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The evolving experience with therapeutic TNF inhibition in sepsis: considering the potential influence of risk of death

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Abstract

Introduction—Septic shock is highly lethal and its incidence is increasing. Although TNF- α plays a key role in sepsis pathogenesis, past efforts to therapeutically inhibit it had limited success. However, there is continued interest in such therapies and there are now ongoing Phase II sepsis trials testing the effects of AZD9773, a TNF-directed polyclonal antibody fragment preparation. Experience with anti-inflammatory agents suggested that their efficacy may relate to sepsis-associated risk of death.

Areas covered—An overview of the biology of TNF and experimental data implicating TNF as a key mediator in sepsis pathogenesis; a review of the earlier clinical experience with anti-TNF therapies demonstrating that when examined across 12 trials, these agents had a highly consistent overall effect which although not reaching significance, was on the side of benefit; a review of data showing that sepsis-associated risk of death may influence the efficacy of anti-inflammatory agents like anti-TNF ones and a review of the rational and clinical experience to date with AZD9773 and its precursor, CytoFab.

Expert opinion—Discusses variables that may need to be accounted for to maximize the success of clinical trials in sepsis testing agents that modulate host inflammation.

Keywords

anti-TNF; clinical trial; drug development; sepsis; therapy

1. Introduction

Despite conventional therapy, infection causing sepsis and septic shock is associated with a high mortality rate [1]. The incidence of sepsis is also rising and is related to several factors [2]. Despite a disappointing clinical experience with mediator-selective anti-inflammatory agents as adjunctive treatments for sepsis during the 1990s, excessive host inflammation is still considered an important pathogenic mechanism underlying sepsis [3]. This point is highlighted by ongoing clinical trials (with enrollment either active or with it complete and results under analysis) or proposed ones of therapies targeting components in the inflammatory response (e.g., corticosteroids [4], eritoran tetrasodium [5], recombinant

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Declaration of interest

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human-activated protein C (rhAPC) [6]). Such agents also include AZD9773 (AstraZeneca, Macclesfield, UK), a polyclonal antibody directed against human TNF- α (ClinicalTrials.gov identifier: NCT01145560 and NCT01144624 [7]).

Continued industry interest in selective TNF inhibitors for sepsis might be unexpected. During the 1990s when there was high industry enthusiasm for the development of mediator-selective anti-inflammatory therapies for sepsis, anti-TNF agents were the most studied (Table 1) [8]. Despite promising preclinical findings, selective TNF inhibitors showed little benefit in more than 10 randomized controlled trials (RCT). For some, this disappointing experience diminished interest in the application of agents selectively targeting host inflammatory mediators like TNF. For others though, this experience provided insights into the complexity of the inflammatory response clinically, as well as ways to potentially improve this therapeutic approach [1,8,9,10]. Notably, examination of the preclinical and clinical experience with mediator-selective anti-inflammatory agents including ones directed against TNF suggested that sepsis-associated risk of death may have influenced their efficacy [8,11–13].

In light of continued interest in the application of anti-inflammatory agents for sepsis and with the ongoing studies of AZD9773, it is relevant to review the rationale for and prior clinical experience with anti-TNF agents. Considering this experience in the context of the potential influence of sepsis-associated risk of death on anti-inflammatory therapies for sepsis is also important. Finally, it is informative to review data now available regarding the use of AZD9773 for sepsis, since this agent is undergoing active clinical testing.

2. TNF biology and data implicating it in the pathogenesis of sepsis

TNF is a cytokine closely associated with regulation of host innate immunity, inflammation and apoptosis and inhibition of tumorigenesis and viral replication. TNF is primarily produced as a 212-amino acid type 2 trimeric transmembrane protein. The soluble cytokine is released from this membrane form via proteolytic cleavage by the metalloprotease TNF converting enzyme (TACE, also called ADAM17). Two receptors, TNF-R1 (TNF receptor type 1, CD120a) and TNF-R2 (TNF receptor type 2, CD120b), bind TNF. TNF-R1 is expressed in most tissues and can be fully activated by both the membrane-bound and soluble trimeric forms of TNF. TNF-R2 is found only in cells of the immune system, and responds to the membrane-bound form of the TNF homotrimer. On contact with TNF, its receptors undergo conformational changes leading to downstream signaling and the activation of at least three different pathways including nuclear factor kappa beta (NF- κ B), mitogen-activated protein kinases (MAPK) and death signaling [14].

