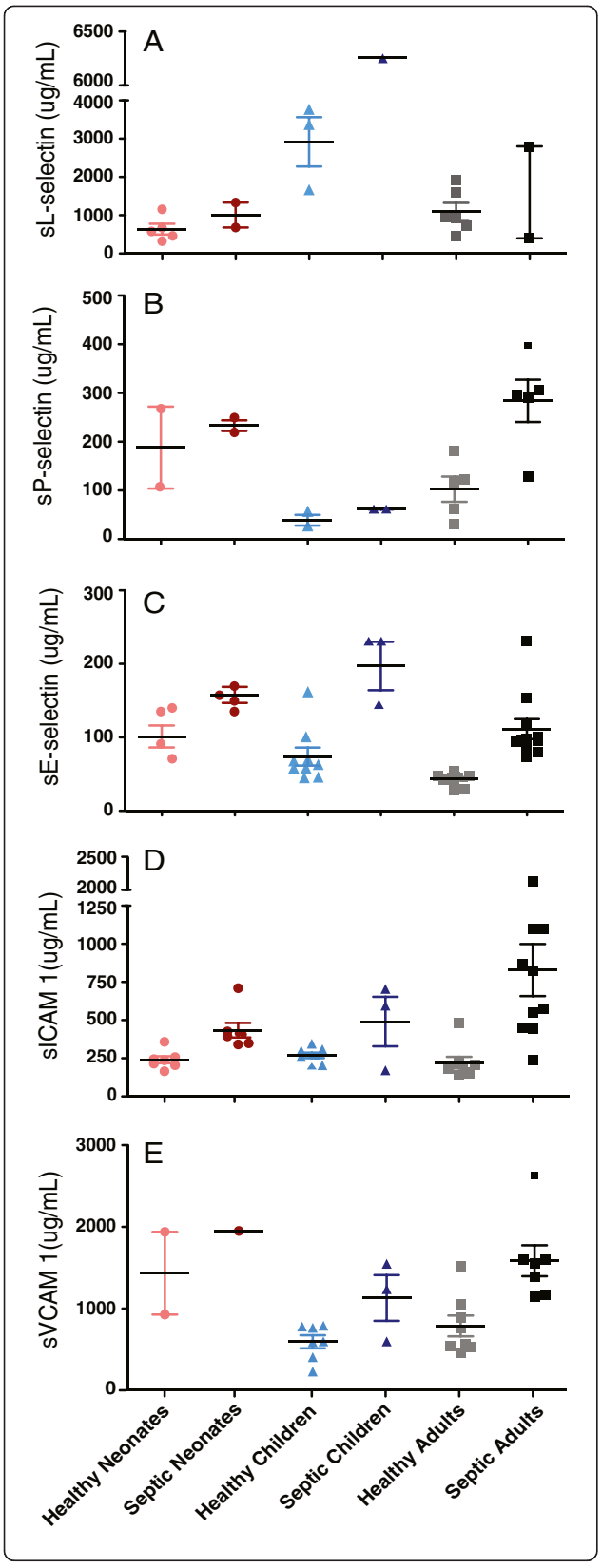


Figure 3 Levels of soluble E-selectin, L-selectin and P-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in healthy and septic neonates, children and adults. Values of soluble adhesion molecules assessed in diverse clinical studies (see Tables 2, 3, 4, 5 and 6) plotted by adhesion molecule to graphically compare absolute and relative amounts in both healthy and septic subjects in distinct age groups. **(A)** Soluble L-selectin (sL-selectin). **(B)** Soluble P-selectin (sP-selectin). **(C)** Soluble E-selectin (sE-selectin). **(D)** Soluble intercellular adhesion molecule-1 (sICAM-1). **(E)** Soluble vascular cell adhesion molecule-1 (sVCAM-1).

ill patients with lower levels of sL-selectin had a higher chance of developing adult respiratory distress syndrome [83], and Seidelin and colleagues found that worse outcomes in septic patients correlated with lesser increases in sL-selectin levels [22]. Interestingly, one experimental study found significantly decreased leukocyte–endothelial interaction in a murine cecal ligation model of sepsis upon addition of exogenous sL-selectin into the circulation at levels comparable with those found in septic adults [27].

Adhesion molecule sheddases in sepsis: a delicate balance

The levels of adhesion molecules are an indirect result of protein cellular expression levels and a direct result of the proteolytic activity of sheddases. Thus, as discussed above (for example, see [42-44]), expression and shedding activities can both independently contribute to overall levels of soluble adhesion molecules in circulation. Several studies have independently assessed levels of circulating sheddases and sheddase antagonists (that is, tissue inhibitor metalloproteinases) in clinical and experimental sepsis in efforts to clarify their contribution to pathology. However, so far these have yielded diverse and inconsistent results showing varied correlation of levels with protection and pathology [84-88], suggesting a delicate balance is required.

