Journal of Intensive Medicine 4 (2024) 34–45

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Review

Optimizing artificial intelligence in sepsis management: Opportunities in the present and looking closely to the future

Darragh O'Reilly[1,#], Jennifer McGrath[1,#], Ignacio Martin-Loeches[1,2,*]

[1] Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St James' Hospital, Dublin, Ireland
[2] Department of Respiratory Intensive care, Hospital Clinic, Universitat de Barcelona, IDIBAPS, CIBERES, Barcelona, Spain

ARTICLE INFO

Managing Editor: Jingling Bao

Keywords:
Artificial intelligence
Data science
Machine learning
Intensive care unit (ICU)
Critical care
Sepsis

ABSTRACT

Sepsis remains a major challenge internationally for healthcare systems. Its incidence is rising due to poor public awareness and delays in its recognition and subsequent management. In sepsis, mortality increases with every hour left untreated. Artificial intelligence (AI) is transforming worldwide healthcare delivery at present. This review has outlined how AI can augment strategies to address this global disease burden. AI and machine learning (ML) algorithms can analyze vast quantities of increasingly complex clinical datasets from electronic medical records to assist clinicians in diagnosing and treating sepsis earlier than traditional methods. Our review highlights how these models can predict the risk of sepsis and organ failure even before it occurs. This gives providers additional time to plan and execute treatment plans, thereby avoiding increasing complications associated with delayed diagnosis of sepsis. The potential for cost savings with AI implementation is also discussed, including improving workflow efficiencies, reducing administrative costs, and improving healthcare outcomes. Despite these advantages, clinicians have been slow to adopt AI into clinical practice. Some of the limitations posed by AI solutions include the lack of diverse data sets for model building so that they are widely applicable for routine clinical use. Furthermore, the subsequent algorithms are often based on complex mathematics leading to clinician hesitancy to embrace such technologies. Finally, we highlight the need for robust political and regulatory frameworks in this area to achieve the trust and approval of clinicians and patients to implement this transformational technology.

Sepsis is a major concern worldwide due to its high morbidity, mortality, and financial cost to health systems.[1] Globally, there are an estimated 30 million sepsis cases yearly, resulting in more than 6 million deaths. Sepsis causes one death every 3–4 seconds.[2]

Recent large-scale epidemiological studies showed that the mortality rate from sepsis has decreased. However, despite this, the incidence of sepsis continues to increase and is likely to be underestimated.[3] The lack of public awareness surrounding sepsis and the serious consequences of delays in its recognition and treatment significantly contribute to the alarming annual increase of 8%–13% in sepsis cases over the last decade.[4]

Sepsis is heterogeneous, with varying etiologies, pathogeneses, and clinical manifestations, making fundamental research, clinical translation, and precision medicine in sepsis more challenging.[5] Government funding is the primary contributor to research and development in sepsis, focusing on developing innovative strategies for diagnosing and managing sepsis while addressing international public health needs. Reasonable and forward-looking funding frameworks will accelerate medical research progress in sepsis and greatly promote human health.[6] A major difference in recent years has been that sepsis has been recognized as a disease with organ failure.[7] This is likely a misinterpretation due to *post hoc* analysis or retrospective evaluation of large databases where sepsis is already known. Future research developments will aim to detect sepsis in patients before organ failure occurs.

During the past decade, the National Institute of Health (NIH) has invested the most in the sepsis field, with 1435 projects and 476.9 million US dollars in funding. The National Natural Science Foundation of China was in second place, with 47.7 million US dollars awarded to 581 projects. The total allocation for sep-

* Corresponding author: Ignacio Martin-Loeches, Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St James's Hospital and Professor at Trinity College, Dublin 8 D08 NHY, Ireland.
E-mail address: ImartinL@tcd.ie (I. Martin-Loeches).
# Darragh O'Reilly and Jennifer McGrath contributed equally to this work.

https://doi.org/10.1016/j.jointm.2023.10.001
Received 22 April 2023; Received in revised form 29 September 2023; Accepted 1 October 2023
Available online 29 November 2023

sis research by the National Grants-in-Aid for Scientific Research (JSPS KAKENHI) Program in Japan was the lowest, with 429 projects and funding of 23.8 million US dollars.[8] Differences in the health care budget for sepsis in various institutions worldwide can also be evaluated. In many countries, there is no record of sepsis-funded projects.[8] Approximately 200 studies containing sepsis-related research were published in the Medline database from 2011 to 2015 by the USA, the European Union's 28 member states, and China. Notably, more than half of these studies were published by authors from the USA, with more than half having a university or government/state funding source. Despite these advantages, sepsis funding remains challenging, and many industry-based companies are current sponsors of major sepsis organizations such as the Surviving Sepsis Campaign (SSC).[9]

When considering future research in sepsis,[10] different research groups proposed several pathways to improving sepsis management. It has been previously discussed for years the need for better design of drug targets (e.g., endothelial cell function). Yet, most of the discussion of the role of artificial intelligence (AI) in sepsis and how we can integrate computer-simulated models. Still, the key element is related to clinical trial design improvements. Personalized medicine needs the identification of specific patient populations that would benefit from each identified intervention. A suggested framework for characterizing a patient with sepsis is PIRO (predisposition, infection, response, and organ dysfunction). To better enrich the selection of the patient population instead of using single biomarker values, it provides a better selection enrichment with multiple biomarkers. For that rationale, we need advanced tools based on complex computational analysis.

This manuscript aimed to introduce some key concepts on the basics of AI in sepsis. We give an overview of AI and its applications in the intensive care unit (ICU), including how AI has played and will play a major role in future research in sepsis. We also outline potential strategic solutions to the challenge of implementing AI into clinical practice.

An Overview of AI and Machine Learning

AI is a broad field of computer science that focuses on developing intelligent machines that can perform tasks that typically require human intelligence, such as visual perception, speech recognition, decision-making, and language translation. The term artificial intelligence is both difficult to define and ever-changing and was coined in 1956 by John McCarthy following the eponymous "Turing" test. Broadly speaking, it is considered the ability of machines to exhibit intelligent behavior in the manner of human thinking, reasoning, and problem-solving.[11]

The core of AI aimed to determine whether a machine could exhibit intelligent behavior to convince a human interrogator it was, in fact, a human when in reality, it was a machine.[12] AI involves various subfields, including machine learning (ML), deep learning, natural language processing (NLP), and robotics. AI has the potential to revolutionize medicine by improving diagnosis, treatment, and patient outcomes. One key area where AI is applied is in medical imaging, such as X-rays, computer tomography scans, and magnetic resonance imaging scans.[13] ML algorithms can be trained to identify patterns in medical images and help radiologists diagnose diseases such as cancer and heart disease faster and more accurately.[14]

AI is also used in patient monitoring and personalized medicine, such as sepsis.[15] Wearable devices equipped with AI algorithms can collect and analyze data on vital signs, such as heart rate, blood pressure, and oxygen levels. It can provide real-time feedback to the doctor and help identify potential clinical complications before they become clinically apparent.[16] By analyzing vast amounts of data, researchers can identify potential new drug candidates more quickly and efficiently than traditional methods.[17]

ML is a subset of AI that involves using algorithms and statistical models to enable machines to improve their performance on a task by learning from data without being explicitly programmed.[18] In medicine, ML algorithms can be applied to various tasks, such as diagnosis, prediction, and personalized treatment. The methods by which this is achieved can be subdivided into two categories: supervised learning and unsupervised learning.[19]

Generally, supervised learning involves ML from input data, e.g., patient characteristics, vital signs, and lab results.[20] These data have been labeled, e.g., "sepsis" or "not sepsis," to predict a known outcome, e.g., sepsis in the future in unforeseen data.[21,22] Thus, supervised learning is concerned with the ability to predict outcomes in the future based on what it has learned from the labeled training data with which it was originally presented.[23]

In contrast, unsupervised learning involves ML from unlabeled data to find hidden patterns and structures within the data. This could potentially highlight homogeneous phenotypes in sepsis, allowing for more individualized therapy approaches.[21] Data in healthcare can be classified as structured, e.g., vital signs and lab values, and unstructured, e.g., free text clinical notes in electronic medical records and radiological images. Most AI in healthcare has focused on structured data, although 80% of healthcare data in electronic healthcare records is unstructured.[24] This reflects the complexity and computational power required to analyze these data.[25] Recent advances in ML and computational power have allowed for unstructured data to be analyzed by a method known as NLP. NLP extracts concepts and meanings from a clinical text note.[26]

NLP is the branch of AI that allows machines to read, understand, and derive meaning from human languages. Where text-based data exist on the internet (e.g., social media reviews of healthcare providers), it is technically possible to capture these using a process called web-scraping.[27] Web-scraping software can be programmed to detect and download specific text from a website (e.g., comments on patient forums), and store these in databases, ready for analysis.[27]