While TNF regulates a wide range of cellular functions, its potential to stimulate the innate immune response and host inflammation most closely implicates it in the pathogenesis of sepsis. Data supporting this association comes in several forms. Bacterial products (e.g., lipopolysaccharide (LPS), peptidoglycan) important in the pathogenesis of sepsis are potent stimulators of TNF release *in vitro* [15,16]. *In vitro* testing has also shown that TNF stimulates a range of effects believed to be important for the development of sepsis including among others: upregulation of adhesion molecules on leukocytes, platelets and endothelial and epithelial cells, activation of both thrombotic and fibrinolytic pathways on endothelial and epithelial cells, augmentation of downstream inflammatory pathways and stimulation of potent vasodilators such as nitric oxide [17–20]. In animal models and human studies, challenge with bacterial products or live bacterial infection increases intravascular or extravascular TNF levels or gene expression [21,22]. In some *in vivo* models the level of cytokine response correlates with the magnitude of the challenge [23]. Nonlethal doses of LPS injected into normal human volunteers also increase serum TNF levels [24–26].

Although increases in TNF during sepsis are not a consistent finding clinically, in some studies TNF levels are increased in septic patients and these changes are greater in groups with more severe disease or infection [12,27–32]. TNF administration alone in preclinical models can also produce cardiovascular, pulmonary, renal and hepatic dysfunction in patterns simulating sepsis itself [33–36].

Some of the most important evidence implicating TNF in the pathogenesis of sepsis, however, comes from *in vivo* sepsis models in which administration of selective TNF antagonists increased survival and reduced organ injury. The first of these studies, and a very influential one, showed that early but not later administration of anti-TNF immune serum to mice increased survival with LPS challenge [37]. Subsequent investigations by the same group of investigators and others utilizing differing TNF inhibitors (e.g., anti-TNF immune serum, anti-TNF antibodies, soluble TNF receptor (TNFR), TNFR fusion proteins, TNF siRNA (small interfering RNA)) confirmed this early finding in models including a range of septic challenges (e.g., LPS, bacterial, fungal, cecal ligation and puncture (CLP) and pneumonia) [8,10].

Notably however, while TNF activation of endothelial cells and leukocytes and the stimulation of downstream signaling pathways may contribute to inflammatory injury, these actions are also critical for host defense during both localized and invasive bacterial infection. Inhibition of TNF has been associated with worsened microbial clearance and outcome in several animal infection models [38,39]. TNF knockout models have similarly supported an important role for TNF in host defense [40].

3. Prior clinical experience with TNF-directed agents in sepsis

Despite the likely divergent effects of TNF in both host defense and the injurious inflammatory response and while many studies of TNF inhibitors employed LPS challenges rather than bacterial ones, reports that anti-TNF agents were protective in animal models appeared to support their clinical application for sepsis. Investigations of this therapeutic approach in patients were initiated in the 1990s. Several different types of agents were studied including monoclonal antibodies against TNF and soluble TNF receptors (Table 1) [8]. A prior analysis found that although these agents did not have significant benefit in any of 12 individual clinical trials, in all larger ones enrolling 500 or more patients, therapy consistently had effects on the side of benefit [8,41]. In smaller trials these effects were more variable. Despite this variability in smaller studies, analysis demonstrates that the effects of anti-TNF agents did not differ significantly across the 12 trials ($I^2 = 0$, $p = 0.803$) and the overall effect of treatment on the odds ratio (OR) of survival (95% confidence interval (CI)) was also on the side of benefit (OR = 1.09 (0.98, 1.21)). This overall effect was not significant however ($p = 0.13$) and is one reason why anti-TNF agents are not routinely used clinically for sepsis today ($p = 0.13$).

