Published in final edited form as:

J Intensive Care Med. 2011 ; 26(2): 73–87. doi:10.1177/0885066610384188.

Interleukin-6 in Surgery, Trauma, and Critical Care Part II: Clinical Implications

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Abstract

A variety of cytokines play a role in the inflammatory response. Interleukin-6 (IL-6)-type cytokines are released in response to tissue injury or an inflammatory stimulus, and act locally and systemically to generate a variety of physiologic responses. Interleukin-6 concentrations are elevated after surgery, trauma, and critical illness. The magnitude of IL-6 elevation correlates with the extent of tissue trauma/injury severity. Furthermore, there is an association between IL-6 elevation and adverse outcome. Interleukin-6 levels can also be used to stratify patients for therapeutic intervention.

Keywords

IL-6; cytokine; critical care; trauma; surgery

The interleukin-6 (IL-6)-type cytokines play an important role in determining the local and systemic inflammatory response. Elevated concentrations of IL-6 in the postoperative period or in critically ill patients indicate the magnitude of the inflammatory response and provide an understanding of some of the mechanisms responsible for an exaggerated inflammatory response and adverse outcome. As extensively discussed in part I (Basic Science) of this 2-part review, IL-6 exhibits pleiotropic effects and its actions are redundant with other members of this cytokine family. This is made possible by its receptor subunits. One component (IL-6 receptor-α [IL-6Rα]) exists in a soluble form (sIL-6Rα) and allows for IL-6-mediated signaling to occur in cells that do not express this IL-6 receptor component. The other component (gp130) is ubiquitous and is a shared subunit for most other members of this cytokine family, namely IL-11, IL-27, oncostatin M (OSM), leukemia inhibitory

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Authors' Note

This work was presented in part at the 4th annual Chinese Medical Biotech Forum in Dalian, China, on 8/09.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

factor (LIF), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC), neuropoietin/cardiotrophin 2 (NP), and ciliary neurotropic factor (CNTF). Interleukin-31, also a member of this family, is unique in that it does not utilize gp130.

In this review, we use the principles of IL-6 type cytokine physiology reviewed in part I to help understand the clinical findings. We examined articles published within the past 10 years via a Medline search that evaluated the clinical applications of IL-6-type cytokines in surgery, trauma, and critical care. Review articles are cited where they provide the groundwork for evaluation of the clinical studies. Although not individually cited, the relevant seminal articles referenced in these reviews were also examined. The original articles discussed herein focus primarily on IL-6 and disclose a diverse and at times discrepant array of findings regarding the relationship of IL-6 to injury, inflammation, and disease. Interpretation of these sometimes discrepant findings should be tempered with the following caveats: (1) the number of patients studied was often small; (2) most studies were not randomized, some were retrospective, and others were observational; (3) the patients varied with respect to their underlying disease process and severity thereof, as well as in the complexity of surgical procedures or injuries that they sustained; (4) normal controls were not always included; (5) there were wide variations in timing and duration of sample collection; (6) a variety of cytokine measurement values were used (ie, mean, median, peak, etc) and therefore a multitude of statistical analyses were employed; (7) there were often substantial interindividual variations in IL-6 concentrations, making tests for statistical significance problematic; and (8) as the inflammatory response may be compartmentalized, measurement of systemic cytokine concentrations may be of limited value.[1]

A final caveat in interpretation of study results is the method used to measure IL-6. Although IL-6 is a naturally occurring plasma protein in healthy individuals, at nanomolar concentrations, it is often detected in only picomolar quantities.[2,3] Measurement of IL-6 concentrations is hampered by the presence of protein chaperones that limit its detectability.[2,4] Because the half-life of unbound IL-6 (ie, not in complex with IL-6Rα) is less than 1 hour, the long duration of detectability suggests ongoing production and/or binding with a soluble receptor (sIL-6Rα) that prolongs its half-life, as well as interaction with chaperones that limit its bioavailability and even its measurement.[2,4,5] The assays used to detect IL-6 have widely varying sensitivities and often detect only a fraction of the circulating IL-6; greater than 10-fold differences in IL-6 concentrations have been reported between assay systems.[6] Furthermore, the mere detection of IL-6 in serum does not necessarily mean that a significant inflammatory event has occurred, as low serum IL-6 concentrations (ie, less than 20 pg/mL) are frequently detected in healthy volunteers, via common assays.[3] Finally, in some cases, although IL-6 concentrations are significantly different between various patient groups, their values are quite low (less than that found in healthy volunteers) and well within the background/noise level of detection. Hence, the presence of a significant difference in IL-6 concentrations among groups does not necessarily mean that there was a meaningful difference between the groups.

As compared to other cytokines, IL-6 is more frequently assayed because of its relatively long duration of detectability in the blood as well as the availability of rapid blood concentration measurement systems.[7] In this regard, there are even rapid bedside qualitative

tests that determine its presence above a fixed threshold. In many studies, IL-6 concentrations are used as a marker for the severity of the illness or injury. As discussed below, elevated IL-6 concentrations correlate with severity of organ dysfunction and adverse outcome. Consequently, IL-6 concentrations have also been used to stratify patients for therapeutic intervention.

Despite the ease of assay performance and the availability of relatively inexpensive assays (eg, Multiplex), IL-6 concentrations are not readily available or utilized at many institutions. However, as IL-6 is a principal mediator of the acute phase response, and C-reactive protein (CRP) is an acute phase reactant, CRP is often used as a more readily available surrogate marker for IL-6 and the systemic inflammatory response.[8,9] C-reactive protein reflects the impact of trauma on the body and is associated with tissue damage; it has been used as an indicator of the severity of surgical stress.[10-12] Plasma CRP concentrations can increase rapidly and by greater than one thousand times after challenge by an acute inflammatory stimulus.[13] After surgery, CRP concentrations generally increase at 4 to 12 hours, peak at 24 to 72 hours, and may remain elevated for approximately 2 weeks.[5,10,12,14] The rise in CRP concentrations tends to be preceded by a rise in IL-6 concentrations.[15] Although a strong or linear correlation between CRP and IL-6 has been noted by some, the lack of precise correlation between CRP and IL-6 concentrations is expected because other cytokines also induce CRP.[5,14]

Surgery

Surgical trauma and anesthesia induce transient immunosupression, which may increase susceptibility to infections in the postoperative period.[16-18] A diminished cytokine response is often cited as an advantage of laparoscopic surgery, as this is believed to correlate with less tissue injury, and consequently less immunosuppression, and therefore faster recovery. Postoperative serum IL-6 elevations that are proportional to the magnitude of the surgical stress have been described.[19-21]

In this section, we first examine laparoscopic versus open abdominal surgery and demonstrate lower IL-6 concentrations in laparoscopic surgery, corroborating the view that laparoscopic surgery incites less stress on a molecular level. We then examine IL-6 concentrations in the setting of vascular surgery (specifically, aortic aneurysm repair) and later trauma. We demonstrate not only an association between injury severity and IL-6 concentrations but also between elevated IL-6 concentrations and adverse outcome, including multiorgan dysfunction (MOD) and death (Table 1). Concentrations of other cytokines, where relevant, are also provided, as concentrations of these other cytokines and/or their ratio to IL-6 concentrations demonstrates important characteristics of the immune response. In addition to measuring cytokine concentrations, several of the studies discussed examined serum acute phase protein concentrations, especially CRP. Correlations between IL-6 and CRP concentrations with surgical wound size, blood loss, and duration of surgical procedure have been described.[22]

Laparoscopic Versus Open Surgery: Cholecystectomy and Colorectal Resection

It is widely held that laparoscopic abdominal surgery as compared to open abdominal surgery incurs less tissue injury and therefore is associated with a lesser stress response. However, data from studies that focused on commonly studied hormonal mediators of the immune response, such as cortisol and cate-cholamines, have failed to demonstrate any significant difference between laparoscopic and open surgical procedures. Hence, the cytokine response to surgery is being investigated.[22] To this end, several articles on laparoscopy are examined, with the focus on 2 common operations that are performed laparoscopically as well as via open surgery: cholecystectomy and colorectal resection.