The text is broken down into constituent sentences and words with NLP. The words then are tokenized, with each word being a token, for example, by matching the words "love," "favorite," and "respect" to a "positive" sentiment and the words "hate," "pain," and "anguish" to a "negative" sentiment. By quantifying the ratio of positive to negative sentiments in a sentence, for example, it is possible to start to understand the sentence's sentiment overall. Unsupervised ML can identify common themes within the text by clustering words or sentiments that frequently appear together, e.g., "topic modeling".[27] Supervised ML algorithms have been combined with NLP to extract patient-centered outcomes from unstructured medical records.[27]

A recently developed AI algorithm, sepsis early risk assessment (SERA) algorithm used structured data and unstructured clinical notes to predict and diagnose sepsis. Their model showed high predictive accuracy 12 h before the onset of sepsis (area under the curve [AUC] =0.94, sensitivity= 0.87, and specificity=0.87).[28] Compared with clinicians' assessment alone, this algorithm increased the early detection of sepsis by up to 32% and reduced false positives by up to 17%. NLP of unstructured clinical notes improved the algorithm's accuracy compared to using only clinical measures alone, providing 12–48 h warning before the onset of sepsis.[28]

Other work by Horng et al.[29] also demonstrated the incremental benefit of using free text data and vital signs and demographic data to identify patients with suspected infection in the emergency department (ED). The best-performing model they found was the model that used all of the free text. They concluded that free text drastically improved the discriminatory ability (increase in AUC from 0.67 to 0.86) of identifying infection compared to previous work that only used structured data such as vital signs and demographic information.[29]

Large language model uses more advanced technology and algorithms to generate sophisticated human text.[30] These systems use neural network models that leverage deep learning methods to train from text-based datasets from articles, books, and other internet-based content. Through this method, Large language models (LLMs) learn how words are used with each other in language and can apply these learned patterns to complete NLP tasks.[31] ChatGPT (OpenAI, San Francisco, USA) has grown increasingly larger from its inception in 2018 with ChatGPT1. With its most advanced update ChatGPT-4, it now has more data from many billions more books, articles, and conversations across the internet and increased computation.[31]

However, such large language models have big problems as regards reliability. Currently, legitimate concerns exist about clinical information quality, evidence level, reliability, or supporting evidence for any LLM model.[32] LLMs reassemble what has been most repeatedly written by humans trained from unchecked datasets and often quote a fabricated resource for referencing.[32]

As a result, these tools currently would not achieve regulation under EU or US law as medical devices, having a limitless range of inputs and outputs, making them almost impossible to control fully.[32] However, this has not stopped their use because they are experimental rather than actual AI tools for clinical use.[32] This is concerning because it has been demonstrated that LLMs can provide profoundly dangerous information when prompted with medical questions.[32] Scientific journals have not allowed accreditation of ChatGPT as an author, suggesting that the technology cannot provide the accountability required for authorship.[31] Tools are currently being developed to detect AI-generated language, but their accuracy is poor.[31]

Future models, however, promise more supervised learning approaches from reputable content, which will improve accuracy and safety.[30–32] Perhaps then they can play an assistive role to the modern clinician rather than an autonomous role due to inherent concerns regarding their safety.[31] This may entail clinical note-taking, administrative letter writing, and summarizing clinical information from dense patient medical records.[30] It could also play a valuable role in clinical research, e.g., summarizing results and rewriting passages to suit specified readerships, thereby reducing the workload of critical appraisal, research reporting, and peer review.[31]

Early Detection: Diagnosing Sepsis on the Ward, in the ED and in the ICU

When discussing AI and its application in patients with sepsis in the ICU and hospital at large, areas to consider include the early detection and accurate diagnosis of sepsis and its subsequent treatment.

Rawson et al.[33] developed a supervised machine learning (SML) algorithm for diagnosing infection on presentation to the hospital. Microbiological data records and blood test parameters (e.g., C-reactive protein, white cell count, etc.) were used to train the SML algorithm. A support vector machine (SVM) binary classifier algorithm was subsequently developed. Many individual patient profiles containing biochemistry and full blood count variables trained and tested the diagnostic ability of the SVM algorithm. A clinical decision support system (CDSS) contains ML modules designed to support antimicrobial selection and dose optimization tools, and a patient engagement module was implemented. They then studied patients admitted to the hospital over 6 months and prospectively inputted them into the SML algorithm.

One out of three patients was diagnosed with infection within 72 h of admission. Almost half individuals had microbiological investigations performed. Treatment was prescribed for most infected individuals and only 6% of those with no identifiable bacterial infection. Mean standard deviation (SD) likelihood estimates for those with and without infection differed significantly. The area under the receiver operating characteristic (AUROC) was 0.84 (95% CI: 0.76 to 0.91). The study demonstrated that clinicians performed well at diagnosing bacterial infection in patients admitted to the hospital, and only less than 10% were not appropriately treated. Moreover, a few individuals did not have evidence of bacterial infection but received antimicrobial therapy regardless (6%).

Another validated ML algorithm used vital signs taken directly from the Electronic health record (EHR), for the detection and prediction of sepsis, severe sepsis, and septic shock in a mixed-ward population, which included patients from the ED and floor units as well as the ICU.[34] This ML algorithm, called "InSight scores," took data from six clinical vital signs; blood pressure, systolic and diastolic, heart rate, respiratory rate, peripheral capillary oxygen saturation, and temperature. They used gradient tree boosting to construct this ML algorithm. The patient's risk score was generated based on their path along the decision tree. They then compared "InSight" predictions for three common scoring systems: Systemic inflammatory response syndrome (SIRS), Sequential Organ Failure Assessment (SOFA), and Maternal Early Warning Score (MEWS). "InSight" outperformed SIRS, MEWS, and SOFA for screening sepsis, severe sepsis, and septic shock and provided predictive capabilities before sepsis onset, aided by analyzing trends and correlations between vital sign measurements.

A third study, in 2017, analyzed how sepsis is diagnosed in the ED. They conducted a retrospective, observational cohort study to trigger clinical decision support at ED triage for sepsis. These data included patient demographics, vital signs, free text chief complaint, and free text nursing assessment (also called the triage note) to trigger a protocol.[29,35] They subsequently trained ML algorithms to predict the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) defined infection using incrementally larger subsets of features. They built four models to predict infection with an SVM to build the model. The best-performing model was the model that utilized the free text as well as vital signs and demographics.[29] Vital sign abnormalities and laboratory results often trigger decision support for sepsis and might have important implications for ED workflow where additional blood work may not have yet become available for admitting physicians to review.

Early detection and prompt intervention play a key role in optimizing the outcome of sepsis patients. Positive outcomes are highly related to effective management in EDs and ward settings since successful treatment is time-dependent.[36] Unfortunately, transferring patients from the ED or ward to an ICU is often ineffective.[36] A recent meta-analysis of 28 papers looking at ML for predicting sepsis found that diagnostic test accuracy when assessed using AUROC was 0.68–0.99 in the ICU, 0.96–0.98 in the hospital, and 0.87–0.97 in the ED.[37]

Models for predicting sepsis ahead of time can be categorized into right-aligned or left-aligned. Left-aligned models predict the likelihood of sepsis following a fixed time point, e.g., admission or pre-operatively.[37] An envisaged case use of a left-sided model would be the identification by the left-sided model of a patient ahead of time likely to develop sepsis ahead of the proposed surgery. Surgery could be postponed, optimizing modifiable risk factors if the patient is identified as likely to develop sepsis. If there is surgery could not wait, a strategy to minimize these risks could be used, such as prolonged peri-operative prophylactic antibiotics or planned post-operative admission to a higher level of care (High dependency unit [HDU]/ICU) than would ordinarily be used for the specific surgery and or patient, thus mitigating the risk.

Right-aligned models utilize EHRs to continuously sample an individual patient's data in real-time, comparing this against retrospective databases of patients to predict sepsis ahead of time.[37] Again, using a patient in the ICU as an example, could be used to change therapies such as antibiotics or place invasive lines in a proactive rather than a reactive manner, thus minimizing the time a patient is at risk of end-organ damage due to hypotension or impaired renal function.

Clinicians are often challenged in differentiating sepsis from other acute conditions due to similar signs or symptoms for other common diseases. AI has the potential to deliver timely and accurate sepsis detection on the ward and in the ED, potentially outperforming current clinical warning scores, which are not based on sophisticated mathematical models.[36] This technology can facilitate treating patients promptly to prevent complications arising from delayed treatment, e.g., multi-organ failure and shock.

To that effect, ML-based early warning systems have been shown to predict circulatory failure with very high accuracy. Hyland et al. [38] constructed two early warning systems, named circEWS (Circulatory Early Warning Score) and circEWS-lite, that were of differing complexity. They alerted clinicians to patients at risk of circulatory failure within an 8-hour time frame. They used publicly available data from a patient database from a large multidisciplinary ICU, which contained data from more than 54,000 ICU admissions. These data were then used to train their early warning systems. These ML-based early warning systems predicted circulatory failure with very high accuracy. These early warning systems could assist ICU staff in identifying patients with sepsis earlier who are at risk for developing circulatory failure.