4. Risk of death and the efficacy of anti-inflammatory agents in sepsis

One striking observation from the experience with anti-TNF agents was their very different effects comparing pre-clinical and clinical sepsis trials [8]. While frequently highly beneficial in preclinical models, these agents had at best only modest benefit clinically. Similar divergent effects had been noted when comparing preclinical and clinical trials of four other mediator-selective anti-inflammatory agents investigated during the 1990s [8]. One possibility for these differences was that variables influencing the agents in clinical trials hadn't been adequately controlled for in preclinical studies. To investigate this possibility, we performed a meta-regression analysis of published controlled preclinical studies which had been cited to support the use of five different mediator-selective anti-inflammatory agents in 22 clinical trials (anti-TNF therapies, IL-1 receptor antagonist

(IL-1ra), anti-bradykinin, platelet-activating factor receptor antagonist (PAF_r) and anti-prostaglandins; Tables 1 and 2) [8]. We also performed prospective experiments in a rat sepsis model examining the influence of the route, type and severity of infection on two anti-inflammatory agents including one against TNF (p75 TNF_sr (TNF-soluble receptor)). Finally, we compared the effects of the agents in the preclinical studies with the clinical ones.

Analysis of the published preclinical studies showed that they were performed at higher control mortality rates than clinical trials (median (25th – 75th quartile)) (88% (79 – 96%) vs 39% (32 – 43%)) (7). On the one hand, this may have been because it is possible to show a significant reduction in mortality in a preclinical study with a smaller number of animals when control mortality is designed to be high. However, we also noted that the effect of the agents on the OR of survival diminished as the risk of death (control mortality rate or control odds of dying) decreased. In fact, among all factors examined in this meta-regression analysis, risk of death explained the majority of the variability (70%) in treatment effect across the preclinical studies. In prospective experiments in the rat model studied over a much broader range of risk than published studies, we found that regardless of the type or route of bacterial challenge, the survival effects of the two different anti-inflammatory agents tested also decreased as the risk of death decreased. When we compared the effects of anti-inflammatory agents in preclinical and clinical studies, we found that at comparable levels of risk (control mortality rate), the agents had very similar treatment effects (Figure 1). Also, in two Phase III trials of either IL-1ra or p-55 TNF_sr, patients were categorized into subgroups by physiology-based scoring systems (modified Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Stratified Acute Physiology Score, respectively). Stratifying by the risk of death score, the treatment effect of these two agents was also significantly related to risk of death ($p = 0.0002$ analyzed across the two agents; Figure 2) [8].

Subsequent findings from both animal and clinical trials by other groups have added support to a relationship between the effects of anti-inflammatory agents in sepsis and sepsis-associated risk of death. A systematic review of animal studies investigating both selective and nonselective TNF inhibitors in animal infection and sepsis models found that the severity of septic challenge (i.e., control mortality rate) was related to the effectiveness of treatment [10]. In a clinical trial testing monoclonal anti-TNF antibody F(ab')₂ (afelimomab) published after our meta-regression analysis, adjusted mortality was significantly reduced with treatment in the prospectively defined subgroup of patients with positive IL-6 levels and a higher control mortality rate (47.6%) but not in the one with negative levels and a lower control mortality rate (28.6%) ($p = 0.041$ and 0.51 , respectively) [12]. However, it was also noted in other analysis of this trial that afelimomab was more beneficial in patients with decreased organ dysfunction at study entry [42].

rhAPC has anti-inflammatory as well as anti-thrombotic effects [43]. In the original Phase III trial (PROWESS) testing rhAPC, this therapy showed significant benefit [43]. However, when stratified based on admission APACHE II score, this benefit was greatest in patients with the highest predicted risk of death [44]. There was no apparent benefit in the lowest-risk patients. Based on this result, rhAPC was approved for patients with a high risk of death as assessed by the APACHE II or other measure (FDA). In subsequent sepsis RCTs both in adults (ADDRESS) and in pediatric patients with lower risks of death, rhAPC was not beneficial [45]. When examined across these trials (and an earlier Phase II trial) and their respective APACHE II subgroups if available, there was a relationship between risk of death and APCs treatment effect (Figure 3A). At this time a confirmatory trial is assessing the effectiveness of rhAPC in septic patients with ongoing shock and a high risk of death [44].

