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Animal models of sepsis

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Sepsis remains a common, serious, and heterogeneous clinical entity that is difficult to define adequately. Despite its importance as a public health problem, efforts to develop and gain regulatory approval for a specific therapeutic agent for the adjuvant treatment of sepsis have been remarkably unsuccessful. One step in the critical pathway for the development of a new agent for adjuvant treatment of sepsis is evaluation in an appropriate animal model of the human condition. Unfortunately, the animal models that have been used for this purpose have often yielded misleading findings. It is likely that there are multiple reasons for the discrepancies between the results obtained in tests of pharmacological agents in animal models of sepsis and the outcomes of human clinical trials. One of important reason may be that the changes in gene expression, which are triggered by trauma or infection, are different in mice, a commonly used species for preclinical testing, and humans. Additionally, many species, including mice and baboons, are remarkably resistant to the toxic effects of bacterial lipopolysaccharide, whereas humans are exquisitely sensitive. New approaches toward the use of animals for sepsis research are being investigated. But, at present, results from preclinical studies of new therapeutic agents for sepsis must be viewed with a degree of skepticism.

In a review article about animal models of sepsis published more than two decades ago, Stephen Heard and I wrote this sentence: "Despite the considerable progress in this field, sepsis is still an important cause of mortality."[1] We also wrote this sentence: "Sepsis, as a clinical entity, is very heterogeneous and clinical data are invariably confounded by the effects of age, coexisting diseases, and supportive therapy." Obviously, these words are as true today as they were in 1990. Sepsis remains a common, serious, and heterogeneous clinical entity, which is difficult to define adequately. Despite its importance as a public health problem, efforts to develop and gain regulatory approval for a specific therapeutic agent for the adjuvant treatment sepsis have been remarkably unsuccessful.

In 1982, Ziegler et al. reported results from a clinical trial in patients with septic shock of a polyclonal antibody directed against lipopolysaccharide (LPS) from a mutant strain of *Escherichia coli* called J5.[2] Since then, approximately 60 phase 2 (P2) or phase 3 (P3) randomized controlled clinical trials of pharmacological agents for the adjuvant treatment of sepsis have been conducted (**Table 1**). From inspection of **Table 1**, it quickly becomes apparent that survival has been favorably affected, at least in a statistically significant way, in only a very few of these trials. The previously mentioned study of an anti-J5 antiserum by Ziegler and colleagues yielded positive results, but not all patients enrolled in the study were included in the evaluation set and not all deaths were counted in the calculation of mortality rates.[2] The first P3 study of HA-1A, a human monoclonal antibody designed to neutralize the deleterious effects of LPS, showed improved survival for patients treated with the experimental agent.[2] The design and conduct of this study, however, were criticized by experts in the field,[3] and when HA-1A was tested in a canine peritonitis model, excess mortality was observed in the animals treated with the monoclonal antibody.[4] Accordingly, a follow-up multicentric randomized controlled clinical trial was performed, and HA-1A was not shown to provide any therapeutic benefit.[5] A statistically significant, dose-dependent reduction in 28-d mortality was observed in a preliminary, open label P2 trial of anakinra (recombinant human interleukin-1 receptor antagonist).[6] Two subsequent P3 studies, however, failed to validate the encouraging findings from the initial P2 trial.[7,8] When results were adjusted using a logistic regression model that included the effects of pre-determined potential confounding variables, treatment with afelimomab, a F(ab')2 fragment of a murine anti-tumor necrosis factor monoclonal antibody, was shown to significantly improve survival in patients with sepsis and a high circulating concentration of interleukin (IL)-6.[9] A statistically significant improvement in survival was observed in a P2 dose-finding study of pafase (recombinant human platelet activating factor acetylhydrolase,[10] but a subsequent larger P3 trial showed no evidence of therapeutic benefit when patients were treated with the recombinant protein.[11] In a P2 trial, enteral administration of talactoferrin (recombinant human lactoferrin) improved survival of patients with severe sepsis and the treatment effect just missed being statistically significant ($P = 0.052$).[12] Unfortunately, when the same drug was evaluated in a much larger P3 study, enrollment of patients was stopped early by the data safety monitoring board (DSMB) because of excess mortality in the talactoferrin-treated arm.[13] The first P3 study of recombinant human activated protein C yielded unequivocally positive results[14] and led to regulatory approval of the agent in North America and Europe. Subsequent clinical trials of this agent, however, were uniformly disappointing,[15-17] and the commercial product (Xigris®) was withdrawn from the market in 2012. A multicentric clinical trial of therapy with hydrocortisone plus a synthetic mineralocorticoid, which was conducted in 19 intensive care units in France,

