Sepsis Experiments on Animals: Scientifically Outdated, Clinically Useless

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SUMMARY

Sepsis, a life-threatening condition resulting from the body's response to infection, affects millions globally every year, leading to high mortality and substantial economic burdens. Despite decades of research, advances in sepsis therapies have been hindered – largely due to the poor translation of findings from experiments using animals, particularly mice, who are commonly used in sepsis research due to their low cost and ease of use. However, their biological responses to sepsis differ significantly from those of humans. These differences include genomic, immunological, and metabolic discrepancies as well as issues with the reproducibility of sepsis induction methods. In 2019, the National Institute of General Medical Sciences (NIGMS), part of the National Institutes of Health (NIH) in the United States, acknowledged these shortcomings and announced plans to shift funding towards more clinically relevant research. Numerous scientists have also called attention to the limitations of using animals in sepsis research. Nevertheless, sepsis studies using animals continue to be conducted and published. Based on the critical scientific and ethical problems with using animals in sepsis research outlined in this report, we recommend that the use of animals in human sepsis research be prohibited by institutional, regional, and national legislative and ethical bodies. Funding agencies should reject grant applications involving the use of animals in sepsis studies and redirect resources to human-relevant, non-animal approaches for sepsis research. Academic journals should lead scientific progress by publishing direct public-facing policies stating that they will not accept manuscripts which include data from animal-based sepsis experiments.

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WHAT IS SEPSIS?

Sepsis is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection".[1] It affects at least 48.9 million people globally each year and kills nearly 11 million of them.[2] It represents 20% of all global deaths and is one of the most expensive conditions to treat.[2,3] Most cases are caused by bacterial infections, but sepsis can also result from viral or fungal infections or even traumatic injuries.[4] Vulnerable populations – such as infants, the elderly, and individuals with weakened immune systems – are at greater risk.[5] Treatment typically involves antibiotics, intravenous fluids, and sometimes oxygen or vasopressors.[6] When identified early, sepsis can be managed successfully, but survivors often suffer from long-term effects, and in many cases it can lead to permanent organ damage or death.[7]

TRANSLATIONAL FAILURES IN SEPSIS THERAPEUTICS

In 2014, Mitchell P Fink, who is considered "one of the most inspiring and influential leaders in the field of intensive care medicine",[8] published an article reviewing over 60 human clinical trials conducted since 1982 for

the evaluation of pharmacological interventions for the treatment of sepsis. Of these, only eight showed any benefit to patients, and none resulted in a cure. Four trials caused further harm, while the remainder provided no clinical benefit. Furthermore, Fink detailed nine specific examples of pharmacological agents that had yielded beneficial results in several animal experiments but produced "negative results in one or more human clinical trials". He concluded that "most animal models of human sepsis are flawed" and warned that "results from these preclinical studies never should be extrapolated directly to the problem of human sepsis".[9]

MURINE SEPSIS IS NOT HUMAN SEPSIS

Mice are the most commonly used species in sepsis experiments, not because they make good "models" of human sepsis but because they are cheap, plentiful, small, and docile.[10] The difficulty in reliably translating results from mice to humans is believed to be the primary cause of the failure of practically all human trials of sepsis therapies.

In 2013, *Proceedings of the National Academy of Sciences* (*PNAS*) published a landmark study that had been 10 years in the making and involved the collaboration of 39 researchers from institutions across North America, including Stanford University and Harvard Medical School. Dr Junhee Seok and his colleagues compared data obtained from hundreds of human clinical patients with results from experiments on animals to demonstrate that humans and mice differ in their genetic responses to serious inflammatory conditions such as sepsis, burns, and trauma.[11]

The *PNAS* paper reveals that in humans, many of the same genes are involved in recovery from sepsis, burns, and trauma but that it was "close to random" which mouse genes might match these profiles.[11] Not only was the genomic response poorly correlated between mouse models and humans, the genomic response timing was also different between the two species.[11]

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The NIH director at the time, Dr Francis Collins, authored an article about these results, lamenting the time and resources spent developing 150 drugs that had successfully treated sepsis in mice but failed in human clinical trials. He called this failure "a heartbreaking loss of decades of research and billions of dollars".[12]