Low-dose corticosteroids have also shown promise for sepsis [46]. These agents have consistently reversed shock in a growing number of trials. However, while they appeared to also increase survival in early smaller trials with higher control mortality rates, in a large multicenter study they did not. A recent meta-analysis examined this combined experience and found a potential relationship between risk of death and the effect of low-dose corticosteroids (Figure 3B) [47]. However, while one published preclinical study in mice supported such a relationship for corticosteroids, another one did not [48,49].

Finally, eritoran tetrasodium is an agent designed to competitively inhibit LPS binding to toll-like receptor 4 and downstream inflammatory cytokine release. Eritoran was beneficial in highly lethal animal sepsis models [50]. Based on this preclinical experience, two doses of eritoran were investigated in a Phase II RCT which prospectively stratified patients into APACHE II quartiles [51]. While eritoran did not significantly reduce overall 28-day mortality, the investigators noted trends toward increased survival in the highest APACHE II score group (APACHE II > 28; $p = 0.105$) and decreased survival in the lowest score group (APACHE II < 21; $p = 0.083$). Examination across all APACHE II quartiles for both eritoran doses combined also showed a relationship between risk of death and treatment effect (Figure 3C) [51–53]. While an international, Phase III multicenter trial in adults with severe sepsis and APACHE II scores between 21 and 37 was recently reported by the manufacturer not to have achieved a significant reduction in 28-day mortality, data from this trial are still under analysis [54].

5. AZD9773

AZD9773 is a therapy based on an earlier one named Cyto-Fab produced by Protherics, Inc. (Brentwood, TN, USA). CytoFab was an affinity-purified preparation of polyclonal ovine Fab IgG fragments derived from the blood of healthy sheep immunized with recombinant human TNF [13]. Compared with monoclonal antibodies to TNF, it has been proposed that polyclonal antibody fragments like CytoFab and AZD9773 have a number of potential advantages [13]. First, their polyclonal nature may allow them to target multiple epitopes on TNF molecules and to potentially achieve higher neutralization levels. Second, a polyclonal antibody may be more broadly applicable in a patient population that includes TNF polymorphisms. Third, Fab fragments are smaller in size than whole IgG and may have greater and more rapid distribution into tissues as well as faster clearance rates. Finally, these fragments may have better safety profiles as they do not bind to antibody (Fc) receptors and cause inappropriate immune activation [13,55–57]. However, just as these modifications may increase the anti-inflammatory effects of such anti-TNF preparations, they may also increase their potential to interfere with TNF's host defense function. It is also noteworthy that the most common TNF polymorphism occurs in the promoter region of the gene and other F(ab')₂ fragment preparations directed against TNF (e.g., afelimomab) did not previously demonstrate therapeutic superiority [12,58].

CytoFab was tested clinically from 1997 to 1998 in a Phase II, randomized placebo-controlled trial of sepsis in 19 intensive care units in the USA and Canada, with results published in 2006 [13]. The primary trial end points included days alive and free from either shock or mechanical ventilation during the first 14 or 28 days, respectively. Secondary end points included 28-day all-cause mortality and cytokine measurements in plasma and bronchoalveolar lavage. Investigators enrolled 81 septic patients with either shock or dysfunction of two organs and randomized them to CytoFab (infused as a 250 unit/kg loading dose, followed by nine doses of 50 unit/kg every 12 h) or placebo (5 mg/kg human albumin). Compared with placebo, CytoFab did not significantly alter shock-free days at day 14 (10.7 vs 9.4, respectively; $p = 0.259$) but did increase ventilator-free days at day 28 (15.9 vs 9.8, respectively; $p = 0.021$). Mortality at 28 days with CytoFab (11 of 43 (26%)) did not

differ significantly from placebo (14 of 38 (37%)) ($p = 0.274$). In subgroup analysis, in the 78 patients who had TNF measured, 45% had detectable plasma TNF levels on admission. Consistent with studies suggesting that TNF levels correlate with the severity of early sepsis, in placebo patients 28-day mortality rate was higher in patients with detectable TNF levels compared with those with undetectable ones (7 of 16 (44%) vs 7 of 20 (35%)) [29]. In patients receiving CytoFab, 28-day mortality rate was similar whether TNF was or wasn't detectable at admission (26% in each). Also, compared with placebo, CytoFab produced trends approaching significance in more shock-free days to study day 14 and more ventilator-free days to day 28 in those with detectable TNF levels ($p = 0.07$ and 0.06 , respectively) but not in those with undetectable TNF levels ($p = 0.92$ and 0.23 , respectively). Although these data are limited, one interpretation is that this type of therapy will have greater efficacy in patients with more severe disease as reflected by a biomarker such as TNF. Alternatively, any differential effect of CytoFab in these TNF subgroups may reflect the presence or absence of the species targeted.