Furthermore, patients with a much lower false alarm rate should be identified than conventional alert systems. These traditional alert systems have previously been demonstrated to cause inherent alarm fatigue for staff. This can lead to cognitive bias and the potential for missed or late diagnosis of patients who are critically ill.[38,39]

Another model predicting model is "Haemodynamic stability index (HSI)" which aims to determine circulatory failure.[40] It is a multiparameter ML model used to provide an early warning of hemodynamic compromise and the need for the initiation of hemodynamic supports. It has been trained by learning from thousands of clinicians' actions, such as the commencement of vasoactive medications, fluids, and blood administration.[40] HSI has demonstrated generalizability across patient populations, apart from the neurosurgical population, and shown better accuracy in predicting instability than single parameters like systolic blood pressure and shock index.[40] It is one step closer to delivering individualized patient care and is a useful decision-support tool for managing circulatory shock in critical care in the future.[41]

Due to advancements in monitoring, we now have vast amounts of data available as clinical decision-support tools in ICUs. However, modeling all these data is challenging due to its high density and heterogeneous nature and the requirement for it to be easily interpretable by clinical decision-makers on the ground.

A proposed solution is the "Recurrent Attentive And Intensive Model (RAIM)" for analyzing continuous physiological data (e.g. Electrocardiograms, telemetry waveforms, vital signs) and irregular clinical data (lab values, clinical interventions) in tandem.[42] This is a type of model that is easily interpretable for clinicians. With the data obtained, "RAIM" generates a guidance matrix to predict dynamic outputs such as the risk of physiological decompensation and/or hospital length of stay. Using evaluations from the Medical Information Mart for Intensive Care III (MIMICIII) Waveform Database Matched Subset, "RAIM" obtained over 90% AUC-ROC scores for predicting physiological decompensation with quite a high accuracy (86.82%) for forecasting length of stay.

Heretofore the use of AI has mainly focused on irregular clinical events and discrete data. The interpretation of physiological waveforms by AI is a novel field that shows much promise. One such example is a physiology-based model which uses waveforms independent of other data in the EHR. Using waveforms and a closed-loop cardiovascular model the system was able to predict sepsis within the first hour of admission with a high degree of success (AUROC=0.92, Area under precision-recall curve=0.90).[43]

Other published papers have shown tools to optimize clinical management, such as fluid and vasopressor support.[44] These tools utilized reinforced learning, to optimize the management of fluids and vasopressors in sepsis to minimize mortality. The model learned the optimal dosing regimen from a large training set of data on patients with sepsis in the ICU. Then, the models were tested against unseen data and compared to the performance of human clinicians. Real doctors would have given more fluids when the AI tool recommended more vasopressors. This has enormous implications as the deviation from the "AI clinician" strategy was associated with an increase in mortality in a dose-dependent fashion.

While AI may not be a panacea for sepsis, clinicians could use it as an aide memoire in their decision-making processes.[45] Exceptions to AI-derived strategy will always exist, and clinicians should continue to make treatment decisions with this in mind. This will enable clinicians to optimize the management of sepsis to reduce the associated morbidity and mortality.

Triaging and Prioritizing Patients for ICU Admission

AI algorithms can also stratify and help to predict which patients are at risk of developing organ failure or sepsis. This can help clinicians allocate resources more effectively, such as identifying earlier patients with acute kidney injury (AKI) who need renal replacement therapy.[46] Another role AI could play in the future is triage and patient selection for intensive care. A "field artificial intelligence triage" tool showed the accuracy of the need for ICU admission and mechanical ventilation predicted by AUROC were 84.8±0.5 and 86.8±0.5 for patients with gunshot wounds.[47]

Resource utilization remains a key concern in intensive care medicine. The effects of limited resources on the delivery of intensive care medicine were brought sharply into focus during the COVID-19 pandemic.

Using data gathered during this time, an AI tool was developed to identify patients likely to require ICU-level care with 97% accuracy and rank these patients based on an "analytical hierarchical process (AHP)".[48] The AHP was deemed to be "close to experienced clinicians' decisions for determining the priority of patients that need to be admitted to the ICU." The proposed use of the AHP in the future is to answer the question of "Which patient positive with COVID-19 will use the ICU first in an emergency or limited resource situation?"

The use of AI for answering such a "life or death" question is fraught with ethical and practical concerns, not least the question of bias. Vinay et al.[49] consider both sides of the discussion, noting that AI could partially unburden healthcare professionals from this moral challenge while conceding that AI is vulnerable to bias and discrimination. One important question stemming from this discussion is how to integrate AI tools for decision-making.

While it could be expected that physicians would have a grounding in the AI tools they would use, it may not be feasible or even possible for a single physician to understand or know the weighing of the variables within every AI tool they use. Some AI tools use more than 40 variables, which will only increase as the tools evolve. The greatest obstacle to implementing AI tools in medicine in a prospective manner will not be that of a logistical or practical manner but rather the broader ethical questions that wider society must answer.

Predictive Algorithms on the Pathogen and Antimicrobial Prescribing

ML algorithms have the potential to help predict and diagnose causative pathogens in sepsis earlier than traditional methods. One such study looked at acute respiratory failure (ARF) in childhood.[50] Due to the significant overlap in signs and symptoms in both bacterial and viral etiology, clinical diagnosis is challenging. This often leads to inappropriate treatment with antibiotics by clinicians. Tools to automatically determine the cause of ARIs could help with early diagnostic accuracy, thus improving healthcare delivery. This study aimed to diagnose common respiratory pathogens in pediatric patients. Clinical features were collected within 24 h of admission to construct the models. They looked at six common respiratory pathogens, including adenovirus, influenza virus types A and B, parainfluenza virus , respiratory syncytial virus, and *Mycoplasma pneumoniae*.

Their subsequent models were trained with nine features (age, event pattern, fever, C-reactive protein, white blood cell count, platelet count, lymphocyte ratio, peak temperature, and peak heart rate).

Using their model, pathogen prediction was automatically produced with each step, and the prediction performance increased when more information was obtained. This study outlined how AI has the potential to enable earlier and more accurate diagnosis of ARF in children, thus helping reduce unnecessary diagnostic tests and medical costs.

However, not all studies in this field have been as positive. A study by Lhommet et al.[51] predicting the microbial cause of community-acquired pneumonia (CAP) in the adult population is one such study. Like upper respiratory infections in the pediatric population, CAP's causative pathogen is generally unknown before the clinician begins treatment. This study evaluated the abilities of experienced physicians and AI to decide on admission if the pneumonia was viral or bacterial. They included patients hospitalized for CAP and recorded all data available in the first 3-h admission periods, including clinical, biological, and radiological information. These authors implemented an ML model using all collected data and tested the pathogen prediction performance against a panel of three clinical experts compared to the AI algorithm. The results showed an AUC of 0.84, which on interpretation, reveals that neither experts nor an ML algorithm could accurately predict the microbial etiology of severe CAP within the first 3-h of admission.

Strategies like rapid molecular respiratory panel assays are more likely to provide optimal treatment options for acute respiratory infections. However conducting more studies to assess if an AI system integrated with point-of-care rapid molecular respiratory panel assays, as the authors suggest, would be informative.[51] The development of systems biology tools, such as metabolomics, has enabled key insights into the change of chemical environment in sepsis. Exploring such concepts allows us to identify causative pathogens in sepsis accurately.[52] In the field of metabolomics, fundamental differences in the host response to infection have been identified, e.g., an increase in glycolytic intermediates and decreased flux through the tricarboxylic acid cycle with elevated multiple inflammatory markers. Indeed, differing responses have also been seen depending on which causative pathogen is involved. Mouse models have shown that *Streptococcus pneumoniae* and *Staphylococcus aureus* pneumonia induce distinct metabolic responses.[52] Research suggests that through exploring plasma pathogen-specific metabolomic biosignatures, a method to develop fast and reliable microorganism identification of sepsis cases may ensue.[52] This study investigated the value of metabolomic biosignatures to identify the causative pathogen among sepsis patients. This approach is in agreement to help with the identification of pathogens. Their results showed that the biosignatures selected by ML algorithms could have diagnostic value in identifying infected patients and Gram-positive from Gram-negative bacteria.

Once a clinical infection is already being diagnosed, AI also has a potential role in prescribing appropriate therapies. Most hospital infections are managed by non-experts in infectious diseases who follow local antimicrobial guidelines and policies. Case-based reasoning (CBR) is a type of AI that is an experience-based approach to solving new problems by adapting previously successful solutions to similar problems. In CBR, the reuse of knowledge from previously solved problems relies on the fact that the more similar the two problems are, the more similar their solutions will be. It offers incremental sustained learning in that each time a problem is solved, a new experience is retained and can be applied to future problems.