Several authors [5,15,23,24] evaluated patients undergoing elective laparoscopic versus open cholecystectomy. In general, significantly higher postoperative IL-6 concentrations were noted in the open surgery group, suggesting greater surgical stress. In some of these studies, corroborating data was obtained by measurement of CRP concentrations, which were also higher in open surgery.[5,15,23] The degree of IL-6 elevation in some of these studies was however rather low, at just above background noise level.

Several investigators[11,17,18,22,25,26] evaluated patients undergoing laparoscopic versus open colonic or colorectal resection for benign and malignant pathology. In general, significantly higher postoperative IL-6 concentrations were found in the open group as compared to the laparoscopic group. In several of the studies, corroborating information was provided by CRP measurement; CRP concentrations were also higher in the open surgery group. [11,18,25,26] Of note, Hildebrandt et al[11] included patients with regional enteritis, including those undergoing small bowel resection only, but had similar findings. However, Dunker et al[16] did not find significantly different IL-6 or CRP concentrations between the laparoscopic and open surgery groups in patients undergoing ileocolic or colonic resection for regional enteritis or colectomy for ulcerative colitis or familial adenomatous polyposis. Factors that may have affected the disparity in IL-6 measurements include heterogeneity of the patient populations, ie malignant versus benign diseases (such as regional enteritis), complexity of the procedure performed and the occurrence of perioperative complications.[27] Furthermore, it is possible that the degree of intestinal manipulation may overcome the effect of the incision size on IL-6 release.[27] Duration of procedure may have also affected IL-6 release. In patients with malignant tumors, laparoscopic surgery may be favored by some because it is associated with less surgical trauma and therefore an attenuated acute phase response. This could help preserve postoperative immunity in patients whose immune response is already compromised by malignant pathology.[27]

Vascular (Abdominal Aortic Aneursym) Surgery—Haveman et al[28] in 2006 evaluated systemic inflammatory cytokine concentrations in 30 healthy controls and 26 patients with ruptured abdominal aortic aneurysms (AAA) who underwent open repair and survived the surgery. Blood samples were collected for up to 2 weeks. They noted significantly higher IL-6 (and IL-10) concentrations on day 1 in 5 nonsurvivors versus 21 survivors (ie median IL-6 concentrations of 543 pg/mL versus 122 pg/mL). Interleukin-10 concentrations were significantly higher on day 1 as well as day 3 in nonsurvivors versus survivors. The nonsurvivors died from multiorgan failure (MOF). They concluded that

elevated IL-6 concentrations in the first days after surgery were associated with multiorgan failure and death. This association indicates that IL-6 concentrations have a predictive value. This predictive value has been harnessed to stratify patients for therapeutic intervention (vide infra).

Bown et al[29] in 2004 prospectively evaluated 135 patients who underwent open AAA repair, electively (n = 100) or for rupture (n = 35). They excluded intraoperative deaths. Blood was taken for cytokine genotyping at anesthesia induction. Cytokine concentrations were measured 24 hours postoperatively. In the elective AAA repair group, there was no significant difference in median IL-6 concentrations between those who developed organ failure, as compared to those who did not. However, patients undergoing elective AAA repair who had the −174 base pair (bp) IL-6 single nucleotide polymorphism (SNP) G allele had a significantly higher incidence of organ failure. In contrast, in the ruptured AAA group, median IL-6 concentrations were significantly higher in patients who developed MODS as compared to those who did not (741.6 pg/mL versus 182.9). However, in the ruptured AAA patients, there was no significant difference in median IL-6 concentrations between the 16 patients who died and those who survived (741.6 pg/mL versus 186.4). In ruptured AAA patients, there were no significant differences in alleles at the −174 bp IL-6 SNP, between patients who did or did not develop MODS and survivors versus nonsurvivors. Possible reasons for this study's findings that differ from the general principles listed above are that only a single time point measurement was done and the wide range of IL-6 values.

Trauma

This section provides further support of the principle that greater tissue trauma results in greater IL-6 release; patients with higher injury severity scores (ISS, a measure of the extent of trauma) exhibit greater IL-6 elevations (Table 1). The articles also demonstrate the importance of multiple IL-6 measurements as IL-6 concentrations vary over time; a single measurement could easily falsely conclude no difference among various groups. Again demonstrated is an association between elevated IL-6 concentrations and adverse outcome. The section concludes with several articles on forensic science that demonstrate that serum IL-6 concentrations persist in measurable quantities after death and that postmortem IL-6 concentrations are higher in traumatic deaths as compared to nontraumatic deaths. Theoretically, this suggests even higher antemortem serum IL-6 concentrations, thereby corroborating the principle that higher IL-6 concentrations are associated with adverse outcome.

Gebhard et al[10] in 2000 evaluated 94 adult trauma patients, of whom there were 66 survivors and demonstrated a time course for IL-6 and CRP elevations. Peripheral blood was collected at the scene of injury, upon arrival to the hospital, and subsequently at varying intervals to 240 hours thereafter. They noted that the time course of IL-6 elevation preceded equivalent production of CRP by at least 12 hours. There was also a positive exponential correlation between maximal IL-6 and maximal CRP concentrations. After 4 hours, there was a clear distinction between the 4 injury severity groups (ISS < 9, 9-17, 18-30, >32) with the highest IL-6 concentrations being seen in patients with the highest ISS and the lowest concentrations being noted in patients with the lowest ISS.

A time course for IL-6 elevations was further elucidated by Maier et al[30] in 2007 in a multicenter prospective observational cohort study evaluating 352 patients with severe traumatic brain injury, multiple body injuries (ISS > 15), or both. Blood was sampled on admission, and at various intervals thereafter to day 28. They found that in all groups, IL-6 concentrations peaked on day 1 and then reached a nadir on day 4. Furthermore, IL-6 concentrations decreased to baseline values on day 10 in the brain injury only group. Patients with late MOF showed a second (ie, biphasic) elevation of IL-6 concentrations. Similarly, Stensballe et al[31] in a prospective, descriptive cohort study of 265 adult trauma patients, found a significant increase of IL-6 as well as IL-10 concentrations over the 24-hour study time period. They also noted an association between IL-6 (as well as IL-10) and injury severity and mortality.

An association between elevated systemic IL-6 concentrations and MOF was demonstrated by Spindler-Vessel et al[32] in 2006. They prospectively evaluated 30 consecutive patients with multiple injuries who were admitted to the intensive care unit (ICU). Blood samples were collected on postinjury days 2 and 4. On day 2, they found significantly higher median IL-6 values in patients with MOF as compared to those without (145 pg/mL versus 61.9 pg/mL, respectively). They found a significant correlation between serum IL-6 values on day 4 and intestinal permeability on day 4.