AstraZeneca obtained the rights to further develop Cyto-Fab, now designated as AZD9773. In a Phase IIA dose escalation study of AZD9773 that treated 70 patients (23 placebo and 47 AZD9773), mean baseline APACHE II score was 26 and 80% of patients demonstrated shock [59]. Higher dose treatment reduced TNF levels during the course of administration. Overall, the 28-day mortality was 27.7% in AZD9773 patients and 26.1% in controls. Adverse event profiles for AZD773 and placebo were reported to be similar. In October 2010, AstraZeneca announced that it had begun dosing patients in a global Phase IIB study designed to compare the efficacy and safety of AZD9773 with placebo in adult patients with severe sepsis or septic shock [60]. This trial is a multicenter, randomized, double-blind, placebo-controlled trial in 300 patients evaluating the efficacy of two intravenous dosing regimens of AZD9773. The primary outcome measure is the number of ventilator-free days over 28 days. Secondary outcome measures include 7- and 28-day mortality and characterization of the safety and tolerability of AZD9773. However, this trial continues to await FDA approval in the USA. AstraZeneca has also initiated a separate Phase II study of AZD9773 in Japan (ClinicalTrials.gov identifier: NCT01144624 [7]). This trial is a dose escalation study assessing the safety, tolerability and pharmacokinetics of intravenous infusions of AZD9773 in patients with severe sepsis or septic shock.

6. Conclusion

A review of prior clinical trials testing TNF inhibitors in sepsis suggests that overall these agents, while not altering survival significantly, did have a highly consistent effect which was on the side of benefit. Clinical experience with mediator-selective and other anti-inflammatory agents in sepsis has also provided insights into more effective application of these therapies. Notably, several lines of evidence suggest that sepsis-associated risk of death is an important variable to account for. The Phase II trial of CytoFab, a preparation of ovine polyclonal Fab fragments to human TNF similar to AZD9773, provided preliminary data suggesting that this type of TNF inhibition holds promise. Trials presently underway with AZD9773 appear to account in part for the potential influence of sepsis-associated risk of death by directing therapy at patients with severe sepsis and either shock or other evidence of evolving organ dysfunction. Whether this approach proves safe and effective awaits the outcome of these trials and may depend on optimization of patient selection.

7. Expert opinion

Host inflammation during infection and sepsis has long been regarded as a double-edged sword [1]. While mediators like TNF may contribute to organ injury, shock and death, they are also central to innate immunity and microbial clearance. These divergent effects could

underlie in part the difficulty in applying anti-inflammatory agents to patients with sepsis. While those with severe sepsis and a maladaptive inflammatory response may benefit from selective inhibitors, patients with less severe disease in whom the response continues to exert protective effects may receive little benefit or even be harmed. If such differences are not accounted for in the design of a study, any benefit of the agent in one subgroup may be masked by its lack of benefit or harm in other subgroups. This possibility is supported by the lines of evidence outlined above suggesting that sepsis-associated risk of death influences the efficacy of anti-inflammatory agents. At present however, measures to accurately define populations with low and high risks of death for therapy in sepsis are not available. While scores such as the APACHE II score do correlate with outcome in sepsis, their usefulness to guide therapeutic interventions has never been tested. Also, such scores frequently include components (e.g., pre-existing disease), which may bear little relationship to those factors influencing the relative usefulness of an anti-inflammatory agent. If sepsis-associated risk of death is to be accounted for when applying anti-inflammatory agents, the measures employed should reflect as much as possible the underlying septic process.

