Biology of Sex Differences

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Sex-based analysis of treatment responses in animal models of sepsis: a preclinical systematic review and meta-analysis

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On behalf of the Canadian Critical Care Translational Biology Group and the Sepsis Canada National Preclinical Sepsis Platform

Abstract

Objectives To examine the effect of biological sex on mortality, inflammation, organ dysfunction, and bacterial burden in preclinical sepsis models.

Data sources MEDLINE and Embase from January 1, 2011, to May 13, 2025.

Study selection We included in vivo animal models of experimentally- induced sepsis with or without intervention that reported sex-stratified data. We excluded non-infectious models and interventions hypothesized to worsen sepsis outcomes.

Data extraction We performed full-text screening and data extraction on mortality (primary outcome), inflammation, organ dysfunction, and bacterial burden. We applied a novel three-level analytic framework to determine: (1) baseline sepsis effect (female versus male differences), (2) unadjusted treatment effect (post-treatment risk differences), and (3) adjusted treatment effect (post-treatment risk differences accounting for baseline sepsis

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See Appendix 1, Supplemental Content.

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differences). Using random-effects models, we pooled outcomes as risk differences (RDs) or difference of standardized mean differences with differences > 0 indicating worse outcomes in males.

Data synthesis We screened 7,896 citations; 94 studies met eligibility criteria, and 83 studies were analyzed quantitatively. Cecal ligation and puncture (CLP) was the most common model (46%), followed by bacteremia (37%). Across the three-level framework (baseline sepsis effect, unadjusted and adjusted treatment effects), effect estimates were generally imprecise. Direction of effect analysis more often suggested worse outcomes in males (69/99 pooled comparisons). For mortality, the pooled RDs were 0.04 [95% CI, -0.02 to 0.10] for baseline sepsis effect, 0.05 [95% CI, 0.00 to 0.09] for unadjusted treatment effect, and 0.07 [95% CI, 0.00 to 0.14] for adjusted treatment effect. We observed similar direction of effects for inflammation (22/27 pooled comparisons) and organ dysfunction (9/12 pooled comparisons). The direction of effect for bacterial burden suggested worse outcomes in females (12/22 pooled comparisons). Most studies had "unclear" risk of bias.

Conclusions Sex-stratified reporting in preclinical sepsis studies remains rare. The available evidence was uncertain but showed a recurring direction toward worse outcomes and less favourable treatment responses in males. Future studies should systematically incorporate sex as a biological variable in their design and analysis to reduce this uncertainty and better define sex-based differences in sepsis and treatment response.

Plain English summary

Sepsis is a life-threatening condition caused by a dysregulated response to infection. Biological sex may influence how sepsis develops and how well treatments work. We reviewed laboratory animal studies of sepsis that reported outcomes separately for males and females. Across 83 studies, males generally experienced worse outcomes, including higher mortality, greater inflammation, and more organ injury. Our findings suggest that future sepsis studies should routinely include both sexes and report sex-stratified results to better understand biological differences in disease severity and treatment response.

Highlights

- We applied a novel three-level analytic framework to better understand disease and treatment-associated sex-dependent effects across preclinical sepsis studies.
- Across 83 studies, effect estimates were generally imprecise, although their direction of effect more often suggested worse outcomes in males.
- The consistency of effect direction across multiple outcome domains supports the importance of considering biological sex in preclinical sepsis research.
- Future studies can build on these findings by incorporating routine sex-stratified analyses, diverse animal populations, and rigorous experimental design practices.

Keywords Sex, Sepsis, Animal models, Systematic review, Meta-analysis

Introduction

The importance of understanding sex differences has been highlighted by "sex as a biological variable" mandates by research funders [1, 2]. Despite this, the impact of biological sex on sepsis pathophysiology and outcomes remains an unresolved issue. Addressing sex differences may be particularly important in sepsis, which is life-threatening organ dysfunction caused by a dysregulated host response to infection [3]. Sepsis research continues to have persistent 'bench-to-bedside' translational challenges, including the poor reproducibility of preclinical findings and the high failure rate of therapies in clinical trials [4, 5]. Sex bias in experimental design and reporting may contribute to these challenges by limiting the generalizability and clinical applicability of preclinical findings.

Biological sex-dependent effects in sepsis have been investigated in clinical studies; however, these investigations are limited by confounding inherent to observational study designs, sociodemographic and gender-related factors, comorbidities, and age. Indeed, recent clinical systematic reviews on impact of sex on sepsis outcomes reported inconclusive results [6–8], underscoring the need for further investigation. In contrast, preclinical animal models of sepsis can directly evaluate the influence of biological sex on disease pathophysiology and treatment responses. These studies can investigate the influence of biological sex in a controlled setting that minimizes confounding present in clinical studies.

Preclinical knowledge synthesis and systematic reviews offer a method to synthesize the preclinical literature in order to understand potential sex-differences in sepsis [9]. In an earlier systematic review [4], our group examined sex-specific outcomes in preclinical models treated with fluids and antibiotics, the cornerstones of clinical sepsis management [10]. Only two studies met the inclusion criteria, both employing a cecal ligation and puncture model and treatment with imipenem/cilastatin. One

reported reduced mortality in males but not females, while the other observed no sex differences in organ dysfunction. Both studies were at high risk of bias. These results highlight the scarcity of sex-stratified data for standard sepsis interventions. Moreover, we recognized that interpretation of treatment effects could be complicated by baseline differences in sepsis severity between males and females. As such, focusing solely on post-treatment effects without accounting for baseline differences may obscure sex-specific responses by misattributing pre-existing severity differences to treatment response. This challenge is further compounded by small sample sizes typical of preclinical studies.

Given the limited evidence, we have expanded the scope of the present review to include a broader range of interventions in preclinical sepsis models, including pharmacologic treatments, genetic manipulations, and other experimental approaches. To better characterize potential sex differences, we applied a three-level analytic framework to first evaluate baseline sex differences (male vs. female differences in treatment independent sepsis-related outcomes), unadjusted treatment effects (male vs. female differences following treatment), and adjusted treatment effects (male vs. female differences following treatment, while accounting for any differences in baseline sepsis severity). This approach was designed to provide a more comprehensive assessment of sex-specific responses and to clarify how biological sex may influence treatment effects in preclinical sepsis studies.

Our research question was: "What is the effect of biological sex on mortality (primary outcome), organ dysfunction, inflammation, and bacterial burden (secondary outcomes) following treatment or biological modifications of in vivo animal models of sepsis?"

Methods

We conducted this systematic review using guidance from the Cochrane Handbook [11] and reported it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [12] (PRISMA 2020 checklists in Additional files 1 & 2). We registered the protocol in the International Prospective Registry of Systematic Reviews (PROSPERO, CRD42022367726), and published a more detailed version separately [13].

Eligibility Criteria

Eligibility criteria for inclusion and exclusion were developed *a priori.* Animals, models of sepsis, intervention, comparator, outcome, and study design (AMICOS) parameters were predefined.

Animals and models

We included animals of all ages and all mammalian species that underwent in vivo experimentally-induced sepsis. We restricted our analysis to models of true infectious sepsis (e.g., fecal-induced peritonitis, cecal ligation and puncture, and bacteremia). In line with current recommendations suggesting the use of infectious challenges over bacterial components [10], we excluded studies of non-infectious models of sepsis (e.g., lipopolysaccharide administration).

Intervention

We included studies with interventions hypothesized to improve outcomes in experimental sepsis. For eligibility purposes, interventions described in the literature included pharmacological (e.g., drugs, supplements, hormones, steroids, antibodies), non-pharmacological (e.g., mesenchymal stem cells, extracellular vesicles), and biological approaches (e.g., knock-in and knock-out animal models). We included studies administering interventions at any time point (i.e., pre-treatment, at the time of sepsis induction, or as rescue therapy). We included studies that reported baseline sex-stratified outcomes following sepsis induction in the absence of an intervention of interest. We excluded interventions hypothesized to worsen sepsis outcomes or contribute to the pathogenesis of sepsis.

Comparators

Since our main analyses compared males versus female animals, studies needed to use both biological sexes and report data in a sex-stratified manner. We excluded studies without sex-stratified data.

Outcomes

The primary outcome was mortality (including cases where animals died or reached humane endpoints), assessed at the latest timepoint recorded. We also assessed mortality at predetermined time intervals after induction of sepsis (0–2 days, 3–4 days, and >4 days). Secondary outcomes included organ dysfunction and injury (liver, lung, heart, and kidney), bacterial burden (assessed by colony-forming units in specific organs or sites), and levels of interleukin-6 (IL-6). IL-6 is a clinically relevant pro-inflammatory cytokine and well-established biomarker of sepsis [14]. We considered IL-6 levels at predetermined time intervals after induction of sepsis (<6 h, 6–24 h, >24 h). We established these windows of outcome ascertainment in previous preclinical systematic reviews of sepsis [15, 16] and acute lung injury [17, 18].

Study design

We included both randomized and non-randomized studies. We included only primary studies that were

published in indexed journals. We excluded abstracts, review articles, letters, editorials, and studies including only in vitro or ex vivo data.