In addition to this landmark study, the criticism of mouse "models" of sepsis has been documented by more than 20 peer-reviewed scientific publications.[13-17] Some of these studies describe the numerous physiological differences between mice and humans, including variations in genetic responses and differences in immune responses, metabolic responses, and immune susceptibility.[11,13,15,18] Others discuss environmental and external variables that impact study outcomes. For example, the mice used in sepsis experiments are young, inbred, and of the same age and weight, and they live in settings that are mostly free of germs (other than those in their own faeces). In contrast, it is mostly infant and elderly humans, who live in a variety of unsterilised, unpredictable environments and frequently have comorbidities such as diabetes or hypertension, who develop sepsis.[9,10,13,18,19] In laboratory settings, pathogens, dosage, and infection are controlled, but in human sepsis, the pathogenic bacteria are often unknown, and patients may not respond to antibiotic treatment when sepsis is caused by more than one type of microbe (polymicrobial).[18] When experimenters induce the condition in mice, the onset of symptoms occurs within hours to days, whereas symptoms can develop over weeks and months in humans.[14] Mice are typically not provided with the supportive therapy that human patients receive, such as fluids, vasopressors, and ventilators.[9,20,21] Another complicating factor is that unlike humans, mice are rarely given pain relief.[22,23] This undermines data of already questionable value, as pain affects other physiological processes.

OTHER ANIMALS USED IN SEPSIS EXPERIMENTATION

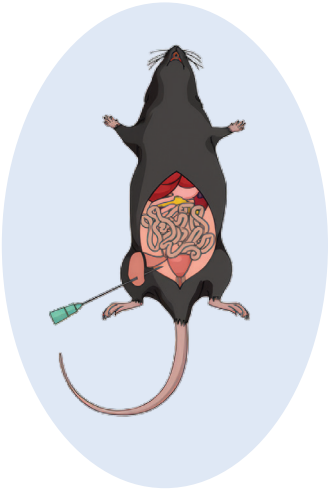
Rats, dogs, cats, pigs, sheep, rabbits, horses, and primates, including baboons and macaques, have also been used in sepsis experimentation around the world. None of these species can reproduce all the physiological features of human sepsis. For example, the pulmonary artery pressure responses of pigs and

sheep differ from those of humans, so this aspect of sepsis cannot be compared between species.[24] Pigs also differ from humans in key genes, immune cell types, microbiome composition, and protein expression related to inflammation.[11,25-27]

Baboons, like mice, are less sensitive than humans to the species of bacteria commonly used to induce sepsis in experimental settings.[9] This may be because animals are housed in faeces-contaminated environments, allowing them to develop a level of resistance to pathogens that is not present in most humans.[18,20] One study found that rhesus macaques and baboons differ markedly in their innate immune response to pathogens compared to humans. Specifically, macaques and humans show different transcriptomic responses to infection, suggesting distinct regulatory mechanisms during the early stages of immune activation.[28] Additionally, both species differ in the number and composition of leukocytes and the quantity of B and T cells, limiting their applicability to immunological human sepsis research.[29]

SEPSIS INDUCTION METHODS

There are several ways by which experimenters induce sepsis or a sepsis-like condition in non-human animals. These can include infection of one animal with excrement from another, induction of sepsis via pneumonia or other organ infections, or the insertion of a stent allowing an animal's faecal matter to enter their abdominal cavity. The following sections focus on the most commonly used methods in the UK: caecal ligation and puncture (CLP); endotoxemia, which involves injection of a toxin, usually lipopolysaccharide (LPS); and injection of live bacteria.



Caecal Ligation and Puncture

To induce sepsis in mice, experimenters cut open the animals' abdomens and puncture their intestines with a needle so that faecal matter and bacteria will leak out. The mice then endure widespread pain and can become so sick that they're unable to move. They may experience fever, chills, diarrhoea, difficulty breathing, lethargy, disorientation, septic shock (when the infection reaches their bloodstream, causing their blood pressure to plummet), and multiple organ failure before being killed.[13] Abhorrently cruel, this method is also scientifically unsound. First, a mouse's responses to CLP vary by age, sex, strain, laboratory, the size of the needle used, and the size of the incision, which makes results between laboratories incomparable.[13,20,21,30,31] Second, the procedure can cause the formation of an abscess, whose effects may disguise or be disguised by the effects of the sepsis itself.[20] This means that an intervention that appears to be beneficial for sepsis may actually be beneficial only because of its effects on the abscess.

Endotoxemia Does Not Induce Sepsis

In endotoxin models, a mouse or other animal is injected with a bacterial toxin, typically LPS. As described by Riedemann, Guo, and Ward, "LPS, the main component of the Gram-negative bacterial cell wall, was known to stimulate release of inflammatory mediators from various cell types and induce acute infectious symptoms when injected into animals."[32] Endotoxin models have been criticised as particularly poor models for human sepsis and perhaps not even accurate models for murine sepsis.