The sensitive relationship between levels/activity of sheddases and outcome/effects in the host during sepsis is best reflected by studies from Long and colleagues investigating the role of ADAM-17 in L-selectin shedding in murine sepsis [12,89]. They found that ADAM-17 in mice acts as a homeostatic (rheostat) molecule to control their neutrophil infiltration at sites of inflammation by regulating surface density of L-selectin. Low ADAM-17 activity results in little L-selectin shedding and too much neutrophil infiltration with subsequent collateral tissue damage. However, excessive activity of ADAM-17 promotes excessive L-selectin shedding and subsequently impairs neutrophil infiltration, which is needed to clear inflammation and infection.

Finally, evidence of age-related changes in sheddases and sheddase antagonists (that is, tissue inhibitor

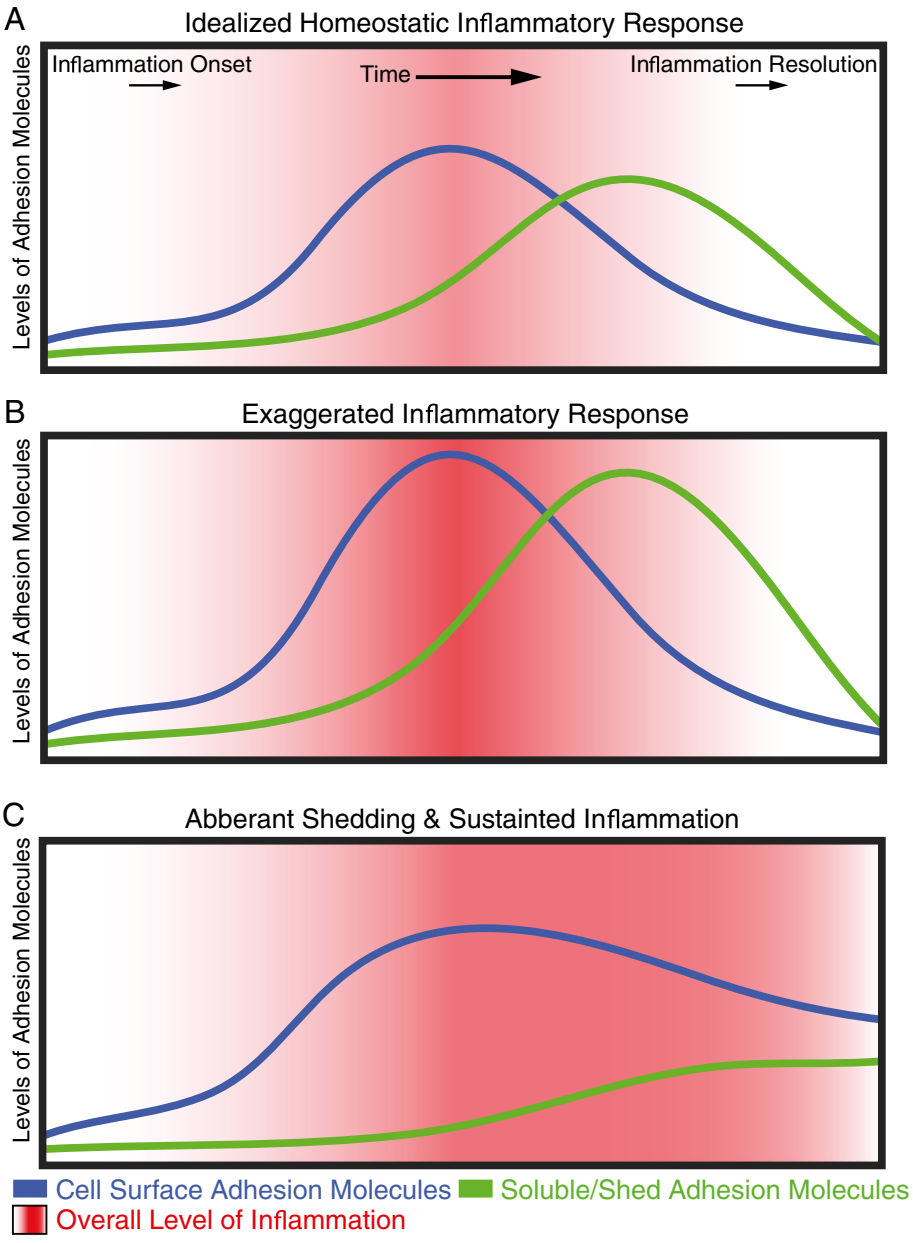


Figure 4 Changes in cell surface and circulating soluble adhesion molecules during progression of inflammatory responses. (A) Idealized homeostatic inflammatory response. Schematic showing the hypothetical increase in cell surface adhesion molecules (blue line) associated with onset of inflammation and the subsequent decrease in them during resolution of inflammation. Shedding and accumulation of circulating soluble adhesion molecules similarly rise and fall (green line), but with a lag in time. Points of highest levels of cell surface adhesion molecules (and not necessarily soluble adhesion molecules) should correlate with the greatest levels of overall inflammation and a propensity for collateral tissue damage (red shading). **(B)** Exaggerated inflammatory and response. Schematic as in **(A)** illustrating a more severe inflammation and greater initial cell surface adhesion molecule expression, and subsequently greater levels of soluble adhesion molecule production. **(C)** Aberrant shedding and sustained inflammation. Schematic as in **(A)** illustrating how a hypothetical deficiency in shedding during inflammation could lead to low levels of soluble adhesion molecules, leaving cell surface adhesion molecules elevated, and allowing for heightened and sustained inflammation.