Search strategy

We developed our search strategies (published in our protocol [13]) in collaboration with an information specialist with expertise in preclinical systematic search strategies. Specific vocabulary related to in vivo preclinical studies including acronyms (e.g. CLP) and relevant terminology (e.g. sepsis) were used in the search strategy, and filters validated for preclinical animal studies [19, 20] were applied. We searched Ovid MEDLINE and Embase, restricting the search to studies published within a 10-year period because of resource and feasibility considerations, and because most studies reporting sex-stratified data were expected to have been published following the major policy changes encouraging the consideration of sex as a biological variable, including the United States National Institutes of Health mandate introduced 2015 [1] and similar guidance issued by the Canadian Institutes of Health Research [2]. Accordingly, we initially conducted the search in 2022, covering studies published from January 1, 2011 onward, and we subsequently updated it in 2025 to capture newly published studies, resulting in a final coverage period from January 1, 2011 to May 13, 2025. We did not apply any language restrictions at the search stage; however, we excluded studies not published in English in the full-text screening.

Study selection

We uploaded studies identified by our systematic search to DistillerSR (Evidence Partners, Ottawa, Canada), a cloud-based and audit-ready platform for systematic reviews. Given the large number of abstracts retrieved, members of Sepsis Canada's National Preclinical Sepsis Platform participated in the study selection and data extraction process. Two reviewers screened each citation independently according to the predefined inclusion and exclusion criteria. Prior to screening, we used a calibration exercise to refine the screening criteria and ensure high inter-rater agreement (kappa > 0.8). Subsequently, we retrieved full-text articles for citations that met inclusion criteria or for which eligibility was unclear. Notably, we retrieved studies that met all inclusion criteria except for explicit mention of sex-stratified data in the abstract or title, as such data are often reported only in the full text or supplementary materials. We performed a second calibration test using 10 full-text articles prior to starting full-text screening. Discrepancies at any stage were resolved through consultation with a senior member of the team (MML, FJ, MQZ). We documented reasons for exclusion at the full-text stage.

Data extraction

The review team designed standardized data extraction forms, piloted them in three representative studies, and uploaded them to DistillerSR. Study characteristics, sepsis model details, and intervention characteristics were extracted in duplicate by two independent reviewers. Discrepancies were resolved by consensus or consultation with a senior team member (MML, FJ). A single reviewer abstracted experimental outcomes reported as numerical data. We extracted data reported in graphical format using Engauge Digitizer (version 12.9). A senior team member (FJ) audited all data and analysis files to ensure data integrity and consistency.

Risk of bias assessment

We assessed risk of bias for all included studies using a modified version of Systematic Review Center for Laboratory Animal Experimentation (SYRCLE)'s risk of bias tool [20]. Our group has demonstrated the feasibility of this modified version in previous systematic reviews [21, 22]. We collected data for concealment of allocation, random sequence generation, description of baseline characteristics, blinding of personnel and endpoint measurements, selective outcome reporting, and completeness of endpoint reporting. Two independent reviewers assessed each domain in duplicate for all studies and assigned a value of low, high, or unclear risk of bias. Any conflicts in scoring were resolved through consultation with a senior team member (MML).

Statistical analysis

We conducted all meta-analyses using inverse variance DerSimonian–Laird random-effects models to account for between-study heterogeneity (R, version 4.3.2, https://www.r-project.org). We pooled dichotomous out comes (e.g., mortality) as risk differences and continuous outcomes were pooled as standardized mean differences, representing differences between groups. We assessed heterogeneity using the Cochrane I^2 and tau^2 statistics. Effect estimates were reported with 95% confidence intervals.

For studies with multiple experimental groups sharing a single control, we adjusted control group sizes by dividing the number of control animals by the number of treatment groups to prevent double-counting participants, consistent with recommended meta-analytic methods [23]. For continuous outcomes, we converted all measures of central tendency (e.g., medians) and variability (e.g., interquartile ranges, 95% confidence intervals, standard errors of the mean) to means and standard deviations using established transformation methods [11]. We provided all R code used for the analyses in Additional file 3.

Evaluation of sex-specific responses to sepsis interventions can be complicated by baseline differences in sepsis severity between males and females. As such, reliance on unadjusted post-treatment estimates alone may lead to divergent interpretations of treatment effects (Fig. 1). To address this, we applied a structured, three-level analytical approach. First, we assessed baseline sex differences in untreated septic animals (hereafter referred to as "sepsis effect", Equation A). Second, we calculated "unadjusted treatment effect" by directly comparing post-treatment outcomes between sexes, without accounting for baseline differences (Equation B). Third, we calculated "adjusted treatment effect" using a difference-of-differences approach, comparing the change from sepsis baseline to post-treatment between females and males (Equation C). We calculated all three analytical approaches for primary and secondary outcomes.

$$\text{A. Sepsis Effect} = [\text{Sepsis}_{\text{female}} - \text{Sepsis}_{\text{male}}]$$

$$\text{B. Unadjusted Treatment Effect} = \begin{bmatrix} (\text{Sepsis and Treatment})_{\text{female}} \\ -(\text{Sepsis and Treatment})_{\text{male}} \end{bmatrix}$$

$$\text{C. Adjusted Treatment Effect} = \left[\begin{pmatrix} (\text{Sepsis and Treatment})_{\text{female}} - \text{Sepsis}_{\text{female}} \\ -(\text{Sepsis and Treatment})_{\text{male}} - \text{Sepsis}_{\text{male}} \end{pmatrix} \right]$$

A narrative elaboration can be found in our protocol [13] as well as Fig. 1.

Conceptually, these three analyses are an exploratory approach to address distinct questions. The baseline sex difference (sepsis effect) evaluates whether males and females differ in outcome severity before treatment. The

