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REVIEW

Clinical Informatics in Critical Care Medicine

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Continuous monitoring and treatment of patients in intensive care units generates vast amounts of data. Critical Care Medicine clinicians incorporate this continuously evolving data to make split-second, life or death decisions for management of these patients. Despite the abundance of data, it can be challenging to consider every accessible data point when making the quick decisions necessary at the point of care. Consequently, Clinical Informatics offers a natural partnership to improve the care for critically ill patients. The last two decades have seen a significant evolution in the role of Clinical Informatics in Critical Care Medicine. In this review, we will discuss how Clinical Informatics improves the care of critically ill patients by enhancing not only data collection and visualization but also bedside medical decision making. We will further discuss the evolving role of machine learning algorithms in Clinical Informatics as it pertains to Critical Care Medicine.

INTRODUCTION

Critical Care Medicine clinicians must make split-second judgments that could mean the difference between life and death when caring for patients with life-threatening illnesses. These patients have pathophysiology that is not only complex but is also dynamic such that it evolves with time and each treatment decision. The clinicians must make life-saving treatment decisions while synthesizing this evolving clinical picture and accounting for the high level of uncertainty that is inherent to critical illness. Additionally, they must do it well within the time constraints required to ensure appropriate and safe care to not only that patient, but other critically ill patients under their care at that same time. The evolving clinical picture of each critically ill patient is constructed of numerous data points that the clinicians must review and understand to deduce the patient's clinical trajectory and potential treatment options in that moment. The clinicians are however unable to utilize all this available data for decision making [1]. This can lead to errors of omission from failure to include pertinent information in decision making [2,3].

The Institute of Medicine's influential report, "To Err is Human" [4], brought the issue of medical errors in healthcare to the forefront and identified system errors

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Abbreviations: HITECH, Health Information Technology for Economic and Clinical Health; ICU, Intensive Care Unit; CDSS, Clinical Decision Support System; CPOE, Computerized Provider Order Entry; AKI, Acute Kidney Injury.

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as the primary culprit. This, along with the Institute of Medicine's second report, "Crossing the Quality Chasm: A New Health System for the 21st Century" [5], were instrumental in increasing focus on minimizing system errors and improving patient safety through optimal use of health information technology. The widespread adoption of electronic health records and their meaningful use as aided by the Health Information Technology for Economic and Clinical Health (HITECH) Act [6] has greatly facilitated development of processes and tools to better utilize available healthcare data at point of care to help with diagnosis and management of patients. This task is achieved by Clinical Informatics, a specialty that focuses on the development of processes and tools for not only acquisition, processing, and interpretation of patient data but also the design, implementation, and evaluation of information and communication systems to improve patient care. Over the past two decades, a natural alliance between Critical Care Medicine and Clinical Informatics has developed due to the abundance of available data in the intensive care units (ICUs) [7-10]. In this review we will discuss the evolving role of Clinical Informatics in Critical Care Medicine.

MEDICAL DECISION MAKING

The goal of Clinical Informatics is to provide relevant data and information to clinicians to enhance their clinical decision making such that it leads to improved patient outcomes and minimizes medical errors. It is therefore important to understand how clinicians make decisions during a clinical encounter. In the words of the American physician and philosopher Edmund Pellegrino, a clinical encounter can be summed up in three questions – 1) What is the problem? 2) What are possible solutions? and 3) What is the best solution for this patient [11]? This is true even today. The first step in this quest is gathering data points which can be in the form of a patient's vital signs, medical history, medications, laboratory values, etc. It is important to remember though that these are just raw data points, such as a temperature of 38.6°C or a heart rate of 120 beats per minute. In isolation they may not mean much. The next step is to compare these data points with known normal values or baseline values for that patient. This provides meaningful information that this patient has fever and tachycardia. This allows clinicians to develop a list of differential diagnoses and/or treatment options. In this example, the list of differentials could include a common cold, new or worsening pneumonia, pericarditis, etc. This is done through a combination of both pattern recognition and Casablanca strategy. Pattern recognition is a crucial step which improves with clinical experience. Casablanca strategy on the other hand involves ruling out the 'usual suspects' for a particular problem or constellation of symptoms [12]. When taken into the right context this step provides valuable knowledge to clinicians. For example, if this patient with fever and tachycardia was also coughing and had a pulmonary infiltrate on a chest X-ray, it may indicate the presence of an underlying pneumonia. In a different context where this patient with pneumonia was already on antibiotics, this new fever and tachycardia might indicate a worsening clinical picture on current therapy. This knowledge then helps clinicians gain wisdom about what actions they can take – should they start new antibiotics for a patient with new pneumonia or maybe switch antibiotics for the one who is getting worse on current treatment so may have resistant organisms. The clinicians thus use this "knowledge pyramid" to guide their decision-making process. Each decision then generates more data points (eg, is the patient getting better, does the patient have a new infection) which are then reconsidered for the next decision point (Figure 1).