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Table 1. Summary of clinical trials of pharmacological interventions for the adjuvant treatment of sepsis, which have been reported since 1982

1st Author	Year	Patients (sample size)	Trial acronym	Experimental agent	Effect on mortality[a]	References
Ziegler	1982	Septic shock (212)		Human antiserum to mutant *E. coli*	Benefit[b]	2
Ziegler		Sepsis and presumed or proven gram-negative infection (543)		HA-1A, a human mAb that binds the lipid A domain of LPS	Benefit	67
McCloskey	1994	Septic shock and gram-negative bacteremia (621)	CHESS	HA-1A, a human mAb that binds the lipid A domain of LPS	No effect[c]	5
Greenman	1991	Gram-negative sepsis (486)		E5, a murine mAb that binds the lipid A domain of LPS	No effect	68
Bone	1995	Gram-negative sepsis with organ dysfunction (847)		E5, a murine mAb that binds the lipid A domain of LPS	No effect	69
Angus	2000	Severe sepsis due to gram-negative infection (1090)		E5, a murine mAb that binds the lipid A domain of LPS	No effect[c]	70
Albertson	2003	Severe sepsis or septic and evidence due to presumed gram-negative infection		MAB-T88, a human mAb directed against an epitope on enterobacterial common antigen	No effect	71
Levin	2000	Children with severe meningococcal sepsis (393)		rBP121, recombinant human bactericidal/ permeability-increasing protein	No effect	72
Abraham	1997	Severe sepsis or septic shock (498)		Lenercept, a recombinant fusion protein that is a dimer of the extracellular portion of the human p55 TNF receptor and the Fc portion of IgG1; it binds and neutralizes TNF	No effect	73
Abraham	2001	Severe sepsis or early septic shock (1342)		Lenercept, a recombinant fusion protein that is a dimer of the extracellular portion of the human p55 TNF receptor and the Fc portion of IgG1; it binds and neutralizes TNF	No effect	74
Fisher	1996	Septic shock (141)		Etanercept, a recombinant fusion protein that is a dimer of the extracellular portion of the human p75 TNF receptor and the Fc portion of IgG1; it binds and neutralizes TNF	Harm	20
Abraham	1995	Sepsis (994)	NORASEPT I	BAY x 1351, a murine anti-TNF mAb	No effect	75
Cohen	1996	Sepsis (564)	INTERSEPT	BAY x 1351, a murine anti-TNF mAb	No effect	76
Abraham	1998	Septic shock (1878)	NORASEPT II	BAY x 1351, a murine anti-TNF mAb	No effect	77
Rice	2006	Severe sepsis or septic shock (81)		CytoFab, F(ab) fragments of an ovine polyclonal antibody to TNF	No effect	78
Reinhart	1996	Severe sepsis or septic shock (122)		Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	No effect	79
Reinhart	2001	Severe sepsis and high serum concentration of IL-6 (446)	RAMSES	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	No effect	80
Panacek	2004	Severe sepsis and high serum concentration of IL-6 (998)	MONARCS	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	Benefit	9
Dhainaut	1995	Septic shock (42)		CDP571, a humanized anti-TNF mAb	No effect	81
Fisher	1993	Severe sepsis or septic shock (80)		CB0006, a murine anti-TNF mAb	No effect	82
Dhainaut	1994	Sepsis (262)		BN 52021, a small molecule PAF receptor antagonist	No effect	83
Dhainaut	1998	Severe sepsis suspected to be caused by gram-negative infection (609)		BN 52021, a small molecule PAF receptor antagonist	No effect	84
Vincent	2000	Clinical suspicion of infection and APACHE II score between 15 and 35 (152)		BB-882, a small molecule PAF receptor antagonist	No effect	85