This technique has helped develop a CDSS for antimicrobial prescribing, which was subsequently integrated into the electronic health record.[53] In the study, prescribing recommendations by a CBR algorithm were compared to decisions made by clinicians on the ground. Results from this study revealed that the ML CDSS made antibiotic selection at a similar level of appropriateness to individual clinicians but with a narrower spectrum of activity. This study showed how ML techniques and CDSS can provide an individualized approach to prescribing and enhanced patient care as a result. Other examples of AI used in antimicrobial prescribing include the TREAT system, a CDSS using causal probabilistic networks. TREAT demonstrated a 9% improvement in the appropriateness of prescribing and a trend toward improved patient survival using this type of system.[54] TREAT requires the development of highly complex decision maps making the systems challenging to develop, and they require large amounts of data sets. Advocates of CBR claim the system is simpler and, therefore, easier to implement into clinical practice.[55] Regardless of which system is used, utilizing them helps avoid issues of accurate recall for busy clinicians and gives access to learnings equivalent to years of clinical experience through this technology.

Precision Medicine

Genomics and precision medicine is a growing area in science and medicine. Many treatments we use in medicine are designed for the average patient but as experience shows successful treatment for one patient does not equate to successful treatment for another, despite the same pathology. Precision medicine is an innovative approach taken from the field of oncology, where the goal is to tailorize treatments to a more individualized approach considering one's genes, lifestyle, and environment. AI and precision medicine combined have the potential to transform how healthcare is delivered in the future.[56]

Sepsis is a clinically and biologically heterogeneous disease with a variable clinical course and includes varying phenotypes.[57,58] Clinically heterogeneity is seen due to differences in age, associated co-morbidities, causative organisms as well as origins of septic foci. Biologically, heterogeneity is seen in differing endotypes and phenotypes in septic patients, indistinguishable from the bedside. Despite this heterogeneity, all sepsis patients receive antibiotics, source control, fluid resuscitation, and organ support if required. It is therefore unsurprising that not all patients respond equally to this therapy and despite improvement in recent decades, mortality from sepsis remains high. Targeted therapeutics and precision medicine approaches could be the solution to this cohort of patients.[57,58]

The pathophysiology of sepsis is varied in patients. Different genetic polymorphisms have been identified in individuals that encode pro-inflammatory and anti-inflammatory cytokines. This is also the case for cytokine receptors, cell signaling pathways, and hemostasis pathways.[57,58]

These all influence the severity and ultimately the mortality in patients with sepsis. The inflammatory stage in sepsis occurs in two phases for all patients. There is the pro-inflammatory phase and an anti-inflammatory phase and depending on which stage the patient is in will influence how they respond to certain treatments. The sequence and duration of these phases are likely genetically pre-programmed, explaining the varied responses seen to immunomodulating treatment like steroids, cytokines, and anti-cytokine antibodies in sepsis. Currently, there is no bedside approach that can identify where in the inflammatory cascade the patients lie in that moment in time. However, if we could rapidly immunophenotype patients, targeted pharmacotherapies could be applied and potentially lives saved as a result.[57,58]

Certainly, bioinformatics and genetics in medicine is a vast field. For example, many factors can alter gene expression without changing the DNA sequence, e.g., DNA methylation, non-coding RNAs, histone variants, and histone post-translational modifications.[58] These epigenetic changes can react to environmental factors by activating or inhibiting gene transcription. For example, septic patients who were shown to have undergone changes in the methylome of their circulating monocytes had subsequently high levels of Interleukin 6 and Interleukin 10 and a high degree of organ dysfunction.[58] Furthermore, by analyzing gene transcription and messenger RNA, there have also been different subtypes in septic patients identified. For example, one such subtype of messenger RNA has been characterized by a significantly increased expression of genes involved in inflammatory and Toll-like receptor-mediated signaling pathways. This profile was found to be associated with a higher prevalence of sepsis.[58]

Biomarkers like procalcitonin, lysophosphatidylcholine, and proadrenomedullin, also have a role to play in sepsis patients, as does pathogen-associated molecular patterns, e.g., endotoxin, a lipopolysaccharide present in the outer cell membrane of Gram-negative bacteria.[58]

Nevertheless, there is some work to be done before we can fully embrace precision medicine in the management of sepsis. This includes further clinical research, investment in rapid assays and point-of-care testing as well as the ability to combine clinical, biological, and genetic data on each patient and extract actionable insights from it for the management of septic patients.[57]

AI may be the bridge that is needed to do just that.[57] The use of multimodal AI and big data analytics could thoroughly phenotype an individual, thereby providing physicians with all the information to accurately diagnose, manage, and predict disease trajectory in these patients using a targeted, most up-to-date, and scientific approach.[57]

AI-Driven Mechanical Ventilation

Another area of promise concerning AI and sepsis is the development of AI-driven mechanical ventilation strategies. A recent systemic review of AI for mechanical ventilation identified the four most common predictions algorithms set out to predict: weaning success, the need for the commencement of mechanical ventilation, complications in ventilated patients, and detecting patient-ventilator asynchrony.[55]

A new reinforced learning algorithm called "VentAI" has been developed and validated using the MIMIC-III data to predict optimal Positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), and tidal volume settings. The VentAI algorithm outperformed physicians' standard care in the outcomes of in-hospital mortality or 90-day mortality. This was achieved by VentAI choosing ventilation regimes with lower tidal volumes (5–7.5 mL/kg), avoiding high (>55%) FiO_2, and recommending PEEP levels of both 5–7 cmH_2O and 7–9 cmH_2O more frequently than physicians.[59]

One clear caveat to this algorithm and, in fact, any algorithm that is not validated *in vivo* is that while a physician may know that ventilation strategy is not optimal for a patient, they are constrained by the real-world physics of ventilation. While a model can predict from data what may occur against the best available data, a physician may try the same strategy *in vivo* and find that the same ventilation strategy is not possible in reality and may have to revert to the "best possible real ventilation strategy" for each patient given the unique circumstances, thus creating a larger perceived outcome different between an algorithm and a physician. As highlighted by this systematic review, what is needed is more prospective and external validation of algorithms.[60]

Few randomized controlled trials (RCTs) exist regarding AI and mechanical ventilation. However, one RCT that should offer hope for the future of AI and physician integration and shared decision-making is that of Hsu et al.[55] This RCT compared ventilator weaning success rates with physician decision-making combined with an AI-derived CDSS *vs.* physician decision-making alone. The combined arm showed a sensitivity of 87.7% *vs.* 61.4% in the physician-only decision-making arm. This equated to 5 days less mechanical ventilation (43.69 *vs.* 38.41).

Identifying New Clinical Phenotypes

ML clustering techniques aim to improve the identification of new clinical phenotypes in sepsis.[61] There is a well-known heterogeneity of the host response to sepsis. Due to problems in the sepsis definition, we may fail to identify the clustering of distinct clinical and biological features in differing patient cohorts. Not surprisingly, patients' phenotypes respond differently to treatments and have a different overall mortality risk.[61] Some research groups used unsupervised learning protocols as an ML algorithm to gather inferences from data sets consisting of input data without labeled responses. The data analyzed was limited to mostly vital signs and laboratory tests, collected within the initial 6 h following hospital presentation. Four different sepsis phenotypes were described, which were derived, validated, and shown to correlate with biomarkers and mortality. This information could be combined with even more clinical data, e.g., other manifestations of sepsis as measured by systems biology and novel gene expression patterns.[62] Then, more targeted immunotherapeutic interventions for these subsets of patients could be developed.

However, as outlined, this will require both expansion of the patient electronic record and access to it so that ML algorithms can analyze the vast arrays of data it is designed to do.[62] This would include past medical histories and patient co-morbidities, not just lab values and vital signs.[61] However, such data access is severely limited. This security and privacy issue regarding data access is a huge barrier curtailing the proper implementation of AI in healthcare.

AI in Clinical Trials and the Role of Personalized Medicine

AI has the potential to improve the success, generalizability, and efficiency of clinical trials. Developing new drugs is a lengthy arduous expensive process and AI can help expedite the process and contribute to more drugs achieving regulatory approval, which is less than 20% with traditional avenues.[17,63] It can help at all stages of drug development from the preclinical stages right through to release to market.[17]

By leveraging huge datasets, it can both identify and predict molecular targets for drugs.[17,55] It can also predict the bioavailability of compounds as well as drug toxicity and can replace the traditional pre-clinical phases frequently done on animal or *in vitro* studies.[17] It can help at the human clinical phase by devising trial protocols and applying simulation techniques to large data sets highlighting quickly potential stumbling blocks to the trial design which may prevent successful trial completion.[17,56] It can help with participant selection and match patients quicker than traditional methods by analyzing combined demographic, lab, and imaging data and verifying suitability for inclusion in the trial.[64,65]

Through access to large datasets, it can overcome previous geographic, sociocultural, and economic disparities when including participants which previously has led to the underrepresentation of certain groups in research.[56] The conduct of the trial can also be influenced by AI technologies with the use of wearable devices which can be combined with other data streams, enhancing the information obtained by study participants thereby increasing the quality of the research conducted.[56] These data can also help monitor remotely for adverse events as well as study outcomes.[56]

With the vast amount of data generated in ICUs, including patient vitals, laboratory results, imaging data, and historical medical records, AI technologies can analyze these data efficiently and provide personalized insights and predictions.