HOW CLINICAL INFORMATICS CAN HELP

With increased digitization of medical records there is more and more information available in the electronic health records. In fact, as shown by Manor-Shulman and colleagues, there were a median 1,348 documented clinical data points for each critically ill patient in a 24-hour time period [13]. This number was much higher for patients requiring more specialized therapies such as dialysis or extracorporeal membrane oxygenation. One would think that clinicians would incorporate all or a majority of this wealth of available information in their decision-making process. However, as it turns out, clinicians are able to utilize only a fraction of this available information. A study at a tertiary care center found that of the 51 data elements identified as being important during an ICU admission, a median of only 11 were used by clinicians. These included elements from history, physical examination, vital signs, and laboratory studies – all data that one would consider relevant for management of critically ill patients [1]. When we put this into context with the amount of data generated during the care of each patient and the time constraints that clinicians work in, it becomes easy to see how these increasing volumes of data can be a double-edged sword. On one hand they can provide valuable clinical information and on the other they can contribute to noise that drowns out that very valuable information. This is where Clinical Informatics can be very helpful. It can help with acquisition and display of relevant data to clinicians in a timely fashion to help with both prediction and identification of patients at risk for worse outcomes. Additionally, Clinical Informatics can help augment medical decision making for both diagnosis and treatment at point of care. Clinical Informatics can thus help clinicians scale the knowledge pyra-

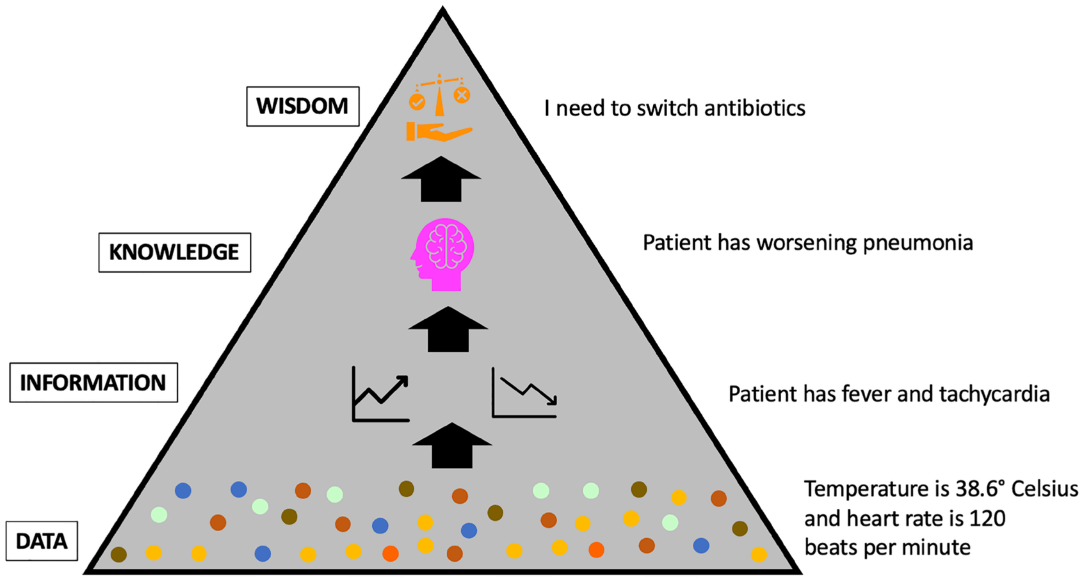

Figure 1. **The Knowledge Pyramid**. Data are raw, unprocessed observations that by themselves lack any meaning. These Data when organized and processed represent Information that can be interpreted. The next level of knowledge pyramid is Knowledge which involves application of this information in recognizing patterns and identifying connections. The final level is Wisdom which encompasses the ability to make sound judgements based on the Knowledge.

mid for medical decision making, much more efficiently and effectively.