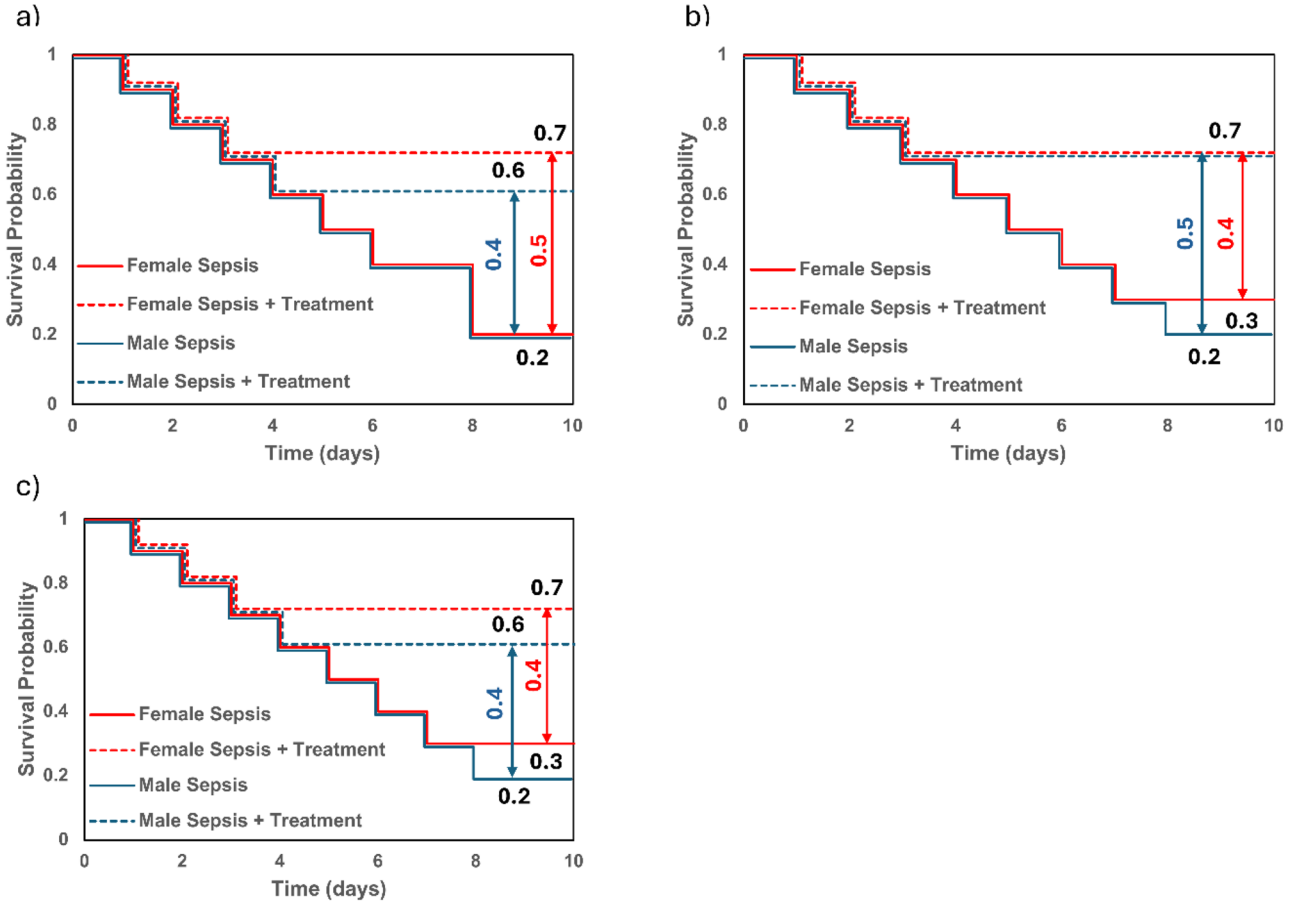

Fig. 1 Conceptual examples illustrating how baseline sex differences in sepsis severity influence interpretation of unadjusted and adjusted treatment-associated effects. (**A**) Example with similar baseline survival and different post-treatment survival. Sepsis effect = 0.0 (0.2–0.2), indicating similar survival in the absence of treatment; unadjusted treatment effect = 0.1 (0.7–0.6) and adjusted treatment effect = 0.1 ((0.7 – 0.2) – (0.6 – 0.2)), both indicating greater treatment effects in females. (**B**) Example with different baseline survival but similar post-treatment survival. Sepsis effect = 0.1 (0.3 – 0.2), indicating better outcomes in females; unadjusted treatment effect = 0.0 (0.7–0.7), indicating similar treatment effect between sexes; adjusted treatment effect = -0.1 ((0.7 – 0.3) – (0.7 – 0.2)), indicating lower treatment effects in females. (**C**) Example with different baseline and post-treatment survival. Sepsis effect = 0.1 (0.3 – 0.2), indicating better outcomes in females; unadjusted treatment effect = 0.1 (0.7 – 0.6), indicating greater treatment effects in females; adjusted treatment effect = 0.0 ((0.7 – 0.3) – (0.6 – 0.2)), indicating similar treatment effects between sexes

unadjusted treatment effect evaluates whether males and females differ in outcome severity after treatment. However, it is important to note that this unadjusted comparison may reflect both baseline sex differences and differences in treatment response. To help distinguish these components, the adjusted treatment effect compares treatment-associated changes between sexes while accounting for the observed baseline differences. Comparing the unadjusted treatment effect to the adjusted treatment effect can help determine whether observed differences between males and female are explained by baseline sex differences in outcome severity, or instead reflect differences in the magnitude of treatment response.

Finally, we also utilized a 'vote counting' approach based on the direction of effect to summarize sex-based differences across all pooled outcomes.

We conducted prespecified subgroup analyses to explore potential sources of heterogeneity and assess robustness of findings. Subgroups included sepsis model (cecal ligation and puncture, fecal-induced peritonitis, and bacteremia), intervention type (conventional or easily administered interventions versus experimental or difficult-to-administer interventions), and biosample assayed (blood or plasma versus other organs or tissues). We assessed publication bias using funnel plots, which visually inspected for asymmetry, and Egger's regression test to evaluate small-study effects.

Deviations from protocol

We could not perform a planned subgroup analysis by species (i.e., small versus large) since 99% of included studies used mice or rats. Based on reviewer feedback, we performed an additional subgroup analysis based on the gram status of infectious agents in bacterial infection models. For cardiac dysfunction, our analysis focused on measures of troponin. We did not perform a prespecified sensitivity analysis due to the absence of extreme outlier data points. Finally, we included a direction of effect analysis to facilitate data synthesis across heterogenous outcomes.

Results

Included studies

Our systematic literature search identified 8,962 citations, and we screened 7,896 articles after duplicate removal. We included 94 studies in this review and 83 were used for quantitative analyses (Fig. 2). Ten studies reported sex-specific outcomes narratively only as line-items without providing quantitative data. Of these, nine reported no observed differences between males and females, while one study reported greater resistance to *K. pneumoniae* infection in females [24]. One additional study presented sex-stratified data as a comparative analysis without numerical values [25], preventing data extraction for meta-analysis. Details of these studies are provided in Additional file 4: Table S1.

Study characteristics for included studies are summarized in Additional files 5 & 6: Table S2 and S3, respectively. 99% of studies ($n = 93/94$) utilized rodent models. C57BL/6 mice were the most commonly reported strain, used in 64/94, 68%). Studies primarily involved adult animals (4 weeks – 18 months, $n = 78/94$, 83%), with few utilizing neonates (1–3 weeks; $n = 3/94$, 3%) and aged animals (> 18 months; $n = 5/94$, 5%). Age was not specified in eight studies. Sepsis was induced using cecal ligation and puncture ($n = 43/94$, 46%), bacteremia ($n = 35/94$, 37%), and fecal induced peritonitis ($n = 16/94$, 17%). Twelve studies (13%) reported consideration of estrous cycle status. Of these, six (50%) explicitly stated that estrous cycle was not controlled for, three (25%) selected animals based on cycle phase, two (17%) incorporated estrous cycle status into the interpretation of their findings, and one considered estrous cycle effects in an in vitro model rather than in the animal experimental design. The total number of males and females in all experimental groups across the included studies ($n = 94$) were 1,819 and 1,903, respectively. We provide a summary of outcomes reported and measured across studies included in the meta-analysis in Additional file 7: Table S4.

Mortality (primary outcome)

Mortality was reported in 63 studies. Across the three comparisons, effect estimates suggested higher mortality in males than females, although none were statistically significant (Fig. 3, Additional file 8: Figures S1-S3).

Restricting analyses to studies that reported data required for all three planned comparisons (baseline sepsis, unadjusted treatment, and adjusted treatment effects; $n = 30$ studies, 41 independent experiments), did not alter outcomes significantly (Additional file 8: Figure S4). Funnel plots for all studies included in the primary analysis did not indicate publication bias (Additional file 8: Figures S5 and S6). Similarly, Egger's regression test was not statistically significant in either dataset (primary analyses: sepsis $p = 0.271$, unadjusted treatment effect $p = 0.865$, adjusted treatment effect $p = 0.639$), indicating no evidence of small-study effects or publication bias.

We conducted subgroup analyses based on sepsis model, bacterial Gram status, intervention type, assessment timepoint, and age (Additional file 8: Figures S7-S11). In studies using CLP and bacterial sepsis models, higher male mortality was observed in treatment analyses (CLP: adjusted treatment effect RD = 0.10; 95% CI, 0.03–0.17; bacterial sepsis: unadjusted treatment effect RD = 0.11; 95% CI, 0.01–0.22). Mortality analyses in the FIP model were heterogenous, with none being statistically significant. In the subgroup of bacterial