Significant elevations of IL-11 have also been demonstrated in trauma patients.[33,34] Although IL-11 concentration elevations did not appear to correlate with injury severity, they were significantly higher in nonsurvivors versus survivors, in a 2005 study of 216 patients by Schinkel et al.[33] Extending on this work, Heizmann et al[34] in 2008 retrospectively evaluated 195 severely injured patients who were admitted to the ICU, with a mean ISS of 32 ± 11.3. Cytokine concentrations were measured from day 1 up to 6 weeks. They noted significantly elevated IL-11 concentrations in patients as compared to healthy controls. Concentrations peaked on day 1 and then gradually decreased over the 6 weeks studied. Furthermore, they noted significantly higher CRP concentrations in nonsurvivors (20.1 ± 12.3 mg/dL) versus survivors (13.1 ± 9.7 mg/dL).

Finally, it is interesting to note that systemic IL-6 elevations persisted after death and were often significantly higher in death from traumatic injury as opposed to other causes, with positive associations between injury severity and IL-6 concentrations, as demonstrated in studies by Mimasaka et al.[35-37]

Critical Care

Critically ill patients are a heterogeneous group, with a variety of acute and chronic disease states that may result in perturbations in the IL-6-IL-6 receptor axis. Study of these patients, albeit complicated, enhances understanding of the interaction between critical illnesses and the IL-6 type cytokines. An examination of several recent studies follows, with the aim of evaluating IL-6 concentrations in a variety of clinicopathological settings, as well as examining the influence of genetics thereof (Table 2). As a general principle, IL-6 is elevated in the setting of critical illness and the degree of IL-6 elevation correlates with the

severity of organ dysfunction and adverse outcome. Several small studies are included in this discussion because they contribute to our understanding.

Severe Inflammatory Response Syndrome (SIRS), Sepsis, Multi-organ Dysfunction Syndrome/Failure (MODS/MOF)

In animal models of sepsis, IL-6 concentrations have been shown to have a “robust” prognostic value for determining lethality.[61] A particularly prominent role for IL-6 as compared to other cytokines was demonstrated in mice with early deaths after cecal ligation and puncture; these mice had up to 20-fold higher concentrations of IL-6 as compared to late deaths or survivors.[61] A possible pathophysiologic role of IL-6 in sepsis was illustrated in an animal model of sepsis, by Andrejko et al.[62] They demonstrated that transcription of 3 hepatic transport proteins was repressed by an IL-6 dependent pathway that involves Signal Transducer and Activator of Transcription-3 (STAT3) and hepatocyte nuclear factor-1α (HNF-1α). Meanwhile, a possible cardioprotective role for cardiotrophin-1 (CT-1) in sepsis was demonstrated by Tanimoto et al[63] in an animal model. They demonstrated that pretreatment with CT-1 inhibits lipopolysaccharide (LPS)-induced reduction of left ventricular systolic function and also inhibits *Jak*/STAT, nuclear factor-κβ (NFκβ), and inducible nitric oxide synthase (iNOS)-mediated signal transduction.

In general, as opposed to many other cytokines, IL-6 appears to be more consistently elevated in sepsis and for longer time periods than other cytokines. This phenomenon may be partly because of the relatively high IL-6 concentrations noted in these conditions, as compared to concentrations of other cytokines. As the degree of IL-6 elevation correlates with adverse outcome, IL-6 concentrations have been used to predict outcomes and to stratify patients for intervention. There also appears to be a correlation between IL-6 concentrations and concentrations of other inflammatory markers such as procalcitonin, CRP, IL-8, and tumor necrosis factor α (TNF-α). Meanwhile, elevated LIF concentrations are also noted in septic patients and are associated with adverse outcome.[64] Similarly, OSM concentrations are increased in patients with septic shock.[65]

Pediatric research.—Most of the papers discussed below demonstrate significant elevations of systemic IL-6 concentrations in septic patients as compared to controls, but a few do not. Pathan et al[38] in 2004 evaluated 140 children with meningococcal septic shock and noted that serum IL-6 concentrations correlated with the severity of shock and with the severity of cardiac dysfunction. They further identified IL-6 as a myocardial depressant factor. In 2005, Pathan et al[39] subsequently evaluated 82 children with meningococcal septic shock and found that IL-6 concentrations were significantly higher in septic shock than in convalescence or controls. Interleukin-6 concentrations in controls were undetectable. They also noted that IL-6 concentrations were significantly higher in nonsurvivors versus survivors. Finally, they noted that sIL-6Rα concentrations were significantly lower in acute meningococcemia and correlated inversely with IL-6 concentrations. This study, like others, demonstrated an association between reduced sIL-6Rα concentrations and sepsis. As such, the authors suggested that rather than examining IL-6 elevations alone in understanding sepsis, a derangement of the IL-6-IL-6 receptor axis should be evaluated.

Sikora et al[40] in a study of 20 septic newborns and infants found that the initial concentrations of IL-6, sIL-6Rα, IL-8, and IL-13 were not significantly different from healthy newborn controls (for IL-6 158.72 versus 23.85 pg/mL, respectively). Blood concentrations were determined at time of sepsis diagnosis, prior to initiation of pharmacotherapy, and also 12 to 24 hours after complete recovery and termination of antibiotic therapy. They noted that mean IL-6 and sIL-6Rα (as well as IL-8, IL-10, IL-13, TNFRII, CRP, and procalcitonin) were all significantly lower at the end of treatment than initial values (for IL-6, 159.72 pg/mL versus 3.79 pg/mL). Interestingly, in septic patients, after treatment, IL-6 concentrations were significantly lower than in the 20 healthy newborn controls. The lack of a significant difference in IL-6 values between septic patients as compared to controls may have been due to relatively small sample sizes and large standard deviations in IL-6 measurement (±374.09 pg/mL).

Stryjewski et al[41] in 2005 prospectively evaluated 56 children with malignant pathology who had received chemotherapy within the previous 10 days and had neutropenic fever. Blood samples were drawn at admission to the hospital and 24 and 48 hours thereafter. They found that unlike IL-8 whose concentrations demonstrated statistically significant differences at all 3 time points, IL-6 concentrations were not significantly different at any of these 3 time points between septic and nonseptic patients. Although this study demonstrates a lack of discriminative activity by IL-6 for sepsis, several explanations for the lack of a difference are possible. First, the control population consists of febrile, neutropenic patients and not healthy controls. Second, a wide range of IL-6 values were observed. Third, a small number of patients were studied. Finally, there is the possibility that chemotherapy and/or the neutropenic state might have interfered with IL-6/IL-6 receptor production.