Use of biomarkers presents an alternative means to potentially direct therapies targeting host mediators like TNF. These markers would presumably reflect either the severity of the underlying disease or activity of the host mediator being targeted. Data regarding the reliability of TNF as a marker are mixed. Interestingly, however, as discussed above stratification by TNF levels in the Phase II study of CytoFab, while confounded by small patient numbers, may have identified a group with more severe disease in which treatment showed greater efficacy [13]. As also discussed, IL-6 levels in both pre-clinical and clinical studies may provide some predictive capability. The reliability of such markers, however, may also be influenced by other factors such as the duration or source of sepsis or the presence of co-morbid conditions.

Besides factors influencing the efficacy of an anti-inflammatory agent, there are others that may simply obscure benefit in clinical trials [1]. For example, early clinical testing of anti-TNF agents was based on the assumption that criteria defining the sepsis syndrome were sufficient to delineate a population of patients that might benefit from treatment. However, these criteria are nonspecific and likely result in the inclusion of patients in trials without actual bacterial infection. Also, while studies have increasingly tried to limit enrollment to patients demonstrating bacterial sepsis itself, the duration of infection prior to presentation may influence a patient's likelihood of recovery. Treatment may be more effective in patients with earlier compared with later stage disease. Substantial data also suggest that the speed to the initiation of conventional supportive measures, especially antibiotic therapy and infection source control and possibly hemodynamic support, influences outcome. The uniformity of these practices across study groups is difficult to either ensure or analyze in clinical trials.

In the case of AZD9773, it is possible that the polyclonal nature and small size of the agent will increase its efficacy compared with other anti-TNF agents so far studied. However, these characteristics may also augment its potential harmful effects. If its administration is not directed toward those patients with a relatively high sepsis-associated risk of death, it may be difficult to demonstrate meaningful therapeutic benefit, whether such benefit is based on mortality itself or other end points such as the need for mechanical ventilation or vasopressor agents. However, even if AZD9773 is an effective agent, variation in the administration of beneficial supportive measures and in infection source control between study groups may blunt evidence of benefit.

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Article highlights

- Limiting host inflammation continues to be a potential therapeutic goal in the treatment of sepsis and septic shock.
- TNF plays a central role in the host inflammatory response.
- Agents targeting TNF continue to be investigated clinically for sepsis.
- Understanding the impact of variables potentially influencing the effect of anti-inflammatory agents for sepsis is important.
- Sepsis-associated risk of death may be an important variable that should be considered when assessing the efficacy of anti-inflammatory agents for sepsis.

This box summarizes key points contained in the article.

Figure 1. The weighted regression line in this figure shows the relationship between control odds and the odds ratio of survival with treatment for preclinical (filled circles) and clinical trials (open circles) of mediator-selective anti-inflammatory agents

The treatment effect of these agents is significantly related to severity of illness as reflected by the control odds of dying ($p = 0.0001$). These agents while appearing most beneficial with a high risk of death were less beneficial as this risk decreased.

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Figure 2. As shown in this figure, in a Phase III trial of IL-1 receptor antagonist (IL-1ra) and one of p-55 TNF-soluble receptors (TNFsr), septic patients were categorized at study entry into groups based on their predicted risks of death as determined by a modified Acute Physiology and Chronic Health Evaluation II or Stratified Acute Physiology score, respectively [8]

Using the same format as Figure 1, this figure shows the observed control odds and the odds ratio of survival with treatment for these risk categories as well as the weighted regression line for the relationship. Overall, this relationship was significant ($p = 0.0002$).