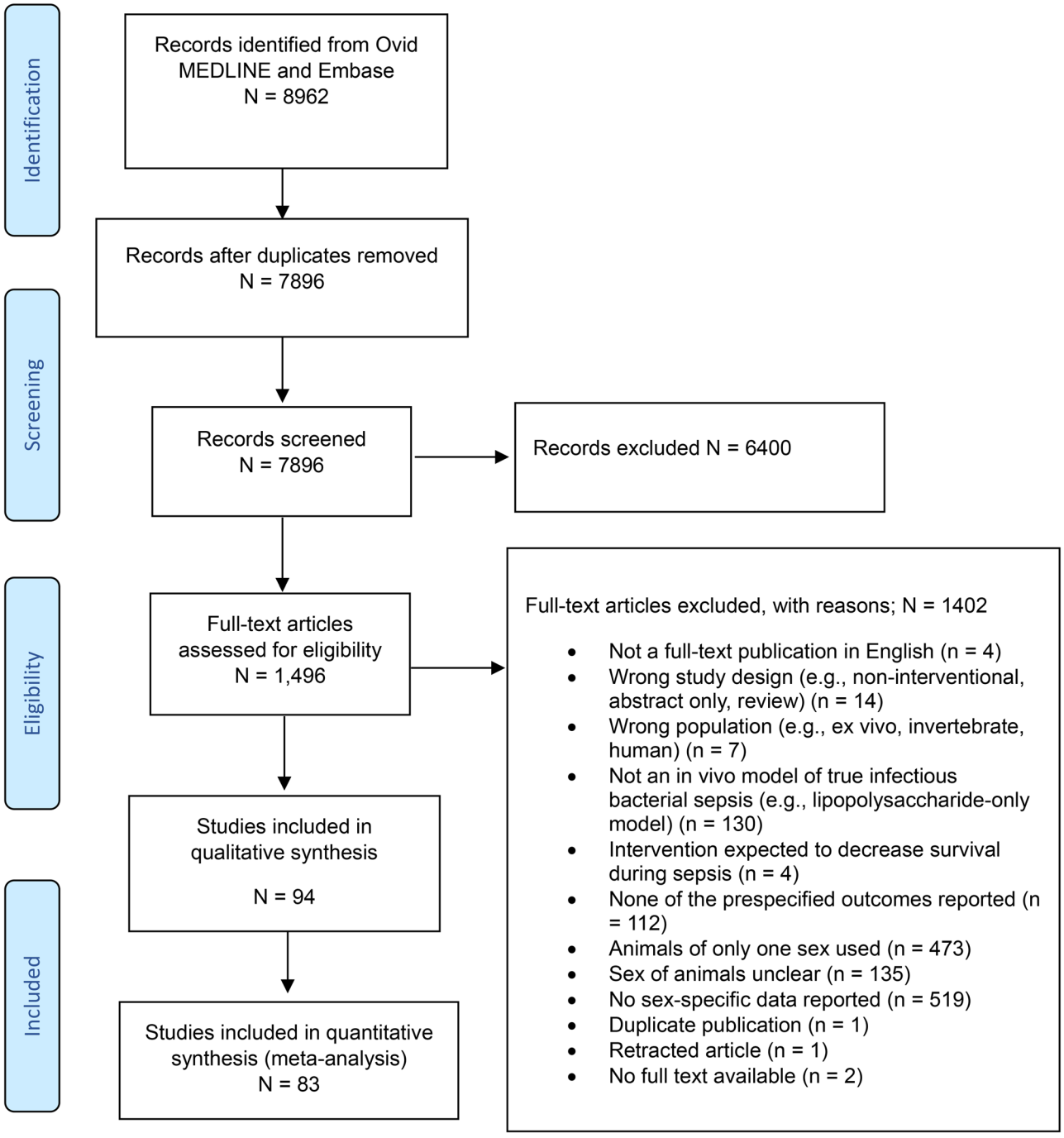

Fig. 2 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram detailing study screening and selection

sepsis model, males had higher mortality at baseline in Gram-positive infections (Sepsis RD = 0.29, 95% CI, 0.06–0.52) and following treatment in Gram-negative infections (unadjusted treatment effect RD = 0.12, 95% CI, 0.01–0.23). When stratified by intervention type, male mortality was higher in genetic manipulation post-treatment (unadjusted treatment effect RD = 0.25; 95% CI, 0.01–0.48; adjusted treatment effect RD = 0.30; 95% CI, 0.02–0.58). Subgroup analyses by timepoint and age also showed consistent point estimates suggesting higher male mortality across groups, although these differences were not statistically significant.

Interleukin-6

Thirty-four studies reported systematic or organ-specific IL-6 comparisons. Males had higher IL-6 post-treatment in the acute phase (< 6 h sepsis) as shown by the adjusted treatment effect analysis (SMD = 0.55; 95% CI 0.01–1.09).

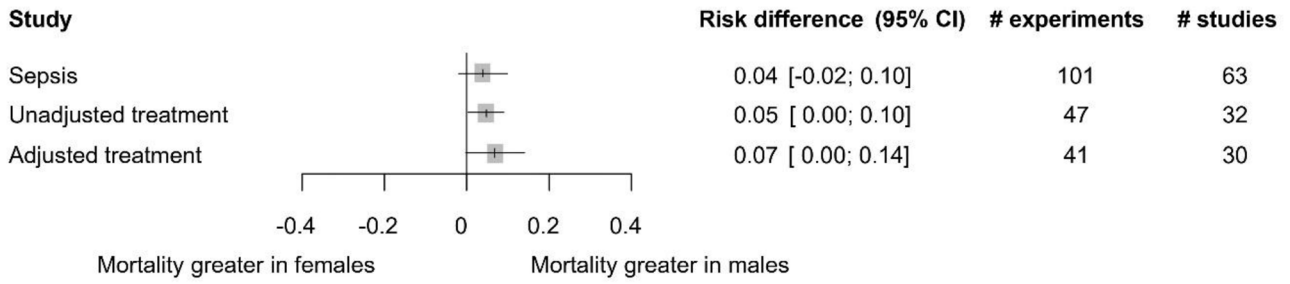

Fig. 3 Summary of meta-analysis of mortality data. Pooled estimates for risk difference and 95% confidence interval (CI) are shown for the survival outcome at the latest experimental timepoint for sepsis, unadjusted or the adjusted treatment effects analyses

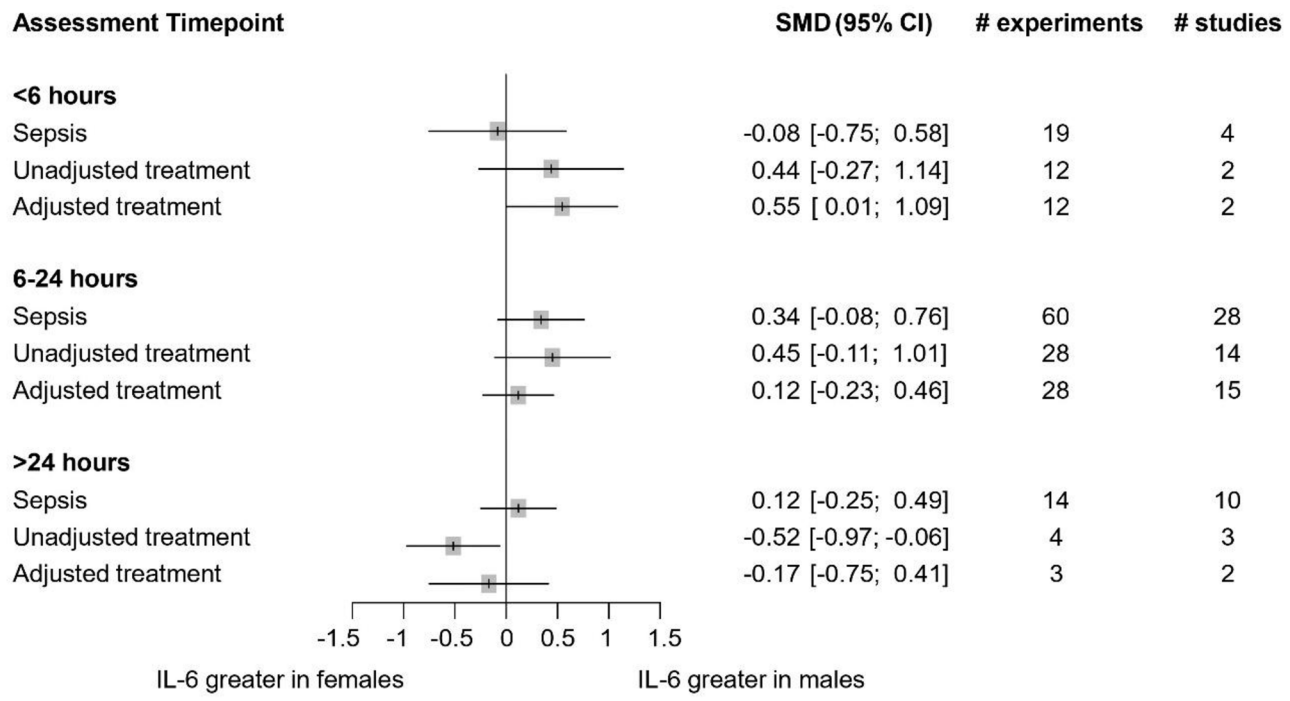

Fig. 4 Summary of meta-analysis for interleukin-6 (IL-6) stratified by assessment time. Pooled estimates for standard mean difference and 95% confidence interval (CI) are shown at different timepoints for sepsis, unadjusted, and adjusted treatment effects analyses

Across analyses, the direction of effect generally suggested higher IL-6 in males (Fig. 4). At > 24 h time points, IL-6 was higher in females post-treatment (unadjusted treatment effect SMD = – 0.52; 95% CI – 0.97 to – 0.06), with a similar direction for the adjusted treatment effect (SMD = – 0.17; 95% CI – 0.75 – 0.41), although not statistically significant. Forest plots for all included studies in these analyses are provided in Additional file 8: Figures S12-S14. Organ-specific IL-6 analyses are shown in Additional file 8: Figure S15.

Organ dysfunction

Organ dysfunction was assessed in 22 studies, including liver ($n = 8$), kidney ($n = 8$), lung ($n = 7$), and heart ($n = 2$) (Fig. 5, Additional file 8: Figures S16-S19). The direction of effect suggested greater organ dysfunction in males, although these differences were not statistically significant.

Bacterial burden

Analyses of bacterial burden revealed complex and sometimes non-concordant trends across organs, with patterns varying by the analysis method (sepsis, unadjusted, and adjusted treatment effects, Fig. 6, Additional file 8: Figures S20-S27). In the brain, bacterial burden was higher in males in the sepsis analysis (SMD = 0.89; 95% CI 0.09–1.68). In the unadjusted and adjusted treatment analyses, the direction of effect indicated higher bacterial burden in females (non-significant). Splenic bacterial burden was higher in males in the sepsis analysis (SMD = 0.25; 95% CI 0.08–0.41) and in the adjusted treatment effect analysis (SMD = 1.46; 95% CI 0.42–2.50).