APPLICATIONS OF CLINICAL INFORMATICS IN CRITICAL CARE MEDICINE

With increasing adoption of electronic health records, the last decade has seen an explosion in utilization of Clinical Informatics in Critical Care Medicine. This has been facilitated by Centers for Medicare and Medicaid incentive programs aimed at increasing the meaningful use of electronic health records in the United States as part of the HITECH Act. There are two major ways that Clinical Informatics can enhance the care of critically ill patients – i) Enhancement of Data Acquisition and Display; ii) Augmentation of Medical Decision Making.

Enhancement of Data Acquisition and Display

Electronic health records serve as the main hub for accessing all medical information for patients. This information is used to develop medical decisions and provide care to patients. It is therefore important to have data from various monitoring and laboratory devices be transmitted into the electronic health records in real-time. The laboratory information systems and picture archiving and communication systems were among the first systems to be integrated with electronic health records. They allowed real-time access to laboratory test results and radiology images to aid in patient care. Since then, advances in technology have allowed for integration of electronic health records with many other devices such as bedside monitors, ventilators, dialysis machines, extracorporeal membrane oxygenation machines, etc. This has allowed for easy access to this data for both immediate patient care and research. This has been instrumental in optimizing management of critically ill patients by allowing clinicians to have access to this information in real time. For example, real-time access to vital signs allows clinicians to monitor disease evolution of critically ill patients much more effectively. Similarly, real-time monitoring of transmembrane pressures in continuous renal replacement therapy machines allows clinicians to monitor and avoid filter clotting. Central patient monitoring systems and remote patient monitoring systems have further enhanced the ability to better monitor patients and have allowed expansion of tele-ICUs which were critical during the coronavirus disease 2019 (COVID-19) pandemic [14]. All these technologies rely on robust Informatics infrastructure to ensure seamless interoperability so that the data can be available in real time for immediate patient care decisions. Clinical Informatics tools have also allowed this available data to be displayed in different formats, such as charts, graphs, and maps at point of care, which make it easier to understand the data and gain valuable information from them. Additionally, Clinical Informatics plays an instrumental role in ensuring that this data can be extracted into data warehouses to be used for quality improvement, research, and business intelligence [15-18].

Augmentation of Medical Decision Making

Clinical Informatics plays an instrumental role in providing Critical Care Medicine clinicians the relevant information and knowledge deduced from clinical data points, to enhance medical decision making. This is primarily achieved by use of clinical decision support systems (CDSS). CDSS have a wide scope and include various tools such as ordersets, medication dosage/interaction guidances, electronic alerts, documentation templates. and other clinical workflow tools such as checklists. The inception of CDSS can be traced to 1959 when Ledley and colleagues described medical decision making by use of logic, probability, and value theory [19]. They were introduced into clinical practice in the 1970s [20,21]. It was, however, not until the 2000s that the adoption of CDSS started to gain traction and acceptance in clinical practice. This was at least in part driven in response to the two Institute of Medicine reports, "To Err is Human" and "Crossing the Quality Chasm" [4,5] which brought attention to the medical errors and potential role of health information technology in reducing them. Their use was further facilitated by the incentives given as part of the HITECH Act for meaningful use of electronic health records.