metalloproteinases) has been observed. It is interesting to speculate that these differences could partially underlie the observed age-related discrepancies in levels of soluble adhesion molecules [90,91].

Conclusion

Increased levels of soluble adhesion molecules generally correlate well with the presence of sepsis in neonates, children and adults. However, their levels are still poorly

predictive of sepsis severity scores, outcome and mortality. Our review raises important issues that need further attention, including age-related discrepancies in soluble adhesion molecule levels and even basic questions about whether these should correlate positively or negatively with mortality.

First, there is a well-articulated hypothesis (and significant experimental support) that shedding is indeed principally a homeostatic process that works to reduce inflammation and promote resolution of inflammation (Figure 4). This is thought to act at two complementary levels: removal of adhesion molecules from cell surfaces directly reduces the ability for cell–cell interaction; and the resulting soluble isoforms serve as competitive antagonists (or decoy ligands) for the remaining cell surface adhesion molecules.

Second, there is substantial evidence that disruption of shedding during sepsis, resulting in substantially lower levels of soluble adhesion molecules (that is, retention of elevated cell surface adhesion molecule levels), could lead to exacerbation of inflammation or promotion of mortality (Figure 4C). Thus, as illustrated in Figure 4, there are many points during the progression of an inflammatory response whereby the functional significance (with respect to the severity of the underlying inflammation) of a given level of soluble adhesion molecule varies greatly. In addition, levels of sheddases are also altered in human and experimental sepsis, suggesting putative functional contribution for these changes in regulating disease progression. The interaction of adhesion molecules and sheddases in the dynamic microenvironment of the cellular surfaces implicates a strong interdependence of these molecules. However, to our knowledge, no studies exist that combine the assessment of both adhesion molecules and their sheddases to assess clinical outcome. Thus, a novel and potentially critical opportunity to enhance clinical efficacy of soluble adhesion molecules exists that remains untapped. Such a combinatorial approach might be particularly useful for improving both sepsis diagnosis (which is greatly needed for the challenging situations in the febrile neonate or extreme older person) and our ability to track efficacy of therapies. Furthermore, serial assessment of the combination of these markers might even be effective in determining morbidity or mortality risk. Finally, it is interesting to consider whether regulation of sheddases and adhesion molecules might be regulated in sepsis at the epigenetic level, potentially offering additional ways to assess disease severity and predict outcomes [92].

Additionally, the age-related and comorbidity-related heterogeneity in levels of soluble adhesion molecules, as well as sheddases, in healthy individuals and septic patients could be an expression of a different basal state, as well as different responsiveness in sepsis, potentially leading to discrepancies in pathophysiology and disease progression between neonates, children or adults. Interestingly, epidemiological research shows a biphasic pattern in age-related differences in incidence and mortality [2-4]. The incidence of neonatal sepsis is 1 to 8 per 1,000 live births with mortality rates of 16%. These rates decrease during childhood (0.2/1,000 children, mortality 10%) and then increase in adults (26.2/1,000 in those over 85 years old, mortality 38.4%) [2-4]. A direct correlation between these rates and levels of soluble adhesion molecules remains speculative, but further attention to this could provide new insights.

In conclusion, while predictive properties of soluble adhesion molecules have been researched intensively, their levels are still poorly predictive of sepsis outcome and mortality. We propose two novel directions for improving clinical utility of soluble adhesion molecules: the combined simultaneous analysis of levels of adhesion molecules and their sheddases; and taking age-related discrepancies into account. Additional investigation of these issues may provide better understanding of the pathophysiology of sepsis and increased usefulness of soluble adhesion molecules as diagnostic and predictive biomarkers.

Abbreviations

ADAM: a disintegrin and metalloproteinase; ICAM-1: intercellular adhesion molecule-1; sE-selectin: soluble E-selectin; sICAM-1: soluble intercellular adhesion molecule-1; sL-selectin: Soluble L-selectin; sP-selectin: Soluble P-selectin; sVCAM-1: soluble vascular cell adhesion molecule-1; VCAM-1: vascular cell adhesion molecule-1.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RZ performed the literature search. RZ, RM, NIS, TWK, FBP and CVC helped draft and revise the manuscript. RZ and CVC prepared the figures. All authors helped to draft the manuscript. All authors read and approved the final manuscript.

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