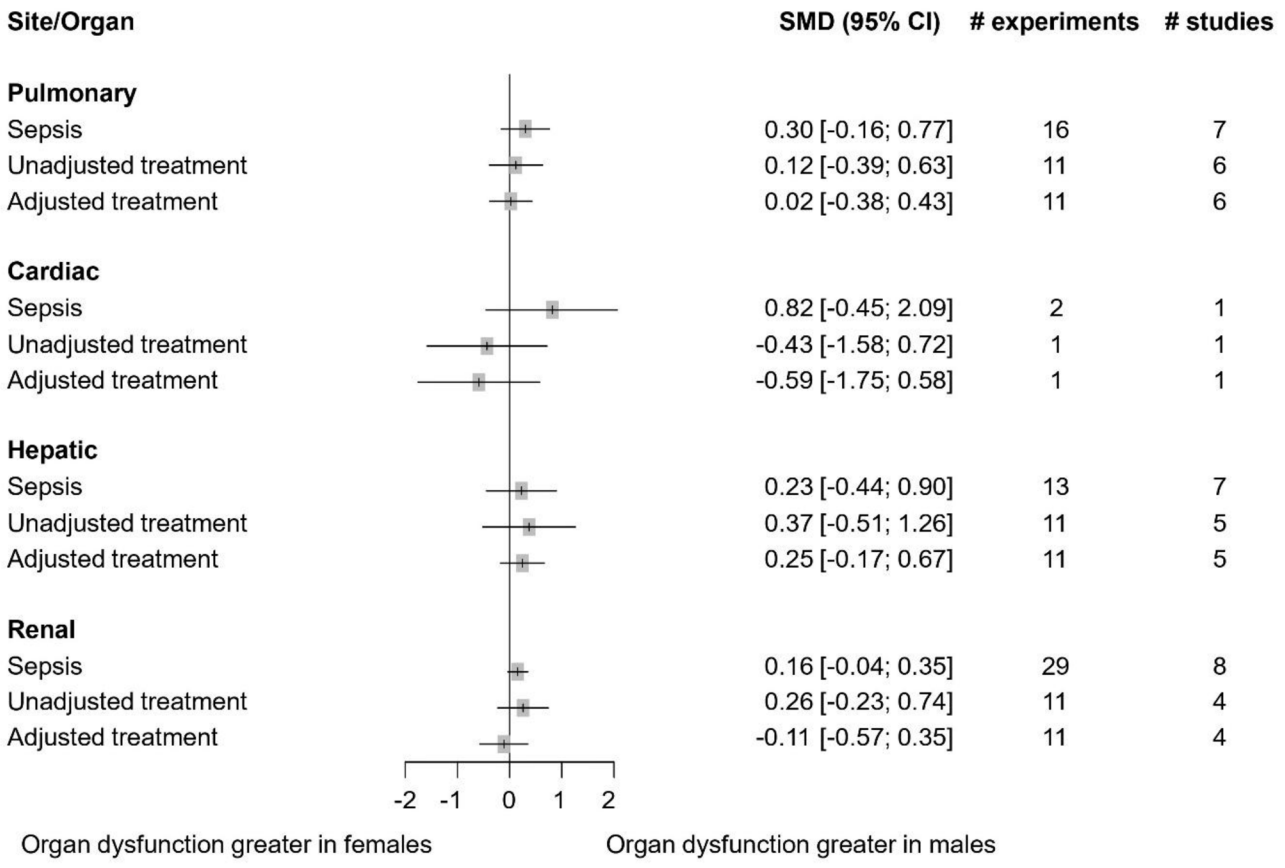

Fig. 5 Summary of meta-analysis of organ dysfunction. Pooled estimates for standard mean difference and 95% confidence interval (CI) are shown for pulmonary, cardiac, hepatic, and renal organ dysfunction across sepsis, unadjusted, and adjusted treatment effect analyses

Point estimates for systematic and lung bacterial burden indicated higher burden in males in the sepsis analysis, and a reversal of this trend following treatment.

Females had higher peritoneal bacterial burden in both the unadjusted (SMD = -3.30; 95% CI -5.20 to -1.40) and adjusted (SMD = -2.00; 95% CI -3.49 to -0.51) treatment effects. Liver bacterial burden was higher in females in both the sepsis analysis (SMD = -0.20; 95% CI -0.39 to -0.01) and the unadjusted treatment effect analysis (SMD = -0.42; 95% CI -0.75 to -0.09). We observed an opposite direction of effect for the adjusted treatment effect analysis (non-significant).

Summary of direction of effect analysis

A heat map summarizing all pooled outcomes is shown in Fig. 7. Overall, 28 of 32 (88%) mortality comparisons demonstrated point estimates of lower mortality in females compared to males. Among secondary outcomes, point estimates also favored females for IL-6 (81%, $n = 22/27$) and organ dysfunction (90%, $n = 9/10$). In contrast, bacterial burden comparisons were distributed more evenly between the two sexes with 55% of comparisons showing higher point estimates of bacterial burden in females ($n = 12/22$ analyses).

Risk of bias assessment

Most studies had an "unclear" risk of bias across the majority of domains (Fig. 8). Blinded assessments were reported in 24% of studies (i.e., lack of detection bias) while personnel blinding for experimental conduct was reported in 7% of the studies included. None of the studies reported allocation concealment, and randomization was reported in 22% of the studies. Risk of bias assessment for individual studies is presented in Additional file 9.

Discussion

In this systematic review and meta-analysis, we have highlighted several key issues regarding sex differences in preclinical sepsis studies. First, sex-stratified reporting in preclinical sepsis research remains rare, despite recommendations that sex-disaggregated data be presented, and mandates underlining the importance of sex as a biological variable [1, 2, 26]. One factor that may contribute to the limited inclusion of both sexes in preclinical sepsis studies is the longstanding concern that fluctuations in female sex hormones introduce additional variability to experimental outcomes. However, accumulating evidence suggests that female animals are not

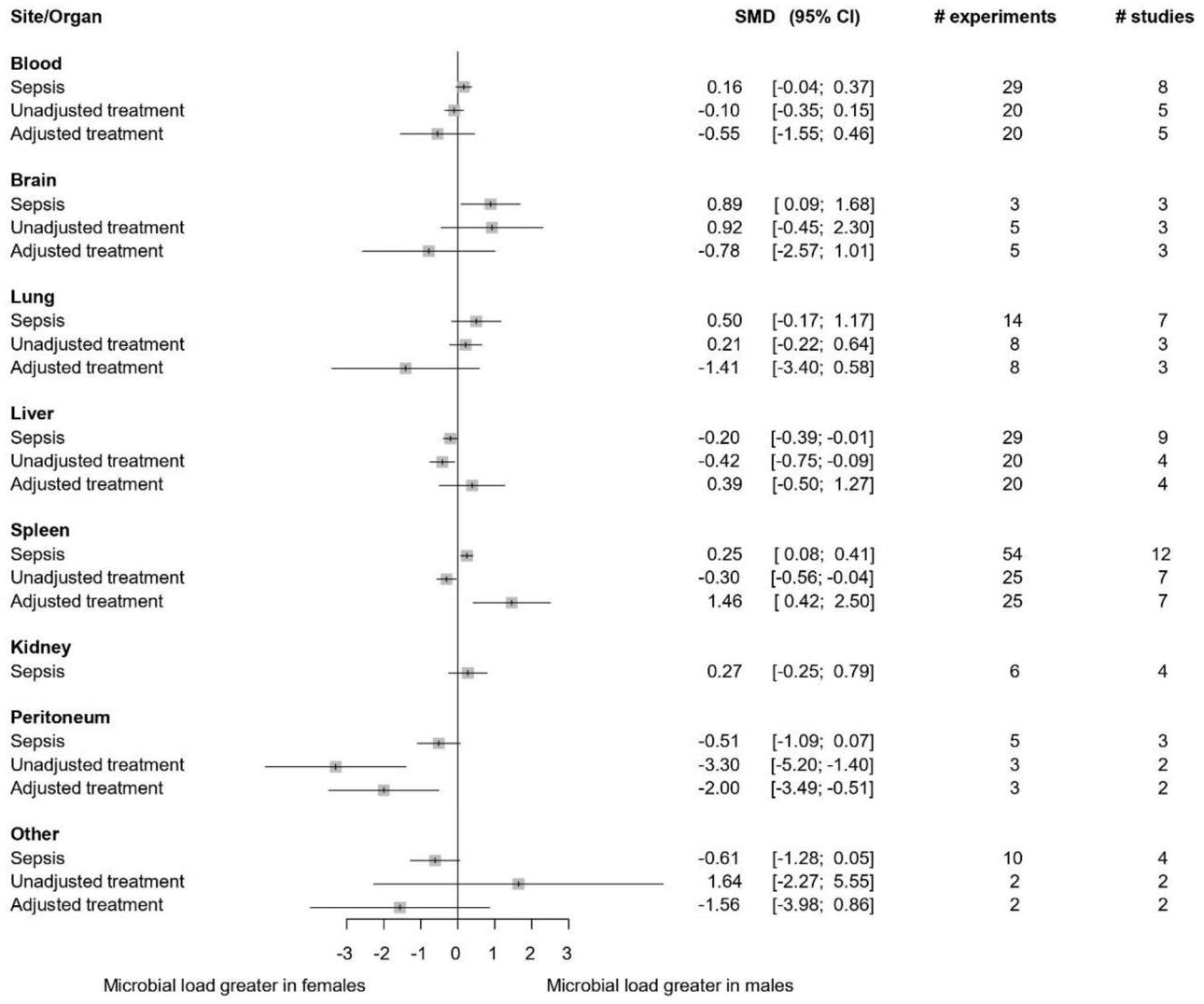

Fig. 6 Summary of meta-analysis of bacterial burden stratified by organ/site. Pooled estimates for standard mean difference and 95% confidence interval (CI) are shown for bacterial burden in blood and different organs across sepsis, unadjusted, and adjusted treatment effects analyses

inherently more variable than males [27–29] and estrous cyclicity does not consistently contribute additional variance across most experimental outcomes. Accordingly, although monitoring estrous cycle status may be important for specific study questions, it is not uniformly required across all study designs [30]. In our review, estrous cycle status was infrequently reported or considered among the included studies.