One of the key ways that CDSS have influenced Critical Care Medicine is by its integration with computerized provider order entry (CPOE) systems. CPOE are computer-based systems for entering orders. Almost all CPOEs have at least some level of CDSS built-in to assist with ordering while minimizing errors, for example, guidance for drug dosing, drug-drug interactions, drug allergies, and ordersets specific to different conditions. The importance of CPOE can be understood by the fact that it was one of the three initial "leaps" emphasized by the Leapfrog group to enhance safe and effective care in hospitals [22]. Utilization of CPOE was also a core requirement to achieve meaningful use of electronic health records. The use of CPOE has had the greatest impact on reducing medication errors. A systematic review of literature identified that use of CPOE was associated with 48% decrease in medication errors [23]. Impact of CPOE on medication errors has also been evaluated in the context of Critical Care Medicine. A study that assessed the impact of implementation of CPOE, using a before and after study design in a 22 bed ICU, found that the incidence of medication errors was decreased to 4.8% with implementation of CPOE in comparison to 6.7% before ($p<0.04$) [24]. Similar results were seen in another study that compared over 2,500 medication prescriptions between ICUs with CPOE-based medication orders vs paper-based medication orders. This study found that medication prescription errors were much lower in the CPOE-based ICU (3.4% vs 27.0%; $p<0.001$) [25]. It also identified less adverse drug events in the CPOE-based ICU (2 vs 12; $p<0.01$). Additionally, there were fewer dosing errors in patients with renal failure in the CPOE-based ICU (12 vs 35; $p<0.001$). A meta-analysis of 16 studies that evaluated the effectiveness of CPOE in decreasing preventable medication errors showed a significant association between decrease in medication errors with implementation of CPOE (pooled risk ratio 0.47; 95% CI: 0.35-0.60) [22]. It also found a that CPOE implementation was associated with a significant decrease in preventable adverse drug events (pooled risk ratio 0.47; 95% CI: 0.31-0.71). Another meta-analysis of nine studies found an 85% reduction in the rate of medication errors on implementation of CPOE in ICUs [26]. This meta-analysis also found a 12% reduction in ICU mortality on implementation of CPOE. It is thus fair to say that implementation of CPOE has had a significant positive impact on processes and outcomes in Critical Care Medicine.

CDSS have also been widely utilized to help with diagnosis and management of critically ill patients outside of CPOE [27]. This is predominantly in the form of electronic alerts to clinicians regarding specific aspects of patient care. A systematic review of 36 randomized controlled trials showed that CDSS improved processes of care in 63% studies [28]. Furthermore 38% of included studies reported increased compliance with guidelines and 67% reported improvement in diagnoses with use of CDSS. CDSS have also been widely employed to aid clinicians in taking care of critically ill patients. CDSS have been utilized in many studies to aid with both identification and prediction of sepsis and its complications. The results on improvement in processes of care, such as time to antibiotics, and outcomes measures, such as hospital mortality have, however, been mixed [29-33]. Similarly, CDSS for acute kidney injury (AKI) have been used extensively to aid in both diagnosis and management but with mixed results. Al-Jaghbeer and colleagues showed that non-interruptive alerts for AKI were associated with a small but significant decrease in mortality among hospitalized patients (9.4% vs 10.2%; $p=0.001$) [34]. In the ICU setting, Colpaert and colleagues found that there were significant improvements in processes of care by giving AKI alerts to critical care medicine physicians on the development or progression of AKI [35]. Wilson and colleagues however found no benefit of AKI alerts in a randomized controlled trial that included both ICU and non-ICU patients [36]. The reasons for these mixed results are complex and likely include heterogenous patient populations, varying positive predictive values of alerts, variability in alert displays and development of alert fatigue.

Recent years have seen a significant increase in use of machine learning algorithms for prediction of diseases