Study	Number of patients (Survivors/total)		Odds Ratio
Author/Yr [Ref]	Placebo	Treatments	(95% CI)
A. rhAPC Trials [38]			
Bernard GR/2001	27/41	64/90	1.28 (0.58, 2.81)
Bernard GR/2001			
APACHE II 3 ~ 19	189/215	185/218	0.77 (0.44, 1.34)
APACHE II 20 ~ 24	165/222	169/218	1.19 (0.77, 1.85)
APACHE II 25 ~ 29	104/162	156/204	1.81 (1.15, 2.86)
APACHE II 30 ~ 53	123/241	130/210	1.56 (1.07, 2.27)
Abraham E/2005			
APACHE II < 25	963/1147	971/1168	0.94 (0.76, 1.17)
APACHE II ≥ 25	120/159	116/165	0.77 (0.47, 1.26)
Nadel S/2007	196/237	199/240	1.02 (0.63, 1.63)
C. Low dose steroid trials [40]			
Sprung CL/2008	165/251	170/248	0.88 (0.61, 1.28)
Annane D/2002	68/150	58/149	1.30 (0.82, 2.06)
Chawla K/1999	17/23	11/21	2.58 (0.73, 9.12)
Confalonieri M/2005	23/23	16/23	21.36 (1.14, 400.53)
Bollaert PE/1998	15/22	7/19	3.67 (1.01, 13.40)
Briegel J/1999	17/20	16/20	1.42 (0.27, 7.34)
Yildiz O/2002	12/20	8/20	2.25 (0.64, 7.97)
Rinaldi S /2006	18/20	18/20	1.00 (0.13, 7.89)
Oppert M /2005	11/18	12/23	1.44 (0.41, 5.04)
Tandan SM /2005	3/14	1/14	3.55 (0.32, 39.14)
Cicarelli DD /2007	7/14	3/15	4.00 (0.77, 20.68)
Mussack T/2005	9/12	7/12	2.14 (0.38 , 12.20)
E. Eritoran trials [44,45]			
Tidswell M /2010			
APACHE II < 21	46/46	41/50	0.05 (0.00, 0.83)
APACHE II 21 ~ 24	30/44	36/48	1.40 (0.56, 3.48)
APACHE II 25 ~ 28	24/38	33/52	1.01 (0.43 , 2.41)
APACHE II > 28	28/64	29/47	2.07 (1.00 , 4.47)

B. rhAPC relationship **D. Low dose steroid relationship** **F. Eritoran relationship**

Figure 3. Panels A, C and E on the left of this figure summarizes clinical trials comparing either rhAPC, low-dose corticosteroids or eritoran tetrasodium with placebo

When possible, trials were divided based on injury severity scores (in all cases the Acute Physiology and Chronic Health Evaluation II score, APACHE II). Panels **B**, **D** and **F** on the right show the relationship between the odds ration of survival with each of the three therapies and risk of death (control odds of dying). The lines in these panels represent weighted regression analyses for the relationship for each treatment.

Table 1

Summary of anti-TNF therapies studied clinically.

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Table 2

Summary of other major mediator-selective anti-inflammatory agents tested in septic patients.

Study author/Yr [8]	Agent		Number of patients (survivors/total)		OR (95% CI)	
	Type	Name	Manufacture	Treatments		
Fisher CJ Jr/1994	IL-1ra	Antril	Synergen	14/25	56/74	2.44 (0.94, 6.33)
Opal SM/1997	IL-1ra	Antril	Synergen	220/346	234/350	1.16 (0.85, 1.58)
Fisher CJ Jr/1994	IL-1ra	Antril	Synergen	199/302	414/591	1.21 (0.90, 1.63)
Dhainaut JF/1994	PAFra	BN52021	Ipsen	64/130	77/132	1.44 (0.89, 2.35)
Dhainaut JF/1998	PAFra	BN52021	Ipsen	156/308	160/300	1.11 (0.81, 1.53)
Bernard GR/1991	Anti-prostaglandin	Ibuprofen	Upjohn	9/13	7/16	0.35 (0.07, 1.61)
Haupt MT/1991	Anti-prostaglandin	Ibuprofen	Upjohn	8/14	13/16	3.25 (0.63, 16.79)
Bernard GR/1995	Anti-prostaglandin	Ibuprofen	Upjohn	139/231	141/224	1.12 (0.77, 1.64)
Rodell TC/1995	Anti-bradykinin	CP0127	Cortech	60/84	105/167	0.68 (0.38, 1.20)
Fein AM/1997	Anti-bradykinin	CP0127	Cortech	74/126	228/378	1.07 (0.71, 1.61)

CI: Confidence interval; IL-1ra: IL-1 receptor antagonist; OR: Odds ratio; PAFra: Platelet-activating factor receptor antagonist.