Secondly across analyses, the direction of effect generally suggested worse outcomes in males. This included mortality, organ dysfunction, and pro-inflammatory responses. Although most differences in the primary analyses were not statistically significant, the consistency in direction of effect supports the possibility of sex-related differences in sepsis severity and treatment responses, in keeping with findings from recent sepsis studies [31, 32]. Subgroup analyses revealed more nuanced patterns with significantly higher mortality in males than females after treatment in live bacterial infection models. This sex-dependent effect appeared to vary according to the Gram status of the infectious agent.

Our three-level analytic approach suggests that the interpretation of sex differences depends on whether baseline severity, unadjusted treatment effects, or adjusted treatment effects are considered. This underscores the importance of accounting for baseline differences when evaluating sex-specific responses to treatment. Although alternative analytical approaches could be applied, including meta-regression or hierarchical modelling strategies, our approach provides a transparent and interpretable framework for exploring baseline and treatment associated sex-dependent effects across heterogeneous preclinical studies. This novel exploratory approach provides a complementary

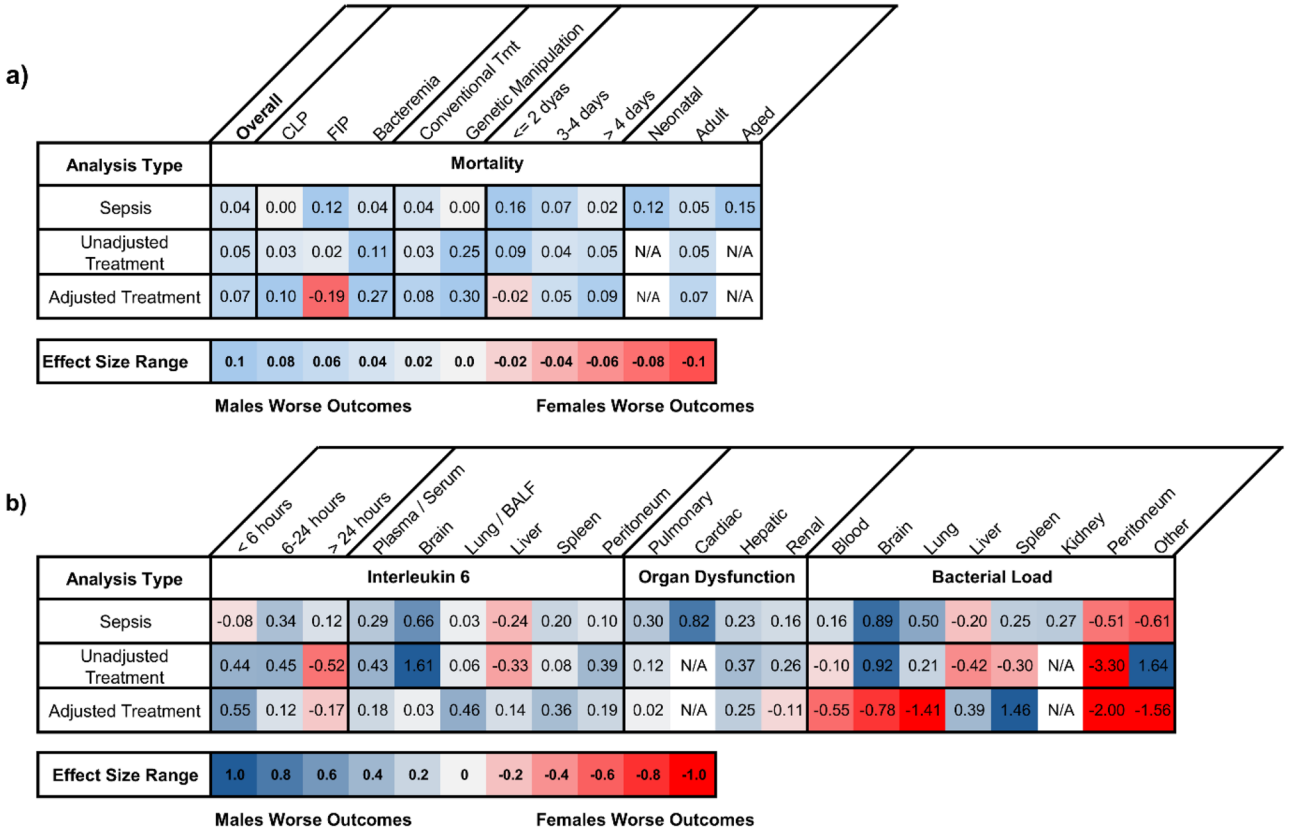

Fig. 7 Heat maps illustrate the direction of effect on the (**a**) mortality (primary outcome) and (**b**) interleukin 6, organ dysfunction, and bacterial load (secondary outcomes). The direction of the effect is visually represented by color: blue signifies that females had better outcomes; red indicates that males had better outcomes. The magnitude of the effect size is depicted through the intensity of shading. Abbreviations: BALF = bronchoalveolar lavage fluid, CLP = cecal ligation and puncture; FIP = fecal induced peritonitis, Tmt = treatment

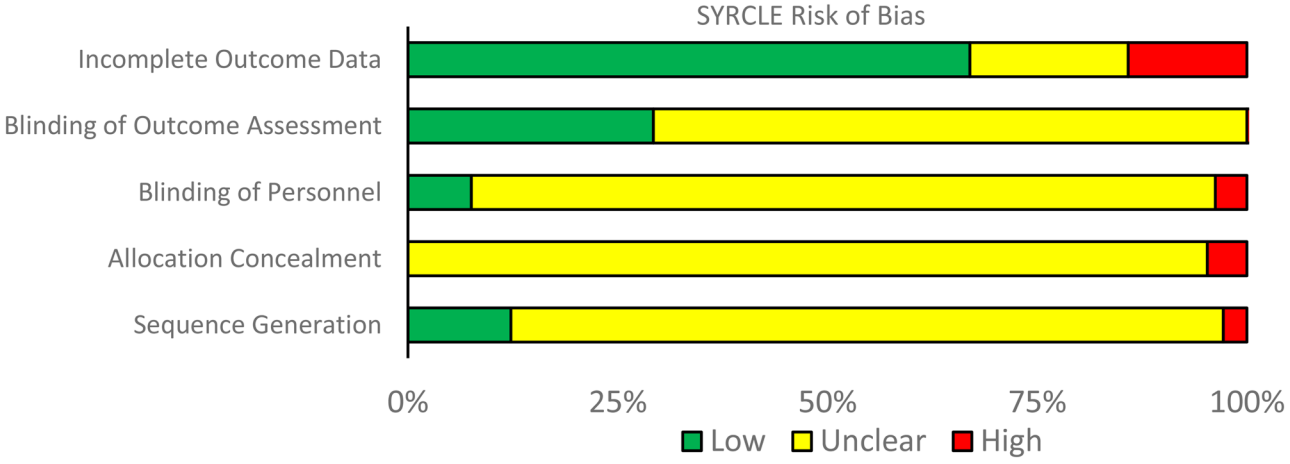

Fig. 8 Risk of bias assessment

perspective for assessing potential sex-dependent treatment effects in preclinical studies and will require external validation in future preclinical meta-analyses.

These potential differences may reflect sex-specific variation in inflammatory profiles, immuno-metabolic adaptations, and gene regulation [4]. They are shaped by sex hormones [33–35], sex-chromosome-related gene expression [36, 37], epigenetic regulation [38–40], and interactions with the gut microbiome [41, 42]. Within our systematic review, four studies investigated the contribution of sex hormones to observed phenotypic differences by comparing ovariectomized females with

intact females, providing insights into the potential role of ovarian hormones in modulating sepsis-related outcomes [26, 43–45]. Recent work suggests that increased illness severity in males may arise from impaired disease tolerance mediated by altered mitochondrial oxidative metabolism, independent of pathogen clearance or canonical immune dysregulation [46]. Similarly, higher early plasma IL-6 levels in males were consistent with exaggerated inflammatory activation [47, 48] and prior evidence suggesting females may mount a more appropriately regulated immune response [49, 50].