There are some areas such as early "disease detection" (real-time patient data to lead to early intervention, potentially preventing the progression of diseases), "predictive analytics" (ML models), drug discovery (AI-driven platforms to identify potential drug candidates and predict their efficacy), clinical decision support (evidence-based recommendations), image analysis (early detection of diseases and improving the overall accuracy of diagnoses), resource optimization (staff scheduling, bed management, and equipment utilization), and reducing medical errors to improves the overall safety of patient care.[66]

There has also been interest in using AI/external data to create a control arm in studies.[56] The United States Food and Drug Administration has already approved drugs based on historic controls so it is conceivable that AI could be used to generate synthetic control arms in time.[56] AI tools can also be used to statistically analyze trial results giving better insights into drug developers in the pharmaceutical industry.[17]

Outside of drug development, there has been an explosion in AI algorithms proposed for clinical practice pertaining to hospital admission and triage, diagnosis, prognosis, and decision support tools as well as treatment planning.[63] There have been concerns raised however from clinicians, the public, and policymakers at large about the robustness of some of this research in the literature. Unfortunately, recent meta-analyses and systematic reviews of AI medical imaging studies confirmed that less than 1% of the 20,000 imaging studies included in these reviews were of sufficient quality to evaluate the use of these algorithms in the real-life clinical environment.[63,67] Similarly, a high degree of bias was also found in the studies.[63] This is despite much of this research being published in reputable scientific journals.

The Enhancing the Quality and Transparency of Health Research (EQUATOR) Network is an international initiative that seeks to improve the quality of healthcare research by promoting the development and use of robust reporting guidelines.[63] This network provides toolkits for researchers to assist in the development, selection, and use of reporting guidelines when conducting clinical research in AI.[63]

Research in AI should still use established methodology including good study design, delivery, and reporting. This is required to ensure transparency, reproducibility, and validity of any AI intervention before it is approved for use.[63,67]

Using such reporting guidelines, e.g., Consolidated Standards of Reporting Trials (CONSORT) AI, Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) AI, and Developmental and Exploratory Clinical Investigations of Decision support systems driven by Artificial Intelligence (DECIDE AI) allows researchers to utilize tools in their research which have an explicit methodology and specify the minimum information required when reporting a study.[63,67,68]

This ensures that their research will be of high quality, is fully understood by readers, and can be replicated by other researchers in the scientific community. Ultimately, it can then be confidently used by clinicians for patients in the era of AI.[63]

Fairness and Equity of AI in Healthcare

Unfortunately, the presumption that AI algorithms are objective and free from biases is highly erroneous. Indeed, due to the mass scales utilized in AI algorithms, inherent biases can be amplified by these systems. Academics and governments have highlighted concerns over racial and gender biases in AI technologies.[69]

Much of this bias is introduced in the data generation process from which these algorithms are trained. These are largely historically based datasets that can display systemic racism or sexism, pervasive in society generally notwithstanding in healthcare. Race or Gender inserted into diagnostic algorithms that correct based on race or sex can lead to clinical decision-making that may direct more attention and or resources to, e.g., white male patients.[70]

Specific examples of biases from data in medicine can be seen in cardiovascular risk prediction algorithms. These algorithms have been trained predominantly on data from male patients leading to inaccuracies in subsequent risk assessment of female patients who present differently and have additional risk factors for cardiovascular disease to men. Algorithms trained on gender imbalanced data will often be inaccurate for the opposing gender which may contribute to poorer health outcomes and delayed diagnoses in these groups as a result.[71]

There are some ML algorithms that use data from portable devices like Fitbit and other wearable monitoring devices. However, these devices have been found to not accurately track heart rates across all races. If data are used from this technology for the purposes of AI, the resulting algorithms will be inaccurate since the measurements used are intrinsically biased. So even if an equal number of patients from all racial demographics are included in the datasets, the results will be skewed.[72]

Biases can also be introduced during the learning of the algorithm itself. An example of this can be seen in a case where an algorithm was shown to be discriminating against black people over white people in a model designed to refer patients to programs for sick patients with complex needs in the US. This was due to the design of the model which used cost as a proxy for healthcare needs leading to an underestimation of the needs of black patients compared to white patients.[71,73]

So, it is clear that AI can perpetuate bias especially when the algorithms use data that is generated through a biased process. Consequentially, the output will also be biased. Aside from data bias and algorithmic bias, there is also the danger of automation bias. This is where clinicians may be more likely to trust decision support systems and discount potentially relevant information from non-automated systems. Indeed, many non-medical factors can influence clinicians' management, e.g., clinical situations with a high cognitive load or decision-making at the end of the working day where clinicians may over-rely on automated systems.[69] It is therefore vital that clinicians are educated on the biases inherent in some AI models so that they can avoid an overreliance on AI-generated solutions and instead use AI as an adjunct and not a replacement for their clinical decision-making.

We can overcome such biases if we develop and promote unbiased AI systems in healthcare that provide accurate diagnoses and treatments for all patients regardless of their gender, race, or ethnicity.[71] This starts with using data from unbiased sources which is representative of the target population the algorithm is trained to operate on. This requires transparency during model development which can help developers, clinicians, and policymakers to determine the applicability of the model to their patient population. This also includes highlighting the model's limitations including potential biases so it can be implemented safely and reliably to the targeted patient population. Developers can also implement sensitivity tools that can track predictions to ensure the models' accuracy as well as potential adjustments that may be required to mitigate model degradation over time.[69] Thereby instead of propagating biases, AI can be used to mitigate bias and help improve fairness in AI.[69,71]

Regular audits on AI systems by external organizations will also safeguard objectivity and aid transparency. This process will help in detecting any biases and will also ensure the algorithms are updated protecting them from model degradation over time.[71]

Addressing the challenges of performance drift over time and external validity in ICU-related AI applications requires an integrative approach. In the healthcare domain, patterns can change over time due to various factors, such as changes in patient demographics, treatment protocols, or the introduction of new medications or technologies.

AI models trained on historical data may face difficulties when these patterns change, leading to what is known as concept drift. A potential solution based on continuous monitoring and periodic retraining of AI models is essential to adapt to changing patterns in ICU data. Regular updates based on recent data ensure that the AI system remains accurate and relevant as patient populations and medical practices evolve.

AI models trained on data from a specific ICU may not perform as well when applied to a different ICU with protocols, patient populations, or equipment variations. Ensuring external validity requires a diverse and representative dataset during the training phase. Including data from various ICUs with different demographics and practices is crucial. Also, models should be rigorously validated in multiple real-world settings to assess their generalizability accurately.[41]

Barriers to AI Implementation

We are approaching a time when the deployment of AI models in sepsis in a prospective manner will need to be considered. We have highlighted multiple retrospective trials that suggest that AI could revolutionize the management of sepsis.

While it may initially appear that implementation of prospective AI models in sepsis across multiple domains at once may seem attractive, the manner in which this is approached in the first instance and the ongoing revalidation of their use is of great importance. We would advocate for a "start small and move slowly" approach due to the multiple potential stumbling blocks and setbacks that may occur with a speedy rollout of such models. What is required is multiple well-designed RCTs comparing AI models plus physicians *vs.* physician-only care. Only when we have demonstrated improved outcomes in a prospective manner and thence revalidated these findings should we look to more broadly implement AI models in sepsis.

Implementing AI in medicine requires careful consideration of various political, financial, ethical, and medicine-specific factors.[74–76] Addressing these barriers will require collaboration between healthcare providers, policymakers, and technology developers to ensure that AI is used responsibly and effectively to improve patient outcomes.[74,75]

Political and regulatory barriers include laws and regulations that restrict AI use in healthcare settings, a lack of government funding, and privacy concerns related to patient data.[74,75] There may be concerns about the security and confidentiality of patient data if AI algorithms are used to analyze medical records.[75] Personal medical information is among the most legally protected data, and there are understandable concerns regarding the exposure of highly sensitive clinical information, which goes against the rights of citizens and the repurposing of data for non-medical gains.[75,77] Informed consent is fundamental to this process. Still, with a limited understanding of how some algorithms operate, it is increasingly difficult for patients to understand the full extent of how their data are shared and reused.