Adult research.—In general, the next several studies demonstrate elevated IL-6 concentrations in sepsis, in a manner that correlates with the severity of illness and is predictive of outcome. Harbarth et al[42] in 2001 prospectively evaluated 78 patients admitted to the ICU with SIRS and suspected infection. The final diagnosis was SIRS in 18 patients, sepsis in 14 patients, severe sepsis in 21 patients, and septic shock in 25 patients. Blood samples were drawn for measurement of cytokines within 24 hours of ICU admission and daily thereafter until discharge from the ICU. They also determined cytokine concentrations in 15 healthy blood donors. They found a statistically significant correlation between IL-6 and TNF-α concentrations. Of the parameters studied, they found that the most discriminative parameter to predict sepsis-related death was an admission IL-6 value greater than 1000 pg/mL. They also noted significantly higher mean IL-6 concentrations in nonsurvivors than survivors. In addition, they noted that CRP concentrations were significantly different between SIRS, sepsis, severe sepsis, and septic shock groups. However, they suggested that plasma measurement of IL-6 and IL-8 concentrations are not optimal for discriminating patients with from those without infectious conditions. This study corroborates the notion that IL-6 is a marker of injury/illness severity and not necessarily of infection, per se.

Selberg et al[43] prospectively evaluated patients in a medical intensive care unit (MICU), of whom 22 had sepsis and 11 had SIRS. They found significantly higher median IL-6 concentrations at less than 8 hours of clinical onset in severe sepsis patients (520 pg/mL) or

sepsis patients (382 pg/mL) as compared to SIRS patients (98 pg/mL). However, there was no statistically significant difference between survivors and nonsurvivors among patients with sepsis or patients with combined sepsis and SIRS. This lack of difference between survivors and nonsurvivors may be related to the degree of IL-6 elevation, which was less in some cases than that reported in some other studies. The range of IL-6 values reported in this study in nonsurvivors was from 110 to 1004, with a median value of 283 pg/mL. As noted previously, an IL-6 value greater than 1000 pg/mL has discriminative power for predicting sepsis-related death.[42]

A study of 76 surgical patients by von Dossow et al[66] found that clinical and laboratory parameters at the time of diagnosis of pneumonia did not significantly differ between those patients who subsequently developed septic shock and those who did not. However, they found that elevated systemic IL-6 concentrations (along with IL-1β, IL-8, and IL-10) were predictive for progression to septic shock.

Genetic studies.—In a study of septic ICU patients by Schluter et al,[44] the −174 bp G/C IL-6 promoter SNP genotype distribution did not differ significantly between patients and healthy controls. However, the GG homozygous genotype was associated with significantly improved survival in sepsis. In the 45 evaluated patients, where blood samples were sequentially collected during septic episodes, they found significantly higher median IL-6 concentrations in nonsurvivors as compared with survivors.

Sutherland et al[45] in 2005 studied haplotype clades in a cohort of 228 white critically ill patients who met at least 2 of 4 SIRS criteria, where a clade is defined as an evolutionarily-related haplotype group. They investigated 4 haplotype clades (C/C/G, G/G/G, G/C/C, and G/C/G) based on 3 SNPs: −174G/C, 1753C/G, and 2954 G/C. The G/C/G haplotype clade was associated with significantly lower 28-day mortality as compared to the other 3 clades. Patients with 2 copies of any of the first 3 clades had significantly greater 28-day mortality as compared with those with 1 or no copies. Patients with 2 copies of the first 3 clades also had significantly fewer days alive and free of cardiovascular dysfunction, vasopressor use, or acute lung injury (ALI). Interestingly, organ dysfunction and 28-day mortality were not associated with the −174 bp G/C SNP.

Watanabe et al[46] examined 113 ICU patients with SIRS whose Sequential Organ Failure Assessment (SOFA) scores were greater than or equal to 5 when their IL-6 concentrations peaked. Of these, 71 patients had sepsis. They found significantly higher maximum concentrations of IL-6 with the allele 2 carriers of the IL-1β −511 bp C/T SNP. An association was suggested between susceptibility to septic shock and allele 2 carriage of IL-1β −511 bp C/T SNP. In another study. Watanabe et al[7] in 2005 evaluated 150 critically ill patients secondary to a variety of diseases and 150 healthy volunteers. Illness types were numerous and some of the included categories were trauma, fulminant hepatic failure, postsurgical, and cardiac or respiratory failure. Blood samples were obtained at ICU admission and consecutively thereafter. Thirty patients had maximal IL-6 values greater than or equal to 10,000 pg/mL. Patients in this high IL-6 concentration group had significantly lower survival, higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, higher SOFA scores, higher ICU admission IL-6 concentrations, higher TNF-α and

IL-1β blood concentrations, were more often septic, and were more often treated with continuous hemodiafiltration. There was a significant association between the presence of the TNF-308*A, IL1RN*2, and IL-1RN*3 alleles and the prevalence of extremely high IL-6 blood concentrations. Of note, they were unable to evaluate the IL-6 −174 bp G/C SNP because this allele was absent in the population studied.

Therapeutic trials in sepsis.—Examination of clinical trials, because of their large sample size and careful patient selection, provides significant insight into the elevation of IL-6 concentrations in sepsis. In these trials, IL-6 concentrations were used not only as a marker of illness severity but also for patient stratification for treatment. In general, IL-6 concentrations greater than 1000 pg/mL were associated with an increased risk of death. These trials, because of the large sample size, were sufficiently powered to conclusively demonstrate the association between elevated IL-6 concentrations and mortality. The discussion here is limited, however, because the findings of these sepsis trials, as they relate to IL-6, have been previously reviewed.[67]

In the well-known PROWESS (Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis) trial of activated protein C in severe sepsis, baseline plasma IL-6 concentrations were elevated in 98.5% of the 1635 patients in whom they were measured. The baseline median IL-6 concentration was approximately 500 pg/mL. Nonsurvivors had significantly higher IL-6 concentrations than survivors.[47,48] Similarly, in the Lenercept Trial of a p55 TNF receptor fusion protein, median IL-6 concentrations were higher in nonsurvivors than in survivors.[49]

Two trials, MONARCS (Monoclonal Anti-Tumor Necrosis Factor-α: A Randomized, Controlled Sepsis Trial) and RAMSES (Randomized Placebo-Controlled Trial of the Anti-Tumor Necrosis Factor Fragment MAK 195F in Hyperinflammatory Response in Severe Sepsis), evaluated the anti-TNF-α antibody, afelimomab, in patients with sepsis. In the MONARCS trial, patients with severe sepsis were divided into 2 groups based on IL-6 concentrations greater than or less than 1000 pg/mL.[50] In the placebo-treated group, patients with IL-6 concentrations greater than 1000 pg/mL had a significantly higher mortality rate than those with concentrations less than 1000 pg/mL (47.6% versus 28.6%). Similarly, in the RAMSES trial, IL-6 concentrations of 1000 pg/mL were used to stratify patients for intervention.[51] They again noted that patients who had IL-6 concentrations greater than 1000 pg/mL had a significantly higher mortality than those who did not (55.8% versus 39.6%, respectively).