We observed divergent patterns in microbial burden. Although systemic bacteraemia did not differ by sex, tissue bacterial burden showed organ-specific differences that were potentially noteworthy. Circulating bacterial counts, measured at isolated time points, are transient and provide limited insight into ongoing host–pathogen dynamics [51, 52]. In contrast, bacterial burden in immuno-regulatory organs may have greater biological relevance. The spleen plays a central role in systemic immune surveillance and bacterial clearance; thus, higher splenic bacterial burden may reflect impaired bacterial clearance and host immune dysfunction [53–56]. In our analysis, females had lower splenic but higher peritoneal bacterial burden, suggesting more effective containment and clearance of infection, consistent with our mortality data suggesting worse outcomes in males. These findings may also reflect infection heterogeneity in sepsis, where sex-specific immune responses to different pathogens may differentially influence infection susceptibility, severity, and pathogen clearance [57].

This review also identified several research gaps. We observed an almost exclusive use of rodent models; only one study used a large-animal model [56]. Furthermore, the use of young adult animals without the inclusion of aged and neonatal models may limit the construct/translational validity of current preclinical sepsis models, given the high susceptibility to sepsis among elderly and infant populations. Finally, very few studies reported implementing rigorous methods for randomization, allocation concealment, and blinding, raising concerns about risk of bias. These limitations underscore the need for improved design and reporting standards in preclinical sepsis research. To address these gaps, we are conducting a confirmatory multi-laboratory study evaluating sex-dependent treatment effects in a fecal-induced peritonitis model using a standardized, trial-like design with enhanced methodological rigor and quality control [58].

There are a few limitations for this study. First, the use of 'vote counting' based on the direction of effect to synthesize findings across studies has inherent limitations as it does not capture effect size magnitude or account for differences in study sample sizes and precision. Therefore, the findings should be interpreted as identifying patterns in the direction of sex differences rather than definitive evidence of sex-based differences. Second, among the 1,496 studies that underwent full-text review, 519 (35%) included both male and female animals in their design but were excluded from our analysis as they failed to report sex stratified data. The inclusion of these studies may have influenced the findings; however, as sex-specific data were unavailable, it is not possible to determine whether their inclusion would have strengthened, weakened, or otherwise altered the observed associations. Finally, including more clinically relevant outcomes in future preclinical sepsis studies and systematic reviews may enhance the translational potential of preclinical evidence.

In conclusion, this study underscores the need for rigorous and systematic consideration and reporting of sex as a biological variable in preclinical sepsis studies.

Abbreviations

AMICOS	Animals, Models, Intervention, Comparator, Outcome, and Study Design
BALF	Bronchoalveolar Lavage Fluid
CFU	Colony-Forming Unit
CI	Confidence Interval
CIHR	Canadian Institutes of Health Research
CLP	Cecal Ligation and Puncture
FIP	Fecal-Induced Peritonitis
IL-6	Interleukin-6
NIH	National Institutes of Health
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RD	Risk Difference
SMD	Standardized Mean Difference
SYRCLE	Systematic Review Centre for Laboratory Animal Experimentation

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

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Author contributions

Conceptualization: MQZ, DAF, MML; Data curation: FJ, MQZ, HL, PP; Formal analysis: WT, SI; Funding acquisition: DAF, AAM, BM, KFM, SEG, CL, JZ, SLB, MTA,

ASK, SQ, GVG, KMF, PCL, AFR, MML; Investigation: FJ, MQZ, RS, CK, HL, EK, ZAF, PK, JM, NC, EKP, BD, ME, NS, KBT, PP; Methodology: FJ, MQZ, RS, CK, HL, EK, ZAF, PK, JM, NC, WT, SI, EKP, BD, ME, NS, RS, KBT; DAF, MML; Project administration: FJ; Resources: DAF, MML; Software: WT; Supervision: DAF, MML; Validation: FJ, EK, ZAF; Visualization: FJ, EK, WT; Writing – original draft: FJ, MML; Writing – review & editing: all authors.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. All R codes used for the analyses are provided in the additional files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. NOT-OD-15-102: Consideration of sex as a biological variable in NIH-funded research. Consideration of sex as a biological variable in NIH-funded research. 2025. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html. Accessed 18 Dec 2025.
2. Government of Canada. How to integrate sex and gender into research - CIHR. 2025. https://cihr-irsc.gc.ca/e/50836.html. Accessed 18 Dec 2025.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):8. https://doi.org/10.1001/jama.2016.0287.
4. Zhang M, Montroy J, Sharma R, et al. The Effects of Biological Sex on Sepsis Treatments in Animal Models: A Systematic Review and a Narrative Elaboration on Sex- and Gender-Dependent Differences in Sepsis. Crit Care Explor. 2021;3(6):6. https://doi.org/10.1097/CCE.0000000000000433.
5. Woitowich NC, Beery A, Woodruff T. A 10-year follow-up study of sex inclusion in the biological sciences. Elife. 2020;9:e56344. https://doi.org/10.7554/eLife.56344.
6. Failla KR, Connelly CD. Systematic Review of Gender Differences in Sepsis Management and Outcomes. J Nurs Scholarsh. 2017;49(3):312–24. https://doi.org/10.1111/jnu.12295.
7. Papathanassoglou E, Middleton N, Benbenishty J, Williams G, Christofi MD, Hegadoren K. Systematic review of gender- dependent outcomes in sepsis. Nurs Crit Care. 2017;22(5):284–92. https://doi.org/10.1111/nicc.12280.
8. Antequera A, Lopez-Alcalde J, Stallings E, et al. Sex as a prognostic factor for mortality in critically ill adults with sepsis: a systematic review and meta-analysis. BMJ Open. 2021;11(9):e048982. https://doi.org/10.1136/bmjopen-2021-048982.
9. Ineichen BV, Held U, Salanti G, Macleod MR, Wever KE. Systematic review and meta-analysis of preclinical studies. Nat Rev Methods Primers. 2024;4(1):72. https://doi.org/10.1038/s43586-024-00347-x.
10. Osuchowski MF, Ayala A, Bahrami S, et al. Minimum Quality Threshold in Pre-Clinical Sepsis Studies (MQTiPSS): An International Expert Consensus Initiative for Improvement of Animal Modeling in Sepsis. Shock. 2018;50(4):377–80. https://doi.org/10.1097/SHK.0000000000001212.
11. Cochrane handbook for systematic reviews of interventions (current version) | Cochrane. 2026. https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current. Accessed 2 Jan 2026.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
13. Zhang M, Fergusson DA, Sharma R, et al. Sex-based analysis of treatment responses in animal models of sepsis: a preclinical systematic review protocol. Syst Rev. 2023;12:50. https://doi.org/10.1186/s13643-023-02189-2.
14. Hamilton FW, Thomas M, Arnold D, et al. Therapeutic potential of IL6R blockade for the treatment of sepsis and sepsis-related death: A Mendelian randomisation study. PLoS Med. 2023;20(1):e1004174. https://doi.org/10.1371/journal.pmed.1004174.
15. Lalu MM, McIntyre L, Pugliese C, et al. Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. PLoS ONE. 2012;7(10):e47559. https://doi.org/10.1371/journal.pone.0047559.
16. Lalu MM, Sullivan KJ, Mei SH, et al. Evaluating mesenchymal stem cell therapy for sepsis with preclinical meta-analyses prior to initiating a first-in-human trial. eLife. 2016;5:e17850. https://doi.org/10.7554/eLife.17850.
17. McIntyre LA, Moher D, Fergusson DA, et al. Efficacy of Mesenchymal Stromal Cell Therapy for Acute Lung Injury in Preclinical Animal Models: A Systematic Review. PLoS ONE. 2016;11(1):e0147170. https://doi.org/10.1371/journal.pone.0147170.