Table 1. Summary of clinical trials of pharmacological interventions for the adjuvant treatment of sepsis, which have been reported since 1982 (cont'd)

1st Author	Year	Patients (sample size)	Trial acronym	Experimental agent	Effect on mortality[a]	References
Suputtamongko	2000	Severe sepsis (131)		BB-882, a small molecule PAF receptor antagonist	No effect	86
Froon	1996	Systemic inflammatory response syndrome (29)		TCV-309, a small molecule PAF receptor antagonist	No effect	87
Poeze	2000	Septic shock (98)		TCV-309, a small molecule PAF receptor antagonist	No effect	88
Schuster	2003	Severe sepsis without established acute respiratory distress syndrome (127)		Pafase, recombinant human platelet activating factor acetylhydrolase	Benefit	10
Opal	2004	Severe sepsis (1425)		Pafase, recombinant human platelet activating factor acetylhydrolase	No effect	11
Rice	2010	Severe sepsis and shock or respiratory failure (274)		TAK-242, a small molecule inhibitor o TLR4-dependent signaling	No effect	89
Tidswell	2010	Severe sepsis (300)		Eritoran, a derivative of lipid A that acts as TLR4 antagonist	No effect	90
Opal	2013	Severe sepsis (1961)		Eritoran, a derivative of lipid A that acts as TLR4 antagonist	No effect	91
Vincent	2013	Severe sepsis and DIC		ART-123, recombinant human thrombomodulin	No effect	92
Guntipalli	2013	Severe sepsis (194)		Talactoferrin, recombinant human lactoferrin	Benefit	12
	2013	Severe sepsis	OASIS	Talactoferrin, recombinant human lactoferrin	Harm	
Dellinger	2009	Severe sepsis due to confirmed or suspected gram-negative infection (1379)		GR270773, a phospholipids emulsion	No effect	93
Abraham	2001	Severe sepsis (210)		Tifacogin, recombinant human tissue factor pathway inhibitor	No effect	61
Abraham	2003	Severe sepsis and elevated international normalized ratio (1754)	OPTIMIST	Tifacogin, recombinant human tissue factor pathway inhibitor	No effect	60
Wunderink	2011	Severe community acquired pneumonia (2138)		Tifacogin, recombinant human tissue factor pathway inhibitor	No effect	62
Fisher	1994	Sepsis or septic shock (99)		Anakinra, recombinant human interleukin-1 receptor antagonist	Benefit	6
Fisher	1994	Sepsis (893)		Anakinra, recombinant human interleukin-1 receptor antagonist	No effect	7
Opal	1997	Severe sepsis or septic shock (696)		Anakinra, recombinant human interleukin-1 receptor antagonist	No effect	8
Fein	1997	Systemic inflammatory response syndrome and presumed infection (504)		CP-0127, a small molecule bradykinin receptor antagonist	No effect	94
Rodell	1995	Systemic inflammatory response syndrome and presumed infection (504)		CP-0127, a small molecule bradykinin receptor antagonist	No effect	
Bernard	2001	Severe sepsis (1690)	PROWESS	Drotrecogin alfa, recombinant human activated protein C	Benefit	14
Nadel	2007	Children with severe sepsis (477)	RESOLVE	Drotrecogin alfa, recombinant human activated protein C	No effect	16
Abraham	2005	Severe sepsis and low risk of death	ADDRESS	Drotrecogin alfa, recombinant human activated protein C	No effect	15

Table 1. Summary of clinical trials of pharmacological interventions for the adjuvant treatment of sepsis, which have been reported since 1982 (cont'd)