Acute Lung Injury/Acute Respiratory Distress Syndrome

The studies in this section demonstrate compartmentalization of the inflammatory response and the beneficial effects of a low tidal volume mechanical ventilation strategy. Acute respiratory distress syndrome (ARDS) patients often have elevated bronchoalveolar and serum IL-6 concentrations.[68] Research suggests that an increase in alveolar-capillary permeability is required for translocation of cytokines from the lungs to the circulation.[69] Furthermore, some clinical work suggests that previous lung damage is necessary for an elevation of systemic cytokine concentrations (IL-6, TNF-α, IL-1ra), following conventional

mechanical ventilation strategies.[69] Mechanical ventilation is postulated to increase the production of cytokines in the lung, which in turn induces a local and systemic inflammatory reaction that injures the lung as well as other organs.[70] As LPS-induced cytokine production diminishes monocyte bacterial killing capacity, a persistent pro-inflammatory state may be a risk factor for ventilator-induced pneumonia.[70] Experimental work has demonstrated that the infected lung leaks pro- inflammatory mediators, which in turn result in increased systemic concentrations of pro- and anti-inflammatory cytokines.[66] Mechanical ventilation also contributes to the development of MODS by enhancing local bacterial dissemination as well as decompartmentalizing bacteria and toxins from the alveolar space and releasing them into the circulation.[70,54,71] Specifically, elevated airway pressures increase bacterial translocation and induce disruption of the alveolar-capillary barrier with resultant migration of pulmonary cytokines into the systemic circulation.[54]

Animal models suggest that IL-6 is important in the pathogenesis of lung injury. It should be noted that type II alveolar epithelial cells and alveolar macrophages can produce IL-6.[72,73] Cuzzocrea et al[74] evaluated lung injury induced by administration of carragennan into the pleural space of an IL-6 knockout mouse as well as in wild-type mice that were treated with an anti-IL-6 antibody. Their results indicated that IL-6 has several pro-inflammatory roles. It enhances TNF-α and IL-1 production, enhances iNOS activity, and increases prostaglandin and leukotriene expression. Interleukin-6 also promotes polymorphonuclear cell (PMN) infiltration, lung myeloperoxidase activity, and lipid peroxidation.[74] Furthermore, IL-6 increases bacterial growth, in vitro.[75] Persistence of pro-inflammatory cytokines, including IL-6, has been demonstrated in ARDS nonsurvivors and associated with higher rates of ventilator-associated pneumonia.[75] In this regard, persistent elevation of pro-inflammatory cytokines in bronchoalveolar lavage (BAL) fluid is associated with failure of intrapulmonary bacterial clearance, despite PMN influx.[75]

Bronchoalveolar IL-6 concentrations have been demonstrated to be significantly higher in mechanically ventilated ARDS and/or pneumonia patients as compared with cardiogenic pulmonary edema patients or controls.[76] Stiletto et al[52] evaluated 14 trauma patients with severe lung contusion and ALI or ARDS. They obtained serum cytokine measurements as well as CT-guided BAL specimens from the area of lung contusion within 24 hours of admission and on day 2. They noted that BAL IL-6 concentrations were several times higher than serum IL-6 concentrations, demonstrating compartmentalization of the inflammatory response. However, they did not find a significant correlation between BAL or plasma IL-6 concentrations and lung injury scores.

Parsons et al[53] evaluated 861 patients who were enrolled in the ARDSnet trial of low tidal volume versus traditional tidal volume mechanical ventilation in ALI/ARDS. Plasma was available for at least 1 cytokine measurement in 703 patients at baseline (upon study entry) and 3 days later. Fewer numbers were available for analysis of 3 cytokines: IL-6, IL-8, and IL-10. The lower limit for detection of IL-6 was 20 pg/mL. Baseline and day 3 plasma IL-6, IL-8, and IL-10 concentrations were each significantly higher in nonsurvivors than survivors. Furthermore, baseline IL-6, IL-8, and IL-10 concentrations were significantly higher in septic patients than other risk groups, with a median IL-6 concentration of 412 pg/mL. Compared with the 12 mL/kg strategy, the 6 mL/kg tidal volume strategy was

associated with a significantly greater early decrease in IL-6 and IL-8 concentrations at 26% and 12%, respectively, over 3 days. They concluded that elevated plasma concentrations of IL-6 and IL-8 are associated with adverse outcomes (morbidity and mortality) in ALI/ARDS and that low tidal volume ventilation was associated with an attenuated inflammatory response.

Similarly, Ranieri et al[54] examined cytokine concentrations in 44 patients in a randomized controlled trial that compared the effects of a ventilator strategy designed to minimize ventilator-induced lung injury with conventional mechanical ventilation. They found that mechanical ventilation increases bronchoalveolar and plasma concentrations of IL-6, as well as several other cytokines. However, bronchoalveolar and plasma concentrations of IL-6 were significantly reduced after initiation of a lung-protective strategy, as compared with the conventional ventilation strategy.

Acute Myocardial Infarction /Cardiogenic Shock/Cardiac Surgery

Increased IL-6 concentrations in cardiac tissue have been reported in patients with a variety of pathologic conditions, including acute myocardial infarction (AMI), congestive heart failure (CHF), cardiopulmonary bypass, and septic cardiomyopathy.[77] Plasma concentrations of IL-6 have been reported to be elevated in AMI and CHF.[78] Leukemia inhibitory factor, CT-1, and overexpression of gp130 have been shown to induce cardiac muscle hypertrophy.[77] Although gp130 expression is abundant in the heart, very little IL-6/IL-6 receptor expression is noted there.[78] Similarly, transgenic mice overexpressing IL-6 and sIL-6Rα demonstrate myocardial hypertrophy.[78] In vitro experiments have demonstrated that IL-6 depresses cardiac contractility via a nitric oxide-dependent pathway as well decreasing cytosolic calcium concentrations.[77] Interleukin-6 mediated activation of inducible nitric oxide synthase and subsequent decreased rat ventricular myocyte contractility is mediated by *Jak2*/STAT3.[77]

The following studies demonstrate that IL-6 concentrations are elevated in cardiogenic shock, but to a lesser extent than in septic shock.[55] Furthermore, in patients with cardiogenic shock, elevated IL-6 values are associated with organ dysfunction.[55] In patients with cardiogenic shock and AMI, IL-6 values are significantly higher in nonsurvivors.[56] It also appears that in patients undergoing percutaneous coronary intervention following AMI, IL-6 concentrations in the infarct-related coronary artery are higher than systemic concentrations and are correlated with plaque size.[57] In patients undergoing cardiac surgery, IL-6 concentrations significantly increase, whereas soluble gp130 (sgp130) concentrations significantly decrease, once again demonstrating perturbations in the IL-6-IL-6 receptor axis in disease.[3] Interestingly, elevated IL-6 concentrations have been demonstrated to be associated with impaired hemostasis following cardiopulmonary bypass surgery.[79]

Geppert et al[55] in 2002 examined plasma samples of 51 patients with cardiogenic shock, 26 patients with septic shock, and 11 noncritically ill controls with known/suspected coronary artery disease (CAD) who were admitted for cardiac catheterization. Patients with septic shock had significantly higher IL-6 concentrations than patients with cardiogenic shock, who in turn had significantly higher concentrations than noncritically ill patients. Also cardiogenic shock patients with acute MI had significantly higher IL-6 concentrations than

those without MI. Interleukin-6 concentrations were significantly higher in cardiogenic shock patients who progressed to MOF as compared to those that did not. An IL-6 concentration, measured within several hours of shock onset, which was greater than 200 pg/mL, had 100% sensitivity and 93% specificity for prediction of MOF development in cardiogenic shock patients.