Notwithstanding, there is also the risk of data breaches in cyberattacks like what the Ireland Health Service Executive faced in 2021, which cost hundreds of millions of euros in recovery efforts. Regulatory frameworks must be built to address these cybersecurity issues and protect citizens from data breaches and repurposing.[75]

Regulatory frameworks for AI in medicine are also fundamentally important to give clinicians the confidence to deploy this technology into clinical practice.[78] The United States FDA has recently begun developing such frameworks. For example, implementing AI systems could be problematic because of uncertainties regarding when an AI algorithm is valid enough to be a part of a standardized care process. The European AI Strategy 2021 proposes that an AI product should meet general requirements, including its intended purpose, its accuracy, and confirming that the training data is reliable, representative, and used sufficiently. However, this may exclude new models developed by innovative but smaller companies that do not have the resources to succeed in bringing their products or services to implementation in standardized care processes.[79] The EU strategy also recommends traceability tools for monitoring AI algorithms once deployed so that they can be audited and monitored for errors or performance degradation over time.[75]

Implementing AI in medicine requires significant financial investment, including the cost of purchasing and maintaining AI systems, hiring trained personnel, and developing and testing algorithms.[80] In some cases, health systems may not have the financial resources to invest in AI technologies.[81] Cost–benefit analysis must be undertaken before any implementation process evaluating original expenditure and ongoing costs against a comparison to alternative technology.[82] This will be a solid basis for making decisions about AI installations before any implementation process.[82]

There may be ethical concerns around the use of AI in medicine, particularly related to bias and fairness issues.[75] For example, if AI algorithms are trained on biased data, they may perpetuate existing inequalities in healthcare.[75] There may also be concerns about the role of AI in decision-making, particularly in cases where decisions have life-or-death implications.[83] Medicine-specific barriers include technical challenges related to integrating AI with existing medical systems and practices and resistance to change among healthcare providers.[79]

It is widely recognized that clinicians involved from the start of the development of AI processes will have an enhanced understanding of the technology and are more likely to integrate it into their clinical practice.[75] Healthcare staff will need the skill set to navigate this new digitized environment, and curriculum updates in medical schools will also need to facilitate and reflect this digitized expansion. New data analytics could be integrated into traditional medical education and professional development programs for current practitioners. Indeed, all staff working in the healthcare environment will need the skillset to navigate this digitalized environment, and whole staff training will be needed to facilitate this expansion.[84,85] This emerging need to understand AI among clinicians is contiguous with the ever-important need for good communication skills and empathy from clinicians.[86] It is important that doctors maintain and cultivate emotional intelligence and compassion when relaying results and recommending interventions from sophisticated AI models to patients who want to make informed decisions regarding their healthcare.[86]

Regarding acceptance into routine practice, stakeholders are also concerned that AI may lead to the automation of jobs with subsequent job losses, which has drawn a lot of attention.[82] Research conducted by Deloitte and the Oxford Martin Institute demonstrated that AI may be responsible for losing 35% of jobs in the United Kingdom within the next 10–20 years.[82] However, the loss of employment may be mitigated by several external factors other than technology. Conversely, there is also the opportunity for new employment to be generated to work with and improve AI technologies. These factors may keep the number of jobs lost to 5% or fewer.[82] However, implementing AI will be challenging because of these beliefs. Therefore, it is important to emphasize to those working with this new technology that AI systems will not replace human clinicians but will supplement their efforts to care for patients and benefit them as a result. Indeed, humans may eventually shift toward activities and job designs that require distinctly human skills, such as empathy, persuasion, and big-picture integration.[82] How this evolution will impact hospital settings and workflows is still unknown. Healthcare workers will also need to see that integrating AI is based on sound coherent thinking and is of value to the patient, the staff, and the organization.[87] This will require staff training and education in AI technology.[79] Ultimately, successful change will require financial investment in resources, infrastructure, and time.[79]

Conclusions

AI can potentially revolutionize sepsis detection, diagnosis, and treatment in critical care settings. AI algorithms can help identify patients at high risk of developing sepsis, allowing healthcare providers to intervene earlier and prevent the condition's progression. AI improves the accuracy and speed of sepsis diagnosis. It can be used to personalize sepsis treatment plans based on individual patient characteristics and responses to therapy. In addition, AI can also be used to monitor patients with sepsis in real-time, alerting healthcare providers to the patient's clinical condition and ensuring an appropriate and timely treatment response.

AI's challenges include the fact that clinicians are not computational experts. These complex technologies may be difficult to comprehend fully, and therefore clinicians are, rightly or wrongly, reluctant to adopt them. To overcome this, AI should be viewed as an assistive tool for clinicians rather than autonomous machines. Clinicians are still part of the workflow, which minimizes the potential for harm to the patient.

In conclusion, using AI in healthcare requires careful consideration of ethical, legal, and regulatory issues to ensure that it is used responsibly and effectively to benefit patients. Regulatory authorities for AI in some medical specialties, such as intensive care medicine, require an in-depth understanding of the relevant technology and embrace discussion among key stakeholders of AI in healthcare. Only then will clinicians be confident to deploy this incredible technology into clinical practice. The future is now.

Author Contributions

Darragh O'Reilly: Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Jennifer McGrath:** Writing – original draft, Writing – review & editing. **Ignacio Martin-Loeches:** Conceptualization, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

Acknowledgments

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper interest.

Data Availability

None.

References

[1] Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, et al. The global burden of sepsis: barriers and potential solutions. Crit Care 2018;22(1):232. doi:10.1186/s13054-018-2157-z.
[2] Dugani S, Veillard J, Kissoon N. Reducing the global burden of sepsis. Can Med Assoc J 2017;189(1):E2–3. doi:10.1503/cmaj.160798.
[3] Yébenes JC, Ruiz-Rodriguez JC, Ferrer R, Clèries M, Bosch A, et al., SOCMIC (Catalonian Critical Care Society) Sepsis Working Group Epidemiology of sepsis in Catalonia: analysis of incidence and outcomes in a European setting. Ann Intensive Care 2017;7(1):19. doi:10.1186/s13613-017-0241-1.
[4] Rodríguez A, Martín-Loeches I, Yébenes JC. New definition of sepsis and septic shock: what does it give us? Med Intensiva 2017;41(1):38–40. doi:10.1016/j.medin.2016.03.008.
[5] Leligdowicz A, Matthay MA. Heterogeneity in sepsis: new biological evidence with clinical applications. Crit Care 2019;23(1):80. doi:10.1186/s13054-019-2372-2.
[6] Kerrigan SW, Martin-Loeches I. Public awareness of sepsis is still poor: we need to do more. Intensive Care Med 2018;44(10):1771–3. doi:10.1007/s00134-018-5307-5.
[7] Lorencio Cárdenas C, Yébenes JC, Vela E, Clèries M, Sirvent JM, Fuster-Bertolín C, et al. Trends in mortality in septic patients according to the different organ failure during 15 years. Crit Care 2022;26(1):302. doi:10.1186/s13054-022-04176-w.
[8] Leng Y, Gao C, Li F, Li E, Zhang F. The supportive role of international government funds on the progress of sepsis research during the past decade (2010–2019): a narrative review. Inquiry 2022;59:004695802210785. doi:10.1177/00469580221078513.
[9] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Executive summary: surviving sepsis campaign: international guidelines for the management of sepsis and septic shock 2021. Crit Care Med 2021;49(11):1974–82. doi:10.1097/CCM.0000000000005357.