1st Author	Year	Patients (sample size)	Trial acronym	Experimental agent	Effect on mortality[a]	References
Ranieri	2012	Infection, systemic inflammatory response syndrome and shock (1697)	PROWESS-SHOCK	Drotrecogin alfa, recombinant human activated protein C	No effect	17
Bernard	1997	Severe sepsis (455)		Ibuprofen, small molecule isoform unselective cyclooxygenase inhibitor	No effect	95
Diaz-Cremades	1994	Sepsis and multiple trauma patients with antithrombin III level < 70%		Antithrombin III	No effect	96
Fourrier	1993	Septic shock with disseminated intravascular coagulation (35)		Antithrombin III	No effect	97
Eisele	1998	Severe sepsis (42)		Antithrombin III	No effect	98
Baudo	1998	Severe sepsis or septic shock with antithrombin III level <70% (120)		Antithrombin III	No effect	99
Warren	2001	Severe sepsis (2314)	KYBERSEPT	Antithrombin III	No effect	100
Sprung	1984	Septic shock (59)		Methylprednisolone or dexamethasone	No effect[d]	101
Bone	1987	Severe sepsis or septic shock (382)		Methylprednisolone	Harm[c]	102
Bollaert	1998	Septic shock (41)		Hydrocortisone	No effect	103
Oppert	2005	Septic shock (41)		Hydrocortisone	No effect	104
Annane	2002	Septic shock and biochemical evidence of adrenal insufficiency (229)		Hydrocortisone and fludrocortisone	Benefit	18
Sprung	2008	Septic shock (499)	CORTICUS	Hydrocortisone	No effect	19
Arabi	2010	Septic shock and cirrhosis (75)		Hydrocortisone	No effect	105
Briegel	1999	Septic shock (40)		Hydrocortisone	No effect	106
Root	2003	Severe sepsis and bacterial pneumonia (701)		Filgrastim, recombinant human granulocyte colony stimulating factor	No effect	107
Presneill	2002	Sepsis and respiratory dysfunction (18)		Sargramostim, recombinant human granulocyte macrophage colony stimulating factor	No effect	108
Orozco	2006	Sepsis and abdominal infection (58)		Sargramostim, recombinant human granulocyte macrophage colony stimulating factor	No effect	109
Meisel	2009	Severe sepsis and biochemical evidence of immunosuppression (38)		Sargramostim, recombinant human granulocyte macrophage colony stimulating factor	No effect	110
Jaimes	2009	Sepsis (319)		Unfractionated heparin	No effect	111
Staubach	1998	Severe sepsis (51)		Pentoxifylline	No effect	112
Bakker	2004	Septic shock (312)		546C88, small molecule isoform unselective nitric oxide synthase inhibitor	No effect	113
Lopez	2004	Septic shock (797)		546C88, small molecule isoform unselective nitric oxide synthase inhibitor	Harm	21

[a]Unless noted otherwise, mortality refers to 28-d mortality from all causes. In some cases, mortality data analyzed after taking into consideration pre-specified covariates. [b]Treatment with the antiserum significantly decreased hospital deaths, which were assessed as being a consequence of gram-negative bacteremia. [c]Primary endpoint of the trial was 14-d all cause mortality. [d]Hospital deaths.

Table 2. Examples of some pharmacological agents, which have been evaluated in an animal model of sepsis and yielded negative results in one or more human clinical trials

Agent	Species	Challenge	Design	Animal study result	References
IL1-RA	Mouse	Intraperitoneal LPS	First dose of IL1-RA administered 20 min after LPS challenge and continued every 4 h for 24 h	Benefit	114
Methylprednisolone sodium succinate (MPSS)	Baboon	Viable intravenous *E. coli*	Infusion of MPSS started 2 h after start of bacterial challenge	Benefit	65
IL1-RA	Baboon	Viable intravenous *E. coli*	Continuous infusion of IL1-RA started at same time as bacterial challenge	Benefit	115
Lenercept	Baboon	Viable intravenous *E. coli*	Pre-treatment 1 h prior to bacterial challenge	Benefit	116
CDP571	Baboon	Viable intravenous *E. coli*	Pre-treatment 2 h prior to bacterial challenge	Benefit	117
BN 5021	Mouse	Intravenous LPS	Pre-treatment 30–45 min prior to LPS challenge	Benefit	118
BB-882	Mouse	Intravenous LPS	Pre-treatment 5 min prior to LPS challenge	Benefit	119
TCV-309	Mouse	Intravenous LPS 24 h after intraperitoneal carrageenan	Pre-treatment 30 min prior to LPS challenge	Benefit	120
TAK-242	Mouse	Intraperitoneal viable *E. coli* injected 13 d after priming with intravenous viable *Mycobacterium bovis*	Treatment with ceftazidime and TAK-142 at 1 h after bacterial challenge	Benefit	121
TAK-242	Mouse	Intraperitoneal LPS	Pre-treatment with TAK-242 1 h before LPS *or* post-treatment TAK-242 up to 4 h after LPS challenge	Benefit	122
Tifacogin	Rabbit	Peritonitis caused by *E. coli* O18:K+	Treatment with gentamicin at tifacogin, beginning 4 h after onset of infection	Benefit	59
Tifacogin	Baboon	Viable intravenous *E. coli*	Treatment with tifacogin started at 30 min after bacterial challenge	Benefit	123
Tifacogin	Mouse	Cecal ligation and puncture (CLP)	Treatment with tifacogin started 30–60 min after CLP	Benefit	66