In another study, Geppert et al[56] in 2006, retrospectively evaluated 38 ICU patients with cardiogenic shock and acute MI. Median time of blood sampling was 24 hours after acute MI symptoms. They found initial plasma IL-6 concentrations were significantly higher in nonsurvivors. Furthermore, patients who died within 24 hours of blood sampling had significantly higher IL-6 concentrations than those who died between 24 hours and 30 days or those who died after 30 days. They found that an IL-6 concentration of 200 pg/mL was the most valuable cutoff for predicting 30-day mortality with 87% specificity and 74% sensitivity. Finally, they noted that patients who were successfully revascularized had significantly lower initial IL-6 concentrations than those who were not accepted for revascularization or in those whom percutaneous coronary intervention (PCI) was unsuccessful (125 pg/mL versus 303.1 pg/mL). This latter finding may simply indicate less severe tissue injury and hence the increased likelihood of successful revascularization.

Funayama et al[57] in 2004 evaluated 36 patients with acute MI, all of whom had cardiac catheterization within 24 hours of infarct onset. They examined IL-6 concentrations from a peripheral vein, the ascending aorta, and the infarct-related coronary artery. They found significantly elevated IL-6 values in all 3 samples as compared to peripheral vein samples from controls. Furthermore, IL-6 concentrations in the infarct-related coronary artery (14.4 pg/mL) were significantly higher than aortic (8.0 pg/mL) or peripheral vein (6.5 pg/mL) concentrations. There were also significant correlations between IL-6 concentrations in the infarct-related coronary artery and plaque size. They also noted significantly elevated concentrations of the proteolytic enzyme matrix metalloproteinase-9 (MMP-9) in the infarct-related coronary artery as compared to the ascending aorta. It is believed that IL-6 along with several other cytokines may be released from vulnerable coronary artery plaques, which in turn activates macrophages. In a subsequent study, they demonstrated an association between elevated postpercutaneous coronary intervention coronary artery IL-6 concentrations and late coronary artery restenosis.[80]

Corbi et al[3] in 2000 evaluated 31 patients undergoing CABG with (n = 19) or without (n = 12) cardiopulmonary bypass (CPB). Of note, the number of grafts per patient was significantly higher in the non-CPB group. Serum IL-6 concentrations were measured at the start of the operation, at 15 minutes before skin incision, and 6 hours later. They noted that in both groups, IL-6 concentrations significantly increased with surgery, while sgp130 concentrations decreased significantly. Serum sIL-6Rα concentrations remained unchanged. They suggested that a decrease in sgp130 concentrations could enhance the inflammatory effect of IL-6 after cardiac surgery. They found no significant differences in IL-6 concentrations between the CPB and non-CPB groups.

Neurologic Dysfunction

Severe head injury is associated with immunodepression. Plasma IL-6 concentrations correlate with the severity of this immunodepression.[81] Elevated concentrations of IL-6 and acute phase proteins such as CRP or fibrinogen are also noted in about 75% of patients with ischemic stroke.[58] Furthermore, the ischemic brain appears to be a major source of IL-6; serum IL-6 concentrations correlate with infarct size.[58] As cerebrospinal fluid (CSF) concentrations of IL-6 are higher than their plasma levels, compartmentalization of the inflammatory response is again demonstrated.[58] It should be noted that gp130 is normally widely distributed in neuronal and glial cells in the brain. Inflammation can upregulate its concentrations.[64] Lipopolysaccharide stimulation can increase gp130 mRNA expression in endothelial cells, suggesting that the blood-brain barrier would then become responsive to the IL-6 family of cytokines.[64] It has been further proposed that cytokine translocation across an altered blood-brain barrier following traumatic brain injury may play an important role in the subsequent development of multiorgan failure.[29] The next several articles demonstrate these findings.

Stroke.—Acalovschi et al[58] in 2003 compared 48 acute stroke patients with 48 age- and sex-matched controls. Patients were excluded if they needed ICU care. Although ICU patients were excluded from this study, it is discussed because of its relevant findings. They measured IL-6, sIL-6Rα, and sgp130 levels. Blood samples were obtained within 24 hours of stroke onset or between 24 and 48 hours of symptom onset, as well as days 3, 7, and 90. Patients with stroke had significantly higher IL-6 concentrations at less than 1 day, 1 to 2 days, 3 days, 7 days, and greater than 90 days after stroke, as compared to controls. Serum sgp130 concentrations at these same time points were significantly lower than controls up to 7 days. Soluble IL-6 receptor-α concentrations did not vary significantly over the 7 days that they were measured. There were no significant correlations between IL-6 and its receptor concentrations. However, significant correlations were noted at various (but not all) time points between IL-6 concentrations and CRP levels, fibrinogen levels, or clinical status of stroke patients as measured by the National Institutes of Health Stroke Scale. Interleukin-6 concentrations also significantly correlated with infarct volume. Finally, examination of 4 haplotypes based on 4 SNPs (−597 G/A, −572 G/C, −373 A(n)/T(n), and −174 G/C) in the IL-6 promoter region in 34 patients and 21 controls revealed that the haplotype A-G-8/12-C was associated with low concentrations of IL-6 after stroke. It should be noted that astrocytes express IL-6 in the ischemic brain.

Dziedzic et al[59] in 2002 evaluated 30 patients with supratentorial intraparenchymal hemorrhage and 16 controls. Samples were collected on the second day of stroke (mean delay from stroke symptoms to collection time was 24 hours). They found significantly increased plasma IL-6 and IL-10 concentrations in patients with stroke. Additionally, IL-6 concentrations inversely correlated significantly with Glasgow Coma Score (GCS) at admission. Concentrations of IL-6 were also significantly correlated with hematoma volume and mass effect. There was also a significant correlation between IL-6 and IL-10 concentrations.

Traumatic brain injury.—Beeton et al[60] in 2004 evaluated 21 patients with head injury and fractures, 10 patients with only head injury, and 13 patients who only had fractures. They demonstrated the importance of evaluating the concentrations of both IL-6 as well as its receptors in understanding brain injury. Their controls included 10 healthy volunteers and 13 additional patients attending outpatient appointments. Blood samples were taken within 12 hours of admission to the hospital, then weekly thereafter in head injury patients. They found significantly higher IL-6 concentrations, within 12 hours of admission, in patients with head injury and fracture as compared with outpatient controls or healthy volunteers, with mean values approaching 150 pg/mL. However, they found that concentrations of IL-6, sIL-6Rα, and sgp130 did not correlate with the GCS score. Blood IL-6 concentrations in patients with head injury and fractures did not change significantly over time. There were no significant differences in sIL-6Rα concentrations, within 12 hours of admission, between the various patient groups and outpatient controls or healthy volunteers. After 1 week, patients with head injury with or without a fracture had significantly higher sIL-6Rα concentrations than initial levels. Patients with only head injury had significantly lower sgp130 concentrations than those who only sustained a fracture. In turn, patients with head injury and fractures had significantly lower sgp130 concentrations than patients with fractures alone, outpatient controls, or healthy volunteers. At 1 week, sgp130 concentrations increased significantly as compared to initial concentrations in patients who had head injury and fracture.

Conclusion and Future Directions

Interleukin-6 can be viewed as a “stress cytokine.” As reviewed in part I (Basic Science), IL-6 carries out a variety of important actions in the inflammatory response, such as the generation of acute phase proteins. Interaction of IL-6 with its receptor results in signaling, where the relative number of receptor molecules determines the limits of signaling. A fine balance appears to exist between soluble IL-6 receptor-α subunits which act as agonists and soluble gp130 receptor subunits, which are competitive antagonists. The production and action of IL-6 and its receptor are regulated by the inciting factor. Furthermore, variations in receptor concentrations are noted in inflammation.