[10] Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. Lancet Infect Dis 2015;15(5):581–614. doi:10.1016/S1473-3099(15)70112-X.
[11] Mintz Y, Brodie R. Introduction to artificial intelligence in medicine. Minim Invasive Ther Allied Technol 2019;28(2):73–81. doi:10.1080/13645706.2019.1575882.
[12] French RM. The Turing test: the first 50 years. Trends Cogn Sci 2000;4(3):115–22. doi:10.1016/S1364-6613(00)01453-4.
[13] Tang X. The role of artificial intelligence in medical imaging research. BJR Open 2019;2(1):20190031. doi:10.1259/bjro.20190031.
[14] Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. Nat Rev Cancer 2018;18(8):500–10. doi:10.1038/s41568-018-0016-5.
[15] Wu M, Du X, Gu R, Wei J. Artificial intelligence for clinical decision support in sepsis. Front Med 2021;8:665464. doi:10.3389/fmed.2021.665464.
[16] Sabry F, Eltaras T, Labda W, Alzoubi K, Malluhi Q. Machine learning for healthcare wearable devices: the big picture. J Healthc Eng 2022;2022:4653923. doi:10.1155/2022/4653923.
[17] Askin S, Burkhalter D, Calado G, El Dakrouni S. Artificial intelligence applied to clinical trials: opportunities and challenges. Health Technol 2023;13(2):203–13. doi:10.1007/s12553-023-00738-2.
[18] What is machine learning? IBM [Internet]. Available from: https://www.ibm.com/topics/machine-learning [Last accessed on 2023 April 18].
[19] Sidey-Gibbons JA, Sidey-Gibbons CJ. Machine learning in medicine: a practical introduction. BMC Med Res Methodol 2019;19(1):64. doi:10.1186/s12874-019-0681-4.
[20] Habehh H, Gohel S. Machine learning in healthcare. Curr Genomics 2021;22(4):291. doi:10.2174/1389202922666210705124359.
[21] Komorowski M, Green A, Tatham KC, Seymour C, Antcliffe D. Sepsis biomarkers and diagnostic tools with a focus on machine learning. EBioMedicine 2022;86:104394. doi:10.1016/j.ebiom.2022.104394.
[22] Moor M, Rieck B, Horn M, Jutzeler CR, Borgwardt K. Early prediction of sepsis in the ICU using machine learning: a systematic review. Front Med 2021;8:607952. doi:10.3389/fmed.2021.607952.
[23] Giacobbe DR, Signori A, Del Puente F, Mora S, Carmisciano L, Briano F, et al. Early detection of sepsis with machine learning techniques: a brief clinical perspective. Front Med 2021;8:617486. doi:10.3389/fmed.2021.617486.
[24] Jensen K, Soguero-Ruiz C, Oyvind Mikalsen K, Lindsetmo RO, Kouskoumvekaki I, Girolami M, et al. Analysis of free text in electronic health records for identification of cancer patient trajectories. Sci Rep 2017;7:46226. doi:10.1038/srep46226.
[25] Kreps GL. Strategic use of communication to market cancer prevention and control to vulnerable populations. Health Mark Q 2008;25(1–2):204–16. doi:10.1080/07359680802126327.
[26] Noor K, Roguski L, Bai X, Handy A, Klapaukh R, Folarin A, et al. Deployment of a free-text analytics platform at a UK national health service research hospital: cogstack at university college london hospitals. JMIR Med Inform 2022;10(8):e38122. doi:10.2196/38122.
[27] Harrison CJ, Sidey-Gibbons CJ. Machine learning in medicine: a practical introduction to natural language processing. BMC Med Res Methodol 2021;21(1):158. doi:10.1186/s12874-021-01347-1.
[28] Goh KH, Wang L, Yeow AYK, Poh H, Li K, Yeow JJL, et al. Artificial intelligence in sepsis early prediction and diagnosis using unstructured data in healthcare. Nat Commun 2021;12(1):711. doi:10.1038/s41467-021-20910-4.
[29] Horng S, Sontag DA, Halpern Y, Jernite Y, Shapiro NI, Nathanson LA. Creating an automated trigger for sepsis clinical decision support at emergency department triage using machine learning. PLoS ONE 2017;12(4):e0174708. doi:10.1371/journal.pone.0174708.
[30] Li R, Kumar A, Chen JH. How chatbots and large language model artificial intelligence systems will reshape modern medicine: fountain of creativity or Pandora's box? JAMA Intern Med 2023;83(6):596–7. doi:10.1001/jamainternmed.2023.1835.
[31] Thirunavukarasu AJ, Ting DSJ, Elangovan K, Gutierrez L, Tan TF, Ting DSW. Large language models in medicine. Nat Med 2023;29(8):1930–40. doi:10.1038/s41591-023-02448-8.
[32] Gilbert S, Harvey H, Melvin T, Vollebregt E, Wicks P. Large language model AI chatbots require approval as medical devices. Nat Med 2023:1–3. doi:10.1038/s41591-023-02412-6.
[33] Rawson TM, Hernandez B, Moore LSP, Blandy O, Herrero P, Gilchrist M, et al. Supervised machine learning for the prediction of infection on admission to hospital: a prospective observational cohort study. J Antimicrob Chemother 2019;74(4):1108–15. doi:10.1093/jac/dky514.
[34] Mao Q, Jay M, Hoffman JL, Calvert J, Barton C, Shimabukuro D, et al. Multicentre validation of a sepsis prediction algorithm using only vital sign data in the emergency department, general ward and ICU. BMJ Open 2018;8(1):e017833. doi:10.1136/bmjopen-2017-017833.
[35] Mehrabi S, Krishnan A, Sohn S, Roch AM, Schmidt H, Kesterson J, et al. DEEPEN: a negation detection system for clinical text incorporating dependency relation into NegEx. J Biomed Inform 2015;54:213–19. doi:10.1016/j.jbi.2015.02.010.
[36] Pepic I, Feldt R, Ljungström L, Torkar R, Dalevi D, Maurin Söderholm H, et al. Early detection of sepsis using artificial intelligence: a scoping review protocol. Syst Rev 2021;10(1):1–7. doi:10.1186/s13643-020-01561-w.
[37] Fleuren LM, Klausch TLT, Zwager CL, Schoonmade LJ, Guo T, Roggeveen LF, et al. Machine learning for the prediction of sepsis: a systematic review and meta-analysis of diagnostic test accuracy. Intensive Care Med 2020;46:383–400. doi:10.1007/s00134-019-05872-y.
[38] Hyland SL, Faltys M, Hüser M, Lyu X, Gumbsch T, Esteban C, et al. Early prediction of circulatory failure in the intensive care unit using machine learning. Nat Med 2020;26(3):364–73. doi:10.1038/s41591-020-0789-4.
[39] Rush B, Celi LA, Stone DJ. Applying machine learning to continuously monitored physiological data. J Clin Monit Comput 2019;33(5):887–93. doi:10.1007/s10877-018-0219-z.
[40] Rahman A, Chang Y, Dong J, Conroy B, Natarajan A, Kinoshita T, et al. Early prediction of hemodynamic interventions in the intensive care unit using machine learning. Crit Care 2021;25(1):388. doi:10.1186/s13054-021-03808-x.
[41] Dung-Hung C, Cong T, Zeyu J, Yu-Shan OY, Yung-Yan L. External validation of a machine learning model to predict hemodynamic instability in intensive care unit. Crit Care 2022;26(1):1–10. doi:10.1186/s13054-022-04088-9.
[42] Xu Y, Biswal S, Deshpande SR, Maher KO, Sun J. RAIM: recurrent attentive and intensive model of multimodal patient monitoring data. In: Proceedings of the 24th ACM SIGKDD International Conference on Knowledge Discovery & Data Mining. ACM; 2018. p. 2565–73. Available from:.
[43] Mollura M, Lehman LWH, Mark RG, Barbieri R. A novel artificial intelligence based intensive care unit monitoring system: using physiological waveforms to identify sepsis. Philos Trans R Soc A 2021;379(2212):20200252. doi:10.1098/rsta.2020.0252.
[44] Komorowski M, Celi LA, Badawi O, Gordon AC, Faisal AA. The artificial intelligence clinician learns optimal treatment strategies for sepsis in intensive care. Nat Med 2018;24(11):1716–20. doi:10.1038/s41591-018-0213-5.
[45] Hassan N, Slight R, Weiand D, Vellinga A, Morgan G, Aboushareb F, et al. Preventing sepsis; how can artificial intelligence inform the clinical decision-making process? A systematic review. Int J Med Inf 2021;150:104457. doi:10.1016/j.ijmedinf.2021.104457.
[46] Bajaj T, Koyner JL. Artificial intelligence in acute kidney injury prediction. Adv Chronic Kidney Dis 2022;29(5):450–60. doi:10.1053/j.ackd.2022.07.009.
[47] Alser O, Dorken-Gallastegi A, Proaño-Zamudio JA, Nederpelt C, Mokhtari AK, Mashbari H, et al. Using the field artificial intelligence triage (FAIT) tool to predict hospital critical care resource utilization in patients with truncal gunshot wounds. Am J Surg 2023;226(2):245–50. doi:10.1016/j.amjsurg.2023.03.019.
[48] Deif MA, Solyman AA, Alsharif MH, Uthansakul P. Automated triage system for intensive care admissions during the COVID-19 pandemic using hybrid XGBoost-AHP approach. Sensors (Basel) 2021;21(19):6379. doi:10.3390/s21196379.
[49] Vinay R, Baumann H, Biller-Andorno N. Ethics of ICU triage during COVID-19. Br Med Bull 2021;138(1):5–15. doi:10.1093/bmb/ldab009.
[50] Chang TH, Liu YC, Lin SR, Chiu PH, Chou CC, Chang LY, et al. Clinical characteristics of hospitalized children with community-acquired pneumonia and respiratory infections: using machine learning approaches to support pathogen prediction at admission. J Microbiol Immunol Infect 2023;56(4):772–81. doi:10.1016/j.jmii.2023.04.011.
[51] Lhommet C, Garot D, Grammatico-Guillon L, Jourdannaud C, Asfar P, Faisy C, et al. Predicting the microbial cause of community-acquired pneumonia: can physicians or a data-driven method differentiate viral from bacterial pneumonia at patient presentation? BMC Pulm Med 2020;20:62. doi:10.1186/s12890-020-1089-y.
[52] Zheng Y, Lan C, Wang N, Xu X, Hu T, Wu Q, et al. Machine learning algorithms identify pathogen-specific biomarkers of clinical and metabolomic characteristics in septic patients with bacterial infections. Biomed Res Int 2020;2020. doi:10.1155/2020/5956412.
[53] Rawson TM, Hernandez B, Moore LSP, Herrero P, Charani E, Ming D, et al. A real-world evaluation of a case-based reasoning algorithm to support antimicrobial prescribing decisions in acute care. Clin Infect Dis 2021;72(12):2103–11. doi:10.1093/cid/ciaa383.
[54] Paul M, Andreassen S, Tacconelli E, Nielsen AD, Almanasreh N, Frank U, et al. Improving empirical antibiotic treatment using TREAT, a computerized decision support system: cluster randomized trial. J Antimicrob Chemother 2006;58(6):1238–45. doi:10.1093/jac/dkl372.
[55] Hsu JC, Chen YF, Chung WS, Tan TH, Chen T, Chiang JY. Clinical verification of a clinical decision support system for ventilator weaning. Biomed Eng Online 2013;12(Suppl 1):S4. doi:10.1186/1475-925X-12-S1-S4.
[56] Acosta JN, Falcone GJ, Rajpurkar P, Topol EJ. Multimodal biomedical AI. Nat Med 2022;28(9):1773–84. doi:10.1038/s41591-022-01981-2.
[57] Calfee CS. Opening the debate on the new sepsis definition. Precision medicine: an opportunity to improve outcomes of patients with sepsis. Am J Respir Crit Care Med 2016;194(2):137–9. doi:10.1164/rccm.201604-0697ED.
[58] Ruiz-Rodriguez JC, Plata-Menchaca EP, Chiscano-Camón L, Ruiz-Sanmartin A, Pérez-Carrasco M, Palmada C, et al. Precision medicine in sepsis and septic shock: from omics to clinical tools. World J Crit Care Med 2022;11(1):1–21. doi:10.5492/wjccm.v11.i1.1.
[59] Peine A, Hallawa A, Bickenbach J, Dartmann G, Fazlic LB, Schmeink A, et al. Development and validation of a reinforcement learning algorithm to dynamically optimize mechanical ventilation in critical care. NPJ Digit Med 2021;4(1):32. doi:10.1038/s41746-021-00388-6.
[60] Gallifant J, Zhang J, Del Pilar Arias Lopez M, Zhu T, Camporota L, Celi LA, et al. Artificial intelligence for mechanical ventilation: systematic review of design, reporting standards, and bias. Br J Anaesth 2022;128(2):343–51. doi:10.1016/j.bja.2021.09.025.
[61] Seymour CW, Kennedy JN, Wang S, Chang CC, Elliott CF, Xu Z, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA 2019;321(20):2003–17. doi:10.1001/jama.2019.5791.
[62] Knaus WA, Marks RD. New phenotypes for sepsis: the promise and problem of applying machine learning and artificial intelligence in clinical research. JAMA 2019;321(20):1981–2. doi:10.1001/jama.2019.5794.
[63] Ibrahim H, Liu X, Denniston AK. Reporting guidelines for artificial intelligence in healthcare research. Clin Experiment Ophthalmol 2021;49(5):470–6. doi:10.1111/ceo.13943.