yielded marginally positive results,[18] but, because benefit was not confirmed in another, larger multicentric study of hydrocortisone,[19] the therapeutic value of adjunctive therapy with corticosteroids remains quite controversial.

With the exception of the positive results mentioned in the previous paragraph, all other P3 trials of adjunctive pharmacological therapies for sepsis or septic shock performed since 1982 have failed to provide evidence for improved survival. Indeed, treatment with etanercept, a recombinant fusion protein that combines two extracellular binding domains of the human p75 TNF receptor (TNFR2) with the Fc portion of human IgG1, was shown to worsen outcome for septic patients.[20] Similarly, treatment with 546C88 (L-monomethyl arginine, an isoform unselective nitric oxide synthase inhibitor) significantly and dramatically worsened survival for patients with septic shock.[21]

This dismal record likely has many causes. For example, neither of the two anti-LPS monoclonal antibodies, which have been tested in P3 clinical trials, has been shown to effectively neutralize the pro-inflammatory effects of LPS.[22,23] In many trials, the duration of therapy with the experimental agent was arbitrarily determined rather than being adjusted based on clinical or biochemical data. Thus, the period of treatment in some cases might have been too short (or, for that matter, too long).

In a few cases, pharmacological agents were advanced into P2 or even P3 clinical trials in the absence of convincing evidence of efficacy from preliminary studies using animal models of sepsis or septic shock. However, in the vast majority of cases, preliminary studies, using various animal models of sepsis or septic shock, provided evidence for efficacy and supported the decision to carry out clinical trials. Some examples of compounds that failed in one or more P3 clinical trials but were effective in one or more animal models are listed in **Table 2**.

The lack of a truly clinically relevant and predictive animal model appears to be one of the key barriers hampering the development of an effective therapeutic for the adjuvant treatment of sepsis. Over the past couple of decades, literally hundreds of different animal models of sepsis have been used by scientists. In some cases, studies using animal models of sepsis have been used as part of the development pathway for novel therapeutic agents. However, more often animal models have been used as a proxy for the human condition in order to gain insights into pathophysiology. Numerous previous reviews have cataloged in considerable detail the myriad approaches, which have been employed in an effort to recapitulate key features of severe sepsis or septic shock in human beings.[1,24-31] Accordingly, no effort will be made here to repeat this exercise. Rather, the discussion will focus on a concise critique of the most

widely employed animal models of sepsis, focusing on why use of these models have failed to lead to the development of one or more useful pharmacological therapies for the syndrome in humans.

The most popular preclinical sepsis models use mice. Being very small mammals, mice pose little or no danger to laboratory personnel. Inbred strains are widely available from suppliers, and, generally speaking, are relatively inexpensive to acquire and maintain. Moreover, using genetically modified strains of mice is an elegant way to explore the importance of particular gene products in the pathogenesis of sepsis (or the response of septic animals to a pharmacological intervention). While laboratory experiments using any species of animal, especially ones that use organ dysfunction or mortality as a read-out, provoke intense scrutiny from regulatory and oversight groups, mice are not regarded as "companion animals" and, therefore, studies using mice may be regarded as being more ethical than are studies that enroll cats, dogs, horses, or non-human primates as research subjects. Finally, numerous immunological reagents and/or assay kits designed for murine systems are commercially available. These reagents and kits facilitate the measurement of cytokines or other mediators in biological fluids.