Systemic IL-6 concentrations increase with surgical procedures. The degree of elevation correlates with the extent of tissue injury, and therefore varies by surgical approach, eg laparoscopic versus open surgery, as well as by procedural complexity, eg cholecystectomy versus colon resection. In trauma victims, IL-6 concentrations correlate with injury severity and measurable amounts persist after death. In addition, there is an association between the degree of IL-6 elevation and adverse outcomes, including organ dysfunction and mortality in trauma and critical illness. Also, in critically ill patients, IL-6 concentrations are higher in patients with septic shock as compared to those with cardiogenic shock. In patients with lung injury or ischemic stroke, there is an initial compartmentalization of the inflammatory response where IL-6 concentrations in the lungs or CSF, respectively, are higher than serum concentrations. Cytokine spill-over into the circulation with subsequent elevation of serum IL-6 concentrations may be seen with more severe injury. Besides acting as biomarkers, the IL-6-type cytokines also play an important pathophysiologic role in critical illness, such as

inducing myocardial depression, altering hepatic transport protein synthesis, activating leukocytes, and affecting a variety of cellular signaling mechanisms.

Based on the accumulated evidence, it can be concluded that IL-6 is a reliable marker of injury severity in the acute inflammatory response in surgery, trauma, and critical care. As expected, situations that incite minimal tissue trauma are associated with a lesser IL-6 response. In situations where the inflammatory response is compartmentalized, the relevance of IL-6 (ie, its paracrine effects) can be ascertained by tissue immunochemistry. Systemic IL-6 concentrations serve not only as markers for disease severity but also allow patient stratification for therapeutic intervention, as demonstrated by the large sepsis trials. Based on the accumulated data, we would argue for a greater role for serial IL-6 measurement in guiding the care of the severely injured or critically ill patient, outside of research protocols. Interleukin-6 detection could be easily (via ELISA) and cheaply (via a Multiplex assay) integrated into a standard laboratory panel. Qualitative, point of care testing for IL-6 elevations above a given threshold is also available. Interleukin-6 values could be used to guide antiinflammatory therapies, such as Activated Protein C. However, until IL-6 sampling is more readily available, we suggest closer monitoring of acute-phase protein concentrations to help guide therapeutic decision making. Specifically, CRP is a more readily available surrogate for IL-6 effects.

One particularly intriguing area for further research is the role of IL-6 SNPs in trauma. Although there has been some work done in this field, specifically in trauma patients with sepsis,[82] clearly more study is needed. To this end, we suggest a larger, multicenter study to not only evaluate the influence of genetics but also to further elucidate the pathophysiologic role of IL-6 in trauma. A large sample size, at least several hundred, is needed to capture the variable SNP frequencies. Studies with smaller numbers of patients have encountered the problem of inadequate sample size to capture the desired genotype. Also, a similar-sized healthy control population would need to be examined, as part of the quality control process. Further, to allow comparison among institutions of IL-6 values, utilization of the same assay system would be advisable, with the appropriate controls. Given the relatively short half-life of IL-6 and the temporal nature of IL-6 elevations, serial measurements of IL-6 are necessary to monitor the inflammatory response. Hence, multiple serum IL-6 measurements, starting with initial IL-6 concentration measurements as early as possible following injury, whether this is in the field or upon hospital admission, and continuing measurements at regular intervals for several days after the injury, should be performed. Collection of multiple samples at an earlier time period would demonstrate the most changes, whereas later sample collection could detect a possible biphasic immune response. Multiple systemic IL-6 measurements are also essential because the *IL-6* gene is induced in various cell types directly and is also indirectly modulated by the trauma/inflammatory process. Furthermore, a time course determination of IL-6 changes in individual patients is important in that the relative changes will define each patient and do not depend on comparison among patients. Measurement of IL-6 as part of a multiplex assay that also determined the concentrations of IL-6 receptors, other cytokines such as IL-10, and acute-phase proteins such as CRP would provide a more complete picture of the role of genetics in trauma. Measurement of CRP would also allow us to generate conclusions about systemic IL-6 activity.

Acknowledgments

Funding

Research in Dr. Heinz Baumann's laboratory was supported by NCI grant CA085580 and RPCI grant 016056.

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Table 1.

Overview of Selected IL-6 Papers in Surgery and Trauma

Reference Number	Condition	Patients (n)	Sample Collection	Results[a]
Laparoscopic versus open surgery Cholecystectomy				
Cholecystectomy				
5	Symptomatic cholelithiasis without cholecystitis	71	Pre-op to 48 hours post-op for IL-6, to 7 days post-op for CRP	IL-6 and CRP levels significantly higher in open group
15	Elective cholecystectomy	40	Pre-op to 12 hours post-op	IL-6 and CRP levels significantly higher in open group
23	Elective cholecystectomy	16	Pre-op to 48 hours after skin incision	IL-6 and CRP levels significantly higher in open group
24	Elective cholecystectomy	30	Pre-op to 24 hours post-op	IL-6 levels significantly higher in open group
Colorectal resection				
11	Crohn disease, colon cancer, or colon adenoma	42	Pre-op to 2 days post-op for IL-6 to 5 days for CRP	IL-6 levels significantly higher post-op in open surgery CRP levels significantly higher in open group up to POD #3
17	Colorectal cancer resection without metastases	40	Pre-op to 7 days post-op	Significantly higher plasma IL-6 to 24 hours post-op in open surgery
18	Rectosigmoid cancer resection patients without metastases	34	Pre-op to 72 hours post-op for IL-6 to 4 weeks post-op for CRP	IL-6 and CRP levels significantly higher in open group
22	Elective colectomy for cancer with or without metastases	97	Pre-op to 72 hours after surgery	IL-6 levels were significantly higher in the open group at multiple time points post-op.
25	Colorectal tumor resection	60	48 hours pre-op to 7 days post-op	IL-6 levels returned to near basal levels at 72 hours Peak and overall IL-6 and CRP levels significantly higher in open surgery
26	Colorectal carcinoma resection	27	Pre-op day to 7 days post-op	IL-6 values significantly higher on postoperative day 1 in open surgery. IL-6 levels returned to preop levels within 3 days of surgery
16	Ileocolic resection for Crohn, ulcerative colitis, or familial adenomatous polyposis	34	Pre-op to 7days post-op	IL-6 levels not significantly different between laparoscopic and open surgery
Vascular surgery				
28	Open repair of ruptured AAA who survived surgery	30	Days 1-14	IL-6 levels significantly higher in nonsurvivors on POD#1
29	Open repair of AAA elective or ruptured AAA	135	24 hours post-op for cytokine levels, pre-op for genotyping	Elective repair patients had no significant difference in median IL-6 levels between those with or without adverse outcomes. Elective repair patients with–174 bp SNP IL-6 G allele had significantly higher incidence of organ failure
Trauma				
10	Adult trauma patients	94	Scene of injury to 240 hours	IL-6 levels significantly higher in patients with higher ISS, at multiple time points
30	Severe traumatic brain injury and/or multiple injuries	352	Admission to day 28	IL-6 levels peaked on day 1 and reached a nadir on day 4. Patients with late multiorgan failure showed a second (biphasic) IL-6 level peak
31	Adult trauma patients	265	Upon arrival to 24 hours	IL-6 (and IL-10) levels increased significantly over 24 hours.