[64] Liu R, Rizzo S, Whipple S, Pal N, Pineda AL, Lu M, et al. Evaluating eligibility criteria of oncology trials using real-world data and AI. Nature 2021;592(7855):629–33. doi:10.1038/s41586-021-03430-5.
[65] Weng C, Rogers JR. AI uses patient data to optimize selection of eligibility criteria for clinical trials. Nature 2021;92(7855):512–13. doi:10.1038/d41586-021-00845-y.
[66] Schork NJ. Artificial intelligence and personalized medicine. Cancer Treat Res 2019;178:265–83. doi:10.1007/978-3-030-16391-4_11.
[67] Shelmerdine SC, Arthurs OJ, Denniston A, Sebire NJ. Review of study reporting guidelines for clinical studies using artificial intelligence in healthcare. BMJ Health Care Inform 2021;28(1):e100385. doi:10.1136/bmjhci-2021-100385.
[68] Vasey B, Nagendran M, Campbell B, Clifton DA, Collins GS, Denaxas S, et al. Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. Nat Med 2022;28(5):924–33. doi:10.1038/s41591-022-01951-8.
[69] Parikh RB, Teeple S, Navathe AS. Addressing bias in artificial intelligence in health care. JAMA 2019;322(24):2377–8. doi:10.1001/jama.2019.18058.
[70] Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight – reconsidering the use of race correction in clinical algorithms. N Engl J Med 2020;383(9):874–82. doi:10.1056/NEJMms2004740.
[71] Ueda D, Kakinuma T, Fujita S, Kamagata K, Fushimi Y, Ito R, Matsui Y, Nozaki T, Nakaura T, Fujima N, Tatsugami F. Fairness of artificial intelligence in healthcare: review and recommendations. Jpn J Radiol 2023 Aug 4:1–3.
[72] Sui A, Sui W, Liu S, Rhodes R. Ethical considerations for the use of consumer wearables in health research. Digit Health 2023;9:20552076231153740. doi:10.1177/20552076231153740.
[73] Ledford H. Millions affected by racial bias in health-care algorithm. Nature 2019;574(7780):608–9. doi:10.1038/d41586-019-03228-6.
[74] Morley J, Murphy L, Mishra A, Joshi I, Karpathakis K. Governing data and artificial intelligence for health care: developing an international understanding. JMIR Form Res 2022;6(1):e31623. doi:10.2196/31623.
[75] Directorate General for Parliamentary Research Services Artificial intelligence in healthcare: applications, risks, and ethical and societal impacts. [Internet]. LU: Publications Office; 2022. Available from: https://www.europarl.europa.eu/RegData/etudes/STUD/2022/729512/EPRS_STU(2022)729512_EN.pdf [Last accessed on 2023 April 12].
[76] Tachkov K, Zemplenyi A, Kamusheva M, Dimitrova M, Siirtola P, Pontén J, et al. Barriers to use artificial intelligence methodologies in health technology assessment in Central and East European Countries. Front Public Health 2022;10:921226. doi:10.3389/fpubh.2022.921226.
[77] Murdoch B. Privacy and artificial intelligence: challenges for protecting health information in a new era. BMC Med Ethics 2021;22(1):122. doi:10.1186/s12910-021-00687-3.
[78] Kelly CJ, Karthikesalingam A, Suleyman M, Corrado G, King D. Key challenges for delivering clinical impact with artificial intelligence. BMC Med 2019;17(1):195. doi:10.1186/s12916-019-1426-2.
[79] Petersson L, Larsson I, Nygren JM, Nilsen P, Neher M, Reed JE, et al. Challenges to implementing artificial intelligence in healthcare: a qualitative interview study with healthcare leaders in Sweden. BMC Health Serv Res 2022;22(1):850. doi:10.1186/s12913-022-08215-8.
[80] Wolff J, Pauling J, Keck A, Baumbach J. Systematic review of economic impact studies of artificial intelligence in health care. J Med Internet Res 2020;22(2):e16866. doi:10.2196/16866.
[81] Wahl B, Cossy-Gantner A, Germann S, Schwalbe NR. Artificial intelligence (AI) and global health: how can AI contribute to health in resource-poor settings? BMJ Glob Health 2018;3(4):1–7. doi:10.1136/bmjgh-2018-000798.
[82] Khanna NN, Maindarkar MA, Viswanathan V, Fernandes JFE, Paul S, Bhagawati M, et al. Economics of artificial intelligence in healthcare: diagnosis vs. treatment. Healthcare (Basel) 2022;10(12):2493. doi:10.3390/healthcare10122493.
[83] Manz CR, Zhang Y, Chen K, Long Q, Small DS, Evans CN, et al. Long-term effect of machine learning-triggered behavioral nudges on serious illness conversations and end-of-life outcomes among patients with cancer: a randomized clinical trial. JAMA Oncol 2023;9(3):414–18. doi:10.1001/jamaoncol.2022.6303.
[84] Blease C, Kharko A, Bernstein M, Bradley C, Houston M, Walsh I, et al. Machine learning in medical education: a survey of the experiences and opinions of medical students in Ireland. BMJ Health Care Inf 2022;29(1):e100480. doi:10.1136/bmjhci-2021-100480.
[85] The topol review [Internet]. Topol Rev. — NHS Health Educ. Engl. Available from: https://topol.hee.nhs.uk/the-topol-review/[Last accessed on 2023 April 12].
[86] Giordano C, Brennan M, Mohamed B, Rashidi P, Modave F, Tighe P. Accessing artificial intelligence for clinical decision-making. Front Digit Health 2021;3:645232. doi:10.3389/fdgth.2021.645232.
[87] Nilsen P, Seing I, Ericsson C, Birken SA, Schildmeijer K. Characteristics of successful changes in health care organizations: an interview study with physicians, registered nurses and assistant nurses. BMC Health Serv Res 2020;20(1):147. doi:10.1186/s12913-020-4999-8.