Sepsis Experiments on Animals Fail to Translate to Humans

Sepsis is a life-threatening reaction to infection that progresses rapidly and affects around 245,000 people annually in the UK. It kills more people in the UK each year than breast, bowel, and prostate cancer combined, and survivors face long-term physical, cognitive, and psychological issues.[1–3] Despite decades of research and billions in funding, effective treatments remain elusive – costing the UK up to £15.6 billion a year in healthcare and economic losses related to sepsis.[4] A major reason for this failure is that sepsis research continues to rely on experiments on animals that cannot replicate the complex, human-specific immune responses driving this condition. The need for targeted, human-relevant therapies has never been more urgent.

TESTING ON ANIMALS IS A DEAD END

In 2014, renowned intensive care expert Dr Mitchell Fink sounded the alarm: despite over 60 clinical trials for sepsis drugs since 1982, only eight offered any patient benefit, none delivered a cure, and four caused harm.[5,6] He concluded that "most animal models of human sepsis are flawed". His message was clear – animal data should not be used in an attempt to predict human outcomes.

SEPSIS EXPERIMENTS ON ANIMALS ARE HOLDING BACK PROGRESS

Mice are commonly the go-to species for sepsis studies – not because they reflect human biology but because they are cheap and easy to use.[7] Valuing ease over accuracy ultimately hinders meaningful advances in human health. To date, animal experimentation has not produced a single targeted, effective drug or treatment for sepsis. A groundbreaking 2013 study authored by 39 researchers from top institutions, including Stanford and Harvard, and spanning a decade in duration, revealed why: mice show little genetic similarity to humans in response to sepsis, burns, or trauma.[8] Commenting on the results in this paper, former US National Institutes of Health (NIH) Director Dr Francis Collins lamented the time and resources spent developing 150 drugs that had successfully treated sepsis in mice but failed in human clinical trials, calling it "a heartbreaking loss of decades of research and billions of dollars".[9]

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MICE DO NOT MIMIC HUMAN SEPSIS

More than 20 peer-reviewed studies have exposed a hard truth: mice are poor "models" for human sepsis.[10–14] The biological gap is vast – mice differ from humans in genetics, immune responses and susceptibility, and metabolism.[8,10,12,15]

Mice used in sepsis experiments are young, inbred, very similar in age and weight, and housed in largely germ-free conditions. Human sepsis, by contrast, usually strikes the very young and the elderly – often with underlying conditions like diabetes or hypertension – living in unsterile, unpredictable environments.[6,7,10,15,16]

In laboratories, infections are tightly controlled, with known pathogens, fixed doses, and rapid onset of symptoms (hours to days). In humans, sepsis can unfold over weeks to months and is often triggered by multiple unknown microbes.[11,15] Patients receive antibiotics but may not respond to them; mice rarely receive the same treatments.[6,15,17,18] Unlike humans, mice are rarely given pain relief, which undermines data of already questionable value, as pain affects other physiological processes.[19,20] The result? Data that are inconsistent, incomparable, and irrelevant.

ABHORRENT METHODS, POOR SCIENCE

Experimenters typically induce sepsis or a sepsis-like condition in animals using three main methods in the UK: caecal ligation and puncture (CLP), the endotoxin model, and injection of live bacteria. All of these methods cause

pain and induce conditions that fail to reflect human sepsis.

To induce sepsis using CLP, experimenters cut open the animals' abdomens and puncture their intestines with a needle so that faecal matter and bacteria leak out. The animals 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.[10]

Abhorrently cruel, this method is also scientifically flawed. Responses to CLP vary by age, sex, strain, laboratory, the size of the needle used, and the size of the incision – making results unreliable and incomparable.[10,17,18,21,22] Worse, the procedure causes abscesses that can mask or mimic the effects of sepsis.[17] This means that an intervention that appears to be beneficial for sepsis may actually be so only because of its effects on the abscess.