Injecting mice with purified LPS ("endotoxin") via either the intraperitoneal (i.p.) route or the intravenous (i.v.) route leads to systemic activation of the innate immune system. If the dose of LPS is large enough, then the animals manifest physiological and biochemical changes that are reminiscent of certain very fulminant forms of gram-negative bacterial infection in humans, most notably overwhelming meningococcemia. Some of the manifestations of acute endotoxemia in mice include systemic arterial hypotension (i.e., shock), lactic acidosis, impaired myocardial contractility, a short-lived monophasic spike in the circulating level of TNF, a more prolonged elevation in the circulating level of IL-6, and a delayed increase in the circulating level of high mobility group box (HMGB)-1. Shock, lactic acidosis, impaired myocardial contractility, and increased circulating levels of TNF, IL-6, and HMGB1 all are features of sepsis or septic shock in humans, although the temporal kinetics and the magnitude of these changes from normal physiology are often different from what is observed in acute murine endotoxemia.

Activation of systemic inflammation by LPS in mice is largely mediated via interaction of the bacterial product with Toll-like receptor (TLR) 4, which is expressed on the surface of both "professional" immune cells, such as monocytes and macrophages, as well as many other cell types, including alveolar epithelial cells and myocardial cells. The intracellular signaling pathways, which are triggered by the interaction of LPS with TLR4, have been extensively investigated and there are many detailed reviews in the literature.[32,33] Certain inbred strains, such as C3H/HeJ mice[34] and TLR4-deficient ("knockout") mice,[34] are hyporesponsive to LPS. It is important to note, however, that C3H/HeJ mice are hyporesponsive but are not entirely unresponsive, to the toxic effects of LPS. For example, the dose of LPS required to induce weight loss in C3H/HeJ mice is about 40-fold less than the dose that is required to produce a similar degree of weight loss in congenic LPS-sensitive C3H/HeN mice.[35] Similarly, there is about a 40-fold difference between the lethal dose of LPS in LPS-responsive (A/HeJ) as compared with LPS-resistant (C3H/HeN) strains of mice.[36]

Compared with humans, mice, even "normally responsive" strains, are remarkably less sensitive to the toxic or lethal effects of LPS. Thus, the dose of LPS, which leads to death in approximately half of mice (i.e., the LD50 dose) is about 1–25 mg/kg.[37-39] This dose is about 1 000 000 times greater than the typical dose of LPS (2–4 ng/kg), which has been used in studies with human volunteer to induce symptoms (e.g., fever or myalgia) and the release of proinflammtory cytokines, such as TNF, into the circulation.[40,41] The LD50 dose of LPS in mice is about 1000-fold to 10 000-fold greater than the dose of LPS that is required to induce severe illness and hypotension in humans.[42] In other words, the roughly 40-fold difference in the dose of LPS that is required to produce toxicity or death in "normally responsive" vs. "hyporesponsive" strains of mice is orders of magnitude smaller than is the difference in LPS dose that is required to produce death or serious illness in "normally responsive" mice as compared with human beings. The biological mechanism(s) that are responsible for the enormous difference between mice and humans with respect to responsiveness to LPS remain to be fully elucidated, but recent evidence obtained by Warren and colleagues suggests that one or more factors, which are present in murine sera, but are absent (or present in much lower concentrations) in human sera, are capable of suppressing the production of pro-inflammatory cytokines by murine (or human) mononuclear cells following stimulation with LPS or other TLR agonists, such as peptidoglycan (major component of the cell wall of gram-positive bacteria), zymosan (a glucan present in the cell wall of yeast) or bacterial DNA.[43] One of these factors may be the iron-binding acute phase protein, hemopexin.[44] Other factors, which have yet to be identified, may be important as well. In any event, the marked discrepancy in LPS sensitivity between mice and people suggests that data obtained using murine models of sepsis may be inapplicable to the human illness.