The endotoxin method elicits a rapid and acute inflammatory response in mice, due to their higher resistance to the toxin, necessitating a much larger bacterial load than would be found in a septic human.[10,20] In contrast, sepsis patients typically experience a more prolonged inflammatory response at lower levels.[13] In addition, certain characteristics of human sepsis, such as haemodynamic changes (alterations in blood flow and pressure), never manifest in endotoxin models.[20] These discrepancies have led to scepticism regarding the efficacy of the endotoxin method and whether it genuinely induces sepsis in animals.[20]

Injection of Live Bacteria

Some experimenters use live bacteria to induce a sepsis-like condition in animals. In these studies, animals are typically injected with a single high dose of bacterial culture composed of one type of microorganism of known antibiotic sensitivity.[18,33] In contrast, human sepsis patients are often infected with multiple, unidentified microbes – including a mix of gram-negative and gram-positive bacteria – that frequently exhibit antibiotic resistance.[18]

After administration into animals, high doses of bacteria usually fail to colonise and replicate due to rapid cell lysis (i.e. cell rupture and disintegration), which causes

the bacterial load to peak and then decline quickly.[20,34] Lysis increases toxin levels, producing a model of intoxication rather than true infection, which can lead to early death in infected animals, preventing the full development of sepsis symptoms.[20,34] These features are in direct contrast with clinical characteristics of human sepsis: patients exhibit a persistent bacterial load,[35] an undetectable to low toxin load,[36-38] and disease progression over weeks and months.[14]

In addition, many experimental parameters act as confounding factors to prevent reproducibility and comparability across studies. This includes infecting bacterial load, microbial strain specificity,[20,39-43] location of infection,[44-49] frequency of administration (e.g. single dose or continuous infusion), and infusion time – all of which affect host response.[18,20,50-52] Moreover, species-specific infectivity fatally compromises the translational value of these studies. For example, *Salmonella typhimurium* infects mice more effectively than it infects humans.[53] Critically, this method fails to reproduce most clinical aspects of human sepsis, including haemodynamic, immunological, and metabolic features.[20,33,54-65]

POOR ETHICS IN SEPSIS AND TRAUMA EXPERIMENTATION

In 2014, researchers from the University of Alberta surveyed 77 papers on animal studies that had been published in three high-impact critical-care journals between January and June 2012 and found that the "[r]eported … ethical quality" of this research was "poor".[23] The results of the analysis speak for themselves:

> Most studies did not report monitoring the level of anesthesia during invasive procedures, even when muscle paralytics were used, nor monitoring or treatment of expected pain. When euthanasia was used, the method was often not stated, and when stated, most methods were not appropriate for the species. A sample-size calculation was rarely used, and animal numbers were often poorly described. No studies performed a systematic review to ensure that the animal research would be useful and not simple repetition. … Most studies were funded with public funds (foundation or government funding). Sepsis models less often met the composite outcome of … using anesthesia and pain control, and stating the method of euthanasia.[23]

The authors note that the disregard for the pain and distress experienced by the animals "may confound the study results, and may thus be a reason for the poor translation of [experiments on animals] to humans". In addition, the report states, "Alternatives to animal models were almost never explicitly considered" – even though consideration of non-animal methods is required by laws and policies. The chronic failure of experimenters who conduct sepsis research to adhere to even the minimum standards for the use of animals in laboratories causes animals to suffer, wastes public funds, and impedes a scientifically rigorous search for a treatment for sepsis in humans.

NON-ANIMAL METHODS FOR STUDYING SEPSIS

The sepsis community has accepted that, like cancer, we should not expect one treatment to cure all sepsis patients.[66] The Global Sepsis Alliance – a non-profit organisation focused on reducing the burden of sepsis through advocacy, research, and education – reports that the future of sepsis treatment hinges on personalised medicine.[67] Human data – from genomics to protein expression and immune pathway activation – are essential for identifying individual risk, enabling early intervention, and informing diagnosis, prognosis, and therapies. Many advanced methods provide human-relevant data, including *in vitro* tools such as cell culture methods, organoids, and organ-on-chip technologies – all of which involve the use of human or even patient-derived cells. Excitingly, multiple organs can be cultured on a single chip, representing the human organism.[68] *In silico* methods, such as the use of AI and computational tools, combined with human genomic data, are already paving the way for early diagnosis and even prediction of sepsis,[69] enabling early intervention –

a critical factor in increasing therapeutic efficacy and patient survival.[70] All of these tools can be used to study human disease progression and immunomodulatory processes in order to understand cell/tissue/organ-specific responses and interactions and to assess potentially therapeutic agents. These are just some recent examples of human-relevant sepsis research:

- Scientists in Tokyo used human induced pluripotent stem cell–derived liver organoids to model the pathological progression of sepsis-associated liver dysfunction and recovery following infection.[71]
- At Temple University in the US, a multidisciplinary team identified an association between neutrophil types and the severity of sepsis using a human lung-on-a-chip model, which can be used to determine the appropriate therapeutic intervention based on sepsis severity.[72]
- Researchers in Hefei, China, created a six-unit microfluidic device that comprehensively analyses a sepsis patient's white blood cell activity to monitor disease progression and severity.[73]
- In the US, Massachusetts General Hospital scientists and physicians created a microfluidic device to accurately detect a biomarker of sepsis pathophysiology using a drop of blood, aiming to improve disease monitoring.[74]
- Because early detection of sepsis is likely the most critical factor in reducing mortality from this condition,[70] researchers around the globe are exploring various artificial intelligence and machine learning tools to aid in the early prediction and diagnosis of sepsis.[75-83]

SHIFT IN SEPSIS PRIORITIES

A 2019 report by NIH's National Advisory General Medical Sciences Council (NAGMSC) sepsis working group found that, despite decades of research and numerous clinical trials, no new drugs for sepsis had emerged. The report recommended that the NIGMS "rebalance" its sepsis research funding portfolio to "include a more clinical focus".[66] Following this, NIGMS issued a Notice of Information, indicating its intention to support more sepsis research that "uses new and emerging approaches, such as clinical informatics, computational analyses, and predictive modeling in patients, and new applications of high-resolution and high-throughput bioanalytical techniques to materials obtained from septic patients" and called the support of "[s]tudies using rodent models of sepsis" a "low priority".[84] At the 2024 and 2025 Shock Society Annual Conferences, NIGMS officials went further, notifying attendees that the institute does not intend to support research using LPS, CLP, and most other rodent models of sepsis and that it feels strongly that sepsis research should be conducted with human-based methods.[85] NIGMS division director Dr Rochelle Long encouraged conference attendees to seek access to clinical samples and collaborate with other researchers using non-animal methods instead of "just going back and doing something in a lab in a way that's easy or was done that way in the past".[86]

The US Food and Drug Administration (FDA) has also published a roadmap[87] to reduce animal testing in preclinical studies, acknowledging that the use of animals fails to provide adequate disease models, particularly in disease areas such as inflammatory disease (a disease category that encompasses sepsis). As a result, the FDA will promote the use of human cell-derived organoids and organs-on-chips in disease research.[87]

NIH LAWSUIT

Because NIH has known – and acknowledged since at least 2013 – that mice do not accurately model human sepsis and because its mandate is to fund research that benefits human health, PETA US challenged the agency's continued funding of animal-based sepsis studies under the US Administrative Procedure Act in 2021. PETA US' case cited the lack of new pharmacological treatments for sepsis despite decades of animal experimentation and NIH's ongoing support for methods that have repeatedly failed. PETA US' legal team argued that awarding these grants is arbitrary, capricious, an abuse

of discretion, not in accordance with the law, and in violation of the agency's legal obligation to reduce the number of animals used in experiments and to minimise their suffering. NIH's motion to dismiss the case was denied, and the case is ongoing.

CONCLUSIONS AND RECOMMENDATIONS

Animals commonly used in sepsis research exhibit significant immunological, genetic, and metabolic differences from humans, undermining the predictive value of their use. Recent decades have seen some experimenters incorporate basic refinement measures into their animal-based sepsis research in an attempt to improve human-relevance and translatability. These measures fail to account for insurmountable species-specific differences and inherent problems with sepsis-induction methods. To date, animal experimentation has not produced a single targeted, effective drug or treatment for sepsis. Nonetheless, experimenters continue to prioritise refinement, neglect replacement, and subject mice, rats, pigs, and nonhuman primates to painful procedures that result in suffering, organ failure, and death. These sepsis experiments on animals waste public funds, animal lives, and research hours.

Animal experimentation has not produced a single targeted, effective drug or treatment for sepsis. Nonetheless, experimenters continue to prioritise refinement, neglect replacement, and subject mice, rats, pigs, and nonhuman primates to painful procedures.

But sepsis researchers could chart a new path in the future. Advanced *in vitro* systems using human cells can reflect human-specific immune responses, cytokine production, and tissue interactions more accurately. Human cell-based systems can also be derived from individual patients, enabling personalised approaches to studying sepsis mechanisms and drug responses. Organ-on-a-chip and other microphysiological systems can simulate key aspects of human physiology, such as tissue interfaces, flow dynamics, and multi-organ interactions. These models increasingly approximate whole-body responses without involving animals. Likewise, computational models can integrate data from various sources to simulate complex sepsis dynamics, offering a whole-system perspective grounded in human data. Using integrated data from multiple human-relevant models can provide better translational value and help overcome the inherent reproducibility and validity issues associated with attempting to model sepsis in animals.

Institutional, regional, and national legislative and ethical bodies should prohibit the use of animals in human sepsis research.

Funders should reject grant applications that propose to use animals for sepsis research and redirect resources to human-relevant, non-animal approaches.

Journals should have a public policy declaring that they will not accept manuscripts that include data from animal-based sepsis experiments.

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