Reference Number	Condition	Patients (n)	Sample Collection	Results[a]
				IL-6 (and IL-10) levels associated with injury severity and mortality
32	Multiply injured patients admitted to the ICU	30	Post-injury days 2 and 4	IL-6 levels significantly higher on day 2 in patients with MOF versus those without. IL-6 levels not significantly different on day 4 in patients with MOF versus those without

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; IL-6, interleukin-6; ISS, Injury Severity Score; MOF, multiorgan failure; POD, postoperative day; SNP, single nucleotide polymorphism.

[a]The results reported are postoperative or postinjury findings. Please note that in several cases the findings of significant differences between various groups only persist for a period of time after the surgical stress. With recovery, IL-6 levels would be expected to normalize and hence the differences between various groups would no longer persist. Please refer to the text for additional details.

J Intensive Care Med. Author manuscript; available in PMC 2018 November 08.

Table 2.

Overview of Selected IL-6 Papers in Critical Care

Reference Number	Condition	Patients (n)	Results[a]
SIRS/sepsis/multi-organ failure			
Pediatric SIRS/Sepsis			
38	Meningococcal septic shock	140	IL-6 concentrations correlated with severity of shock and severity of IL-6 identified as a myocardial depressant factor cardiac dysfunction.
39	Meningococcal septic shock	82	IL-6 concentrations significantly higher in nonsurvivors. IL-6Rα concentrations correlate inversely with IL-6 concentrations
40	Newborns with sepsis	20	Mean IL-6 concentrations and sIL-6Rα concentrations were significantly lower at end of treatment than initial values. Initial IL-6 and sIL-6Ra concentrations not significantly different from controls
41	Malignancy with febrile neutropenia	56	No significant difference in IL-6 concentrations between septic and nonseptic patients
Adult SIRS/Sepsis/Multiorgan failure			
42	ICU patients with SIRS and suspected infection	78	Significantly higher IL-6 concentrations in nonsurvivors versus survivors. Admission IL-6 value greater than 1000 pg/mL had greatest discriminative power for predicting death. Statistically significant correlation between IL-6 and TNF concentrations
43	MICU patients with SIRS or sepsis	33	Significantly higher median IL-6 concentrations obtained less than 8 hours of onset in severe sepsis patients versus SIRS patients. No significant difference in IL-6 concentrations between sepsis survivors and nonsurvivors
Genetic Studies			
44	Septic ICU patients	45	Significantly higher median IL-6 concentrations in nonsuvivors. −174 bp G/G IL-6 promoter SNP associated with significantly improved survival
45	White critically ill patients with SIRS	228	IL-6 promoter with G/C/G haplotype (at positions −174G/C, 1753C/G, and 2954G/C) associated with significantly lower mortality
46	SIRS ICU patients with SOFA > 5	113	Significantly higher maximum IL-6 concentrations in allele 2 carriers of the IL-1β-511 bp C/T SNP. Susceptibility to septic shock associated with allele 2 carriage for IL-1β −511 bp C/T SNP
7	Critically ill patients	150	30 patients had maximal IL-6 values greater than or equal to 10,000 pg/mL had significantly lower survival, higher APACHE II scores, higher SOFA scores, and were more often septic. TNF-308*A, ILIRN*2, and IL-IRN*3 alleles were significantly associated with extremely high IL-6 blood concentrations
Therapeutic trials in sepsis			
47, 48	PROWESS - Activated Protein C 1635		Nonsurvivors had significantly higher IL-6 concentrations
49	Lenercept	1342	Nonsurvivors had significantly higher IL-6 concentrations
50	MONARCS – afelimomab antibody	2634	In placebo group, patients with IL-6>1000 pg/mL had significantly higher mortality
51	RAMSES – afelimomab antibody	944	IL-6 concentration >1000 pg/mL used to stratify patient therapy with either afelimomab or placebo. Patients with IL-6>1000 pg/mL had significantly higher mortality
Acute lung injury/acute respiratory distress syndrome			

Reference Number	Condition	Patients (n)	Results[a]
52	Trauma patients with severe lung contusion and ALI or ARDS	14	BAL IL-6 concentrations significantly higher than serum concentrations. No significant correlation between BAL or serum IL-6 concentrations and lung injury score
53	ALI/ARDS patients enrolled in ARDSnet trial	861	Baseline and day 3 IL-6 concentrations significantly higher in nonsurvivors. Baseline IL-6 concentrations significantly higher in septic patients. Low tidal volume strategy associated with significantly greater decrease in IL-6 levels
54	ARDS patients	44	Concentrations of IL-6 and several other cytokines are significantly reduced after initiation of a lung-protective ventilation strategy
Myocardial infarction/cardiogenic shock/cardiac surgery			
55	Cardiogenic or septic shock	77	IL-6 concentrations significantly higher in sepsis than cardiogenic shock. IL-6 concentrations significantly higher in patients with cardiogenic shock with MI or MOF, than those without
56	Cardiogenic shock and AMI	38	Significantly higher initial IL-6 concentrations in nonsurvivors
57	AMI patients undergoing cardiac catheterization	36	Significantly higher IL-6 concentrations in infarct-related coronary artery as compared to systemic concentrations. IL-6 concentrations in infarct-related coronary artery correlated with plaque size
3	Patients undergoing CABG	31	Serum IL-6 concentrations significantly higher at 6 hours versus initial values in both groups. No significant difference in IL-6 concentrations between CPB and non-CPB groups. sgp130 concentrations decreased significantly from initial values. sIL-6Rα concentrations at 6 hours versus initial values were unchanged
Neurologic dysfunction			
Stroke			
58	Ischemic stroke (excluded patients requiring ICU care)	48	Significantly higher IL-6 concentrations in patients with stroke versus controls at all time points. sIL-6Rα concentrations did not vary significantly over 7 days. sgp130 concentrations significantly lower in patients with stroke up to 7 days. No significant correlation between concentrations of IL-6 and its receptors
59	Stroke with supratentorial intraparenchymal hemorrhage	30	Significantly increased plasma IL-6 and IL-10 concentrations in patients with stroke. IL-6 concentrations significantly correlated inversely with admission GCS. IL-6 concentrations significantly correlated with hematoma volume and mass effect. CRP concentrations significantly elevated on days 3 and 7 as compared to day 1
Traumatic brain injury			
60	Severe head injury and fractures, head injury alone, fractures alone	44	Significantly higher initial IL-6 concentrations in patients with head injury and fractures as compared with healthy volunteers or outpatient controls. Concentrations of IL-6, sIL-6Rα, sgp130 did not correlate with GCS score

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; AMI, acute myocardial infraction; BAL, bronchoalveolar lavage; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; CRP, C-reactive protein; GCS, Glasgow Coma Score; IL-6, interleukin-6; MOF, multiple organ failure; SIRS, severe inflammatory response syndrome.

[a]Please note that in several cases, the findings of significant differences among various groups only persisted for a period of time after the onset of illness. With recovery, IL-6 levels would be expected to markedly decrease and hence the difference in groups would no longer persist. Also, unless otherwise indicated, IL-6 findings refer to its systemic levels. Please refer to the text for additional details.