Endotoxin models – in which a mouse or other animal is injected with bacterial toxins like lipopolysaccharide (LPS) – have been heavily criticised. They do not just fail to mimic human sepsis; they may not even reflect sepsis in mice, who require massive toxin doses to trigger a response due to their natural resistance. This produces a fast, acute inflammation – unlike the slower, prolonged immune response seen in human patients with much lower bacterial loads.[7,10,17] Crucial features of human sepsis, such as changes in blood pressure and flow, are not observed in mice.[17] These fundamental differences cast serious doubt on whether endotoxin models replicate sepsis at all.[17]

Live bacteria models – in which animals are injected with cultured microorganisms – also face major criticism. They typically rely on a single, high dose of an antibiotic-sensitive strain, unlike the diverse, resistant infections seen in human sepsis.[15,23] In animals, these doses often break down rapidly, rather than replicating, triggering toxin overload, rather than true infection, and early death before the full onset of sepsis.[17,24] Key variables – strain, dose, infection site, timing – and species-specific differences in infectivity and immune response make these results highly inconsistent and incapable of replicating key clinical features of human sepsis.[15,17,23,25-51]

SUPERIOR METHODS FOR STUDYING SEPSIS

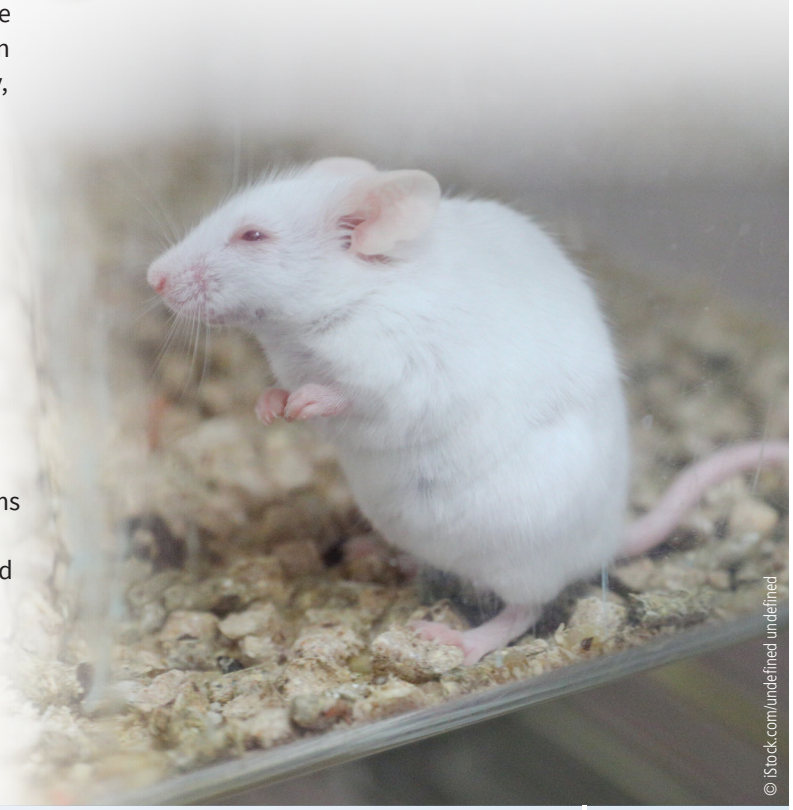
Fortunately, researchers can study sepsis without using animals. Human-relevant methods include *in vitro* models for studying sepsis mechanisms and progression,[52,53] systems and computational biology for studying inflammatory processes,[54] and human genomic information to understand individual risk and disease progression.[55–63] Scientists have used liver organoids, made from human cells, to model the pathological progression of sepsis-associated liver dysfunction and recovery following infection.[52] A US 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.[53] Because early detection of sepsis is likely the most critical factor in reducing mortality from this condition,[64] researchers around the globe are exploring various artificial intelligence and machine learning tools to aid in the early prediction and diagnosis of sepsis.[55,56,62] These are just a handful of examples.

GLOBAL SHIFT IN SEPSIS PRIORITIES

The tide is turning. In the US, growing awareness of the stark physiological differences between mice and humans has sparked major reform in sepsis research. The US National Institute of General Medical Sciences has stopped funding flawed methods like LPS injection and CLP, urging a move towards animal-free science.[65] NIH has launched a progressive initiative to "prioritize human-based research technologies",[66] even closing a laboratory that used animals in sepsis studies.[67] Meanwhile, the US Food and Drug Administration has unveiled a roadmap to reduce animal testing, promoting cutting-edge tools like organoids and organs-on-chips made from human cells.[68]

The UK must not lag behind. With a national commitment to phasing out animal testing, now is the moment for the Home Office to stop licensing experiments on animals for sepsis research – and for the Department for Science, Innovation, and Technology to champion modern, human-relevant methods that can deliver real breakthroughs for patients.

Click here for references, and for more information, read our comprehensive sepsis report.



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