This view is strengthened by recently published findings from a systematic analysis of the genomic responses in three human conditions, which are associated with activation of the innate immune system, namely burn injury, trauma, and acute endotoxemia, and the corresponding insults in murine models.[45] In this important study, total cellular RNA was extracted from leukocytes isolated from blood, and gene expression profiles were obtained using appropriate Affymetrix GeneChip arrays. The samples from trauma and burn patients were obtained at 7 Level I trauma centers or 4 burn centers in the United States in the course of The Inflammation and Host Response to Injury, Large Scale Collaborative Research Program ("Glue Grant"), which was funded by the National Institutes of Health. The human endotoxemia samples were obtained from eight healthy volunteers, who were challenged with a small i.v. dose of LPS (2 ng/kg). Of note, there was high degree of similarity in the gene expression profiles in leukocytes from human subjects with burn injuries, major trauma, or acute endotoxemia. In marked contrast, there was minimal correlation of expression changes between the human conditions and their murine orthologs in the mouse models. For example, when the gene expression profile for human

endotoxemia was compared with the gene expression profile for murine endotoxema, the Pearson correlation analysis yielded an R^2 value of 0.01 (i.e., essential no correlation at all). Interestingly, the time to recovery (i.e., the time required to restore normal gene expression levels) was far longer in humans (months) as compared with mice (hours to days).

Of course, some concerns have been raised, regarding the findings from the Glue Grant program, which were summarized in the previous paragraph.[46] For example, the gene expression responses of humans were compared with those of only one inbred strain of mice, and it is well known that strain differences in the murine system can markedly affect immunological responses. Furthermore, some of the differences between "mice and men" might reflect the impact of therapeutic interventions rather than just differences between the species with regard to gene expression responses to acute insults, such as trauma or infection. Still, the results obtained by Seok et al.[45] should prompt all researchers to be appropriately skeptical about extrapolating findings from murine sepsis models to the problem of sepsis in patients.

All acute endotoxemia models, irrespective of whether the animals under study are mice or some other species, suffer from the same problem. In these models, activation of the innate immune system can only have deleterious effects; therefore, any intervention that blunts the inflammatory response is likely to be beneficial. In contrast, sepsis in patients is triggered by an infectious process and the immunological responses to microbial challenge can have both salutary and deleterious effects.

Because sepsis in patients often starts with a focus of infection in the lungs or peritoneal cavity,[31] investigators and funding agencies have grown enamored in recent years with animal, especially murine, models of pneumonia and peritonitis. Because of its simplicity and, when performed correctly, its reproducibility, cecal ligation and puncture (CLP), which is a murine model of bacterial peritonitis, has been regarded, at least until the publication of the paper by Seok et al. cited above, as the "gold standard" animal model of sepsis. CLP in mice reproduces a number of key features of secondary bacterial peritonitis in humans, including polymicrobial infection,[47] persistently elevated circulating HMGB1 levels,[48] hyperdynamic circulatory system,[49] and development of acute lung injury.[50] Moreover, some studies, using the murine CLP model, yielded results, which are concordant with the lack of efficacy in human clinical trials of some important pharmacological approaches for the adjuvant treatment of sepsis, such as the administration of antibodies against TNF[51,52] or the administration of IL-1RA.[53] In other cases, however, studies performed using the murine CLP model suggested that therapeutic interventions, such as administration of a PAF receptor antagonist[54] or exogenous PAF acetylhydrolase,[55] would improve survival. In clinical trials, however, these approaches were unsuccessful.

Although the murine CLP paradigm has some features to recommend it, this model of severe sepsis also has some serious flaws. First, as already discussed, at a gene expression level, acute systemic inflammatory responses in mice appear to be quite different from those that occur in humans. Second, sepsis in humans is, by and large, a disease that occurs at the extremes of age.[56] In contrast, in the vast majority of studies using the murine CLP model, sepsis is induced in young adult animals without any co-morbid conditions. It is noteworthy in this regard that CLP-induced sepsis in young adult mice is not associated with the development of acute kidney injury (AKI), a common problem in human sepsis, whereas CLP-induced sepsis in aged animals does lead to development of AKI.[57] Third, septic patients typically receive multiple forms of supportive care, including: mechanical ventilation, if indicated; resuscitation of intravascular volume; infusion of vasopressors and/or inotropic agents; administration of anti-microbial agents; renal replacement therapy, if indicated; surgical source control, if indicated; and enteral (or, less commonly, parenteral) administration of nutritional supplements. Some of these forms of supportive of care, such as the administration of antibiotics, are sometimes included in murine studies. However, the more complex interventions, such as renal replacement therapy or prolonged mechanical ventilation, are rarely, if ever, employed. Fourth, the temporal course of the septic process—from the onset of symptoms to death—in the murine CLP model is compressed into an interval that lasts at most a few days. In contrast, patients with lethal sepsis often survive for weeks before succumbing to their illness.