18. Lalu MM, Moher D, Marshall J, et al. Efficacy and safety of mesenchymal stromal cells in preclinical models of acute lung injury: a systematic review protocol. Syst Rev. 2014;3:48. https://doi.org/10.1186/2046-4053-3-48.
19. de Vries RBM, Hooijmans CR, Tillema A, Leenaars M, Ritskes-Hoitinga M. A search filter for increasing the retrieval of animal studies in Embase. Lab Anim. 2011;45(4):268–70. https://doi.org/10.1258/la.2011.011056.
20. Hooijmans CR, Rovers MM, De Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14(1):43. https://doi.org/10.1186/1471-2288-14-43.
21. Suen CM, Stewart DJ, Montroy J, et al. Regenerative cell therapy for pulmonary arterial hypertension in animal models: a systematic review. Stem Cell Res Ther. 2019;10:75. https://doi.org/10.1186/s13287-019-1172-6.
22. Lalu MM, Montroy J, Dowlatshahi D, et al. From the Lab to Patients: a Systematic Review and Meta-Analysis of Mesenchymal Stem Cell Therapy for Stroke. Transl Stroke Res. 2020;11(3):345–64. https://doi.org/10.1007/s12975-019-00736-5.
23. Vesterinen HM, Sena ES, Egan KJ, et al. Meta-analysis of data from animal studies: A practical guide. J Neurosci Methods. 2014;221:92–102. https://doi.org/10.1016/j.jneumeth.2013.09.010.
24. Vered K, Durrant C, Mott R, Iraqi FA. Susceptibility to klebsiella pneumonaie infection in collaborative cross mice is a complex trait controlled by at least three loci acting at different time points. BMC Genomics. 2014;15(1):865. https://doi.org/10.1186/1471-2164-15-865.
25. Speer EM, Adedeji AA, Lin J, et al. Attenuation of acute kidney injury in a murine model of neonatal Escherichia coli sepsis. Front Cell Infect Microbiol. 2025;14. https://doi.org/10.3389/fcimb.2024.1507914.
26. Sun Z, Pan Y, Qu J, Xu Y, Dou H, Hou Y. 17β-Estradiol Promotes Trained Immunity in Females Against Sepsis via Regulating Nucleus Translocation of RelB. Front Immunol. 2020;11:1591. https://doi.org/10.3389/fimmu.2020.01591.
27. Prendergast BJ, Onishi KG, Zucker I. Female mice liberated for inclusion in neuroscience and biomedical research. Neurosci Biobehavioral Reviews. 2014;40:1–5. https://doi.org/10.1016/j.neubiorev.2014.01.001.
28. Beery AK. Inclusion of females does not increase variability in rodent research studies. Curr Opin Behav Sci. 2018;23:143–9. https://doi.org/10.1016/j.cobeha.2018.06.016.
29. Shansky RM. Are hormones a female problem for animal research? Science. 2019;364(6443):825–6. https://doi.org/10.1126/science.aaw7570.
30. Woitowich NC, Beery A, Woodruff T. A 10-year follow-up study of sex inclusion in the biological sciences. Sugimoto C, Rodgers P, Shansky R, Schiebinger L, eds. eLife. 2020;9:e56344. https://doi.org/10.7554/eLife.56344.
31. Carlin S, Dwivedi DJ, Cani E, et al. Impact of streptozotocin-induced hyperglycemia on the host response to sepsis. J Thromb Haemost. 2025;23(10):3386–98. https://doi.org/10.1016/j.jtha.2025.07.004.
32. Sharma N, Dwivedi DJ, Fux L, et al. Intravenous Delivery of Long-Acting Dnase I (PRX-119) In a Murine Model of Polymicrobial Abdominal Sepsis. Shock. 2026;65(1):76. https://doi.org/10.1097/SHK.0000000000002666.
33. Albertsmeier M, Pratschke S, Chaudry I, Angele MK. Gender-Specific Effects on Immune Response and Cardiac Function after Trauma Hemorrhage and Sepsis. Viszeralmedizin. 2014;30(2):91–6. https://doi.org/10.1159/000360149.
34. Erikoğlu M, Şahin M, Özer Ş, Avunduk MC. Effects of Gender on the Severity of Sepsis. Surg Today. 2005;35(6):467–72. https://doi.org/10.1007/s00595-004-2958-3.
35. Knöferl MW, Angele MK, Diodato MD, et al. Female sex hormones regulate macrophage function after trauma-hemorrhage and prevent increased death rate from subsequent sepsis. Annals of Surgery. 2002;235(1):105. https://journals.lww.com/annalsofsurgery/abstract/2002/01000/female_sex_hormones_regulate_macrophage_function.14.aspx. Accessed 18 Dec 2025.
36. Markle JG, Fish EN. SeXX matters in immunity. Trends Immunol. 2014;35(3):97–104. https://doi.org/10.1016/j.it.2013.10.006.
37. Fischer J, Jung N, Robinson N, Lehmann C. Sex differences in immune responses to infectious diseases. Infection. 2015;43(4):399–403. https://doi.org/10.1007/s15010-015-0791-9.
38. Singmann P, Shem-Tov D, Wahl S, et al. Characterization of whole-genome autosomal differences of DNA methylation between men and women. Epigenetics Chromatin. 2015;8(1):43. https://doi.org/10.1186/s13072-015-0035-3.
39. Tsai HW, Grant PA, Rissman EF. Sex differences in histone modifications in the neonatal mouse brain. Epigenetics. 2009;4(1):47–53. https://doi.org/10.4161/epi.4.1.7288.
40. Binnie A, Tsang JLY, Hu P, Carrasqueiro G, Castelo-Branco P, dos Santos CC. Epigenetics Sepsis Crit Care Med. 2020;48(5):745. https://doi.org/10.1097/CCM.0000000000004247.
41. Valeri F, Endres K. How biological sex of the host shapes its gut microbiota. Front Neuroendocr. 2021;61:100912. https://doi.org/10.1016/j.yfrne.2021.100912.
42. Yurkovetskiy L, Burrows M, Khan AA, et al. Gender Bias in Autoimmunity Is Influenced by Microbiota. Immunity. 2013;39(2):400–12. https://doi.org/10.1016/j.immuni.2013.08.013.
43. Youssef H, Stashenko P. Interleukin-1 and estrogen protect against disseminating dentoalveolar infections. Int J Oral Sci. 2017;9(1):16–23. https://doi.org/10.1038/ijos.2016.61.
44. Vandereyken MM, Singh P, Wathieu CP, et al. Dual-Specificity Phosphatase 3 Deletion Protects Female, but Not Male, Mice from Endotoxemia-Induced and Polymicrobial-Induced Septic Shock. J Immunol. 2017;199(7):2515–27. https://doi.org/10.4049/jimmunol.1602092.
45. Newsome CT, Flores E, Ayala A, Gregory S, Reichner JS. Improved Antimicrobial Host Defense in Mice following Poly-(1,6)-β-Glucopyranosyl-(1,3)-β--Glucopyranose Glucan Treatment by a Gender-Dependent Immune Mechanism. Clin Vaccine Immunol. 2011;18(12):2043–9. https://doi.org/10.1128/CVI.05202-11.
46. Dobson B, Strayer K, Wijesinghe A, et al. Differential disease tolerance mediates sex-biased illness severity in sepsis. Proc Natl Acad Sci. 2026;123(9):e2522764123. https://doi.org/10.1073/pnas.2522764123.
47. Hack CE, De Groot ER, Felt-Bersma RJ, et al. Increased plasma levels of interleukin-6 in sepsis. Blood. 1989;74(5):1704–10.
48. Friedland JS, Porter JC, Daryanani S, et al. Plasma proinflammatory cytokine concentrations, Acute Physiology and Chronic Health Evaluation (APACHE) III scores and survival in patients in an intensive care unit. Crit Care Med. 1996;24(11):1775–81. https://doi.org/10.1097/00003246-199611000-00003.
49. Zellweger R, Wichmann MW, Ayala A, Stein S, DeMaso CM, Chaudry IH. Females in proestrus state maintain splenic immune functions and tolerate sepsis better than males. Crit Care Med. 1997;25(1):106–10. https://doi.org/10.1097/00003246-199701000-00021.
50. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: Cardiovascular and immunological aspects. Virulence. 2014;5(1):12–9. https://doi.org/10.4161/viru.26982.
51. Rittirsch D, Huber-Lang MS, Flierl MA, Ward PA. Immunodesign of experimental sepsis by cecal ligation and puncture. Nat Protoc. 2009;4(1):31–6. https://doi.org/10.1038/nprot.2008.214.
52. Buras JA, Holzmann B, Sitkovsky M. Animal models of sepsis: setting the stage. Nat Rev Drug Discov. 2005;4(10):854–65. https://doi.org/10.1038/nrd1854.
53. Delano MJ, Scumpia PO, Weinstein JS, et al. MyD88-dependent expansion of an immature GR-1(+)CD11b(+) population induces T cell suppression and Th2 polarization in sepsis. J Exp Med. 2007;204(6):1463–74. https://doi.org/10.1084/jem.20062602.
54. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. Nat Rev Dis Primers. 2016;2(1):16045. https://doi.org/10.1038/nrdp.2016.45.
55. Carreno D, Wanford JJ, Jasiunaite Z, et al. Splenic macrophages as the source of bacteraemia during pneumococcal pneumonia. EBioMedicine. 2021;72:103601. https://doi.org/10.1016/j.ebiom.2021.103601.
56. Jubel JM, Barbati ZR, Burger C, Wirtz DC, Schildberg FA. The Role of PD-1 in Acute and Chronic Infection. Front Immunol. 2020;11:487. https://doi.org/10.3389/fimmu.2020.00487.
57. Zeng Z, Surewaard BGJ, Wong CHY, et al. Sex-hormone-driven innate antibodies protect females and infants against EPEC infection. Nat Immunol. 2018;19(10):1100–11. https://doi.org/10.1038/s41590-018-0211-2.
58. Jahandideh F, Mendelson AA, Liaw PC, et al. Assessing the effects of fluids and antibiotics in an acute murine model of sepsis: study protocol for the National Preclinical Sepsis Platform-01 (NPSP-01) Study. F1000Research. 2025. https://doi.org/10.12688/f1000research.163800.1.

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