The CLP model likely can be improved, but the fixes are expensive and certainly not guaranteed to improve the model enough to make it a reliable step in the pathway toward the development of effective pharmacological agents for the adjuvant treatment of human sepsis. One improvement, already noted above, is to use aged mice, as described by the Star laboratory at the National Institutes of Health.[27,57] Another improvement is to use "humanized mice" as described by Unsinger and colleagues.[58] These mice are generated by transplanting human $CD34^+$ cord blood hematopoetic stem cells into gamma-irradiated neonatal NOD-scidIL2rγ^{null} mice. These mice develop a complete lineage of human cells of the innate and adaptive immune systems, including monocytes, macrophages, plasmacytoid and myeloid dendritic cells, NK cells, T cells, and B cells. Sepsis is induced by performing CLP. Although the model might be useful, it is important to note that many key cell types, such as endothelial cells and intestinal and respiratory tract epithelial cells, are still murine. And, these cells, although not components of the "professional" immune system, are nonetheless important in the pathogenesis of the septic phenotype. Furthermore, generating "humanized" mice is a complex, time-consuming, and very expensive process, which is unlikely to be widely adopted. Finally, as yet, it is unknown whether results obtained with this model can predict the outcome of a clinical trial of a novel pharmacological intervention in patients with severe sepsis or septic shock.

Another way to solve some of the problems of the murine CLP model is to use a larger animal species, especially one that is more like humans with regard to sensitivity to LPS and possibly other pathogen-associated molecular pattern (PAMP) molecules. Following this sort of reasoning, our laboratory developed a rabbit peritonitis model, wherein sepsis was induced by i.p. injection of a known quantity of viable bacteria mixed with substances, namely hemoglobin and mucin, which are known to enhance the lethality of infections.[59] We employed a highly pathogenic strain

of bacteria (*E. coli* O18:K1). The animals were treated with an appropriate antibiotic and were adequately resuscitated via an indwelling i.v. catheter. Studies performed with the rabbit paradigm indicated that tifacogin is an effective therapeutic agent, but contrary results were obtained in clinical trials.[60-62] Thus, even this rabbit paradigm, which was developed to address many of the problems with earlier sepsis models, failed to predict the results of human clinical trials.

Sheep are docile large animals. Like humans, they are extremely sensitive to LPS. For example, continuous infusion of LPS at a rate as low as 9 ng/kg per h leads to marked changes in pulmonary arterial pressure, cardiac output, and lung microvascular permeability.[63] True sepsis, rather than endotoxemia, can be induced in sheep in a variety of ways, such as by infusing viable *Pseudomonas aeruginosa* i.v.[64] For ethical reasons, sheep are rarely used for survival studies, and thus it is not known whether ovine models of sepsis should be incorporated into the critical pathway for the development of new pharmacological agents for the treatment of sepsis.

In view of their close phylogenetic proximity to humans, nonhuman primate species, such as *Papio anubis*, would seem be good choices for preclinical models of sepsis. But, baboons and other monkey species tend to be remarkably resistant to the lethal effects of intravenously administered LPS or viable bacteria. Thus, in the classic Hinshaw model of lethal sepsis in baboons, the animals are infused with more than 10^{10} colony forming units (cfu)/kg of viable *E. coli* bacteria.[65] Blood cultures in this model contain 10^3 to 10^7 cfu/ml, i.e., levels of bacteria that are much greater than are commonly observed in lethal human septic shock. In numerous studies (**Table 2**), findings obtained using this model to test pharmacological interventions have failed to predict the outcome of human clinical trials.

In summary, most animal models of human sepsis are flawed. Studies using very complex models, such as ones that employ "humanized" mice, may represent a major advance, but, at present, data obtained in this way are quite limited. Experiments using animal models will remain in the critical pathway for the development of new agents for the pharmacological treatment of severe sepsis or septic shock. But, results from these preclinical studies never should be extrapolated directly to the problem of human sepsis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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