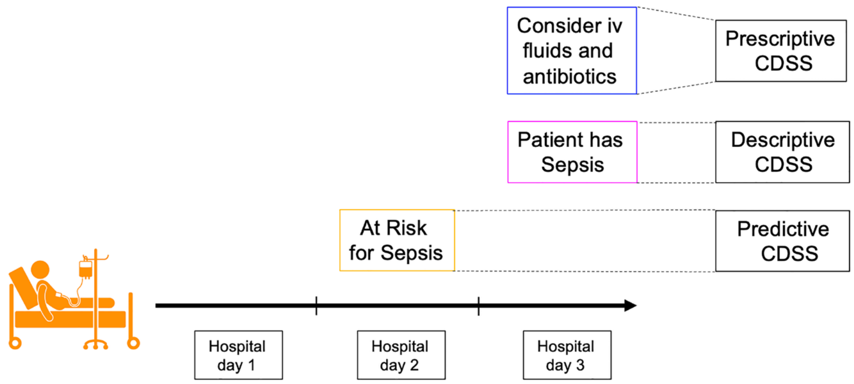

Figure 2. **Types of Clinical Decision Support Systems (CDSS) Based on their Analytical Capabilities**. Different CDSS can offer recommendations based on the patient's changing clinical picture for a patient who has been admitted to the hospital. The patient was reported to be at risk of acquiring sepsis on hospital day 2 due to worsening clinical condition, for which the Predictive CDSS can alert the clinical team. When the patient truly develops sepsis on day 3, Descriptive CDSS would alert the team to that fact, and Prescriptive CDSS would provide management advice specific to this patient.

and outcomes. Using data from 49 urban community hospital emergency departments, Delahanty and colleagues developed a machine learning-based sepsis screening tool, Risk of Sepsis score, to predict the risk of developing sepsis during that encounter [37]. This risk score was a better discriminant screening tool than SOFA score in predicting the risk of sepsis just 1 hour after the first vital sign or laboratory result was recorded in the electronic health record (Area under the receiver operating characteristic curve, AUROC, for the Risk of Sepsis score was 0.93, with sensitivity 67.7% in comparison to AUROC of 0.90 and sensitivity of 49.2% for that of SOFA score). Similarly using data from over 121,000 patients at a tertiary care medical center, Koyner and colleagues developed a machine learning model to predict the risk of developing AKI [38]. Their model had an AUROC of 0.87 to predict the risk of developing stage II AKI and an AUROC of 0.96 to predict the risk for needing dialysis in 48 hours. At a probability threshold of 0.022 or more, their algorithm had a sensitivity of 84% and a specificity of 85% to predict stage II AKI. More recently, Peine and colleagues have used reinforcement learning to develop an individualized strategy for management of mechanical ventilators for critically ill patients [39]. These machine learning algorithms provide excellent foundations for developing machine learning guided CDSS. For example, Giannini and colleagues developed and implemented a machine learning based alert for severe sepsis and septic shock at a tertiary care hospital [40]. The implementation of this alert was associated with an increase in the testing of serum lactate (11.7% vs 8.0%; $p<0.01$) and administration of intravenous fluid boluses (25.5% vs 21.7%; $p<0.01$) within 3 hours of the alert.

CDSS can be classified based on their analytical capabilities into three categories – predictive, descriptive, and prescriptive (Figure 2). Predictive CDSS is based on predictive analytics and provides a reasonable prediction about the risk for desired diseases or outcomes. For example, a CDSS based on a predictive model for sepsis can identify and alert the clinicians regarding patients at high risk for developing sepsis. This can give clinicians a head-start to manage these patients which can result in improved outcomes [41]. A descriptive CDSS in comparison notifies clinicians about what has already happened. In this example it would notify clinicians that the patient has developed sepsis. Finally, a prescriptive alert provides clinicians with guidance regarding management of these patients as guided by practice guidelines. In this case it would include recommendations for guideline directed therapy for sepsis. Thus, CDSS can serve as very powerful tools for clinicians at point of care in both diagnosis and management of patients.

CDSS alerts can also be classified according to how they are displayed to the end user. One of the frequent display formats is interruptive alerts that pop-up into the chart and require immediate attention from the end-user. This is in the form of an action listed in the alert or acknowledgement of the alert. This, however, interrupts the clinician's workflow which can be detrimental as was shown in a study that evaluated the impact of interruptions on physician workflow in the emergency department of a 400-bed teaching hospital [42]. The study showed that interruptions were not only associated with significant increases in time to task completion, but physicians failed to return to over 18% of interrupted tasks. Interruptions have also been associated with errors in medication dispensation by pharmacists and administration by nurses [43,44]. Additionally, interruptive alerts have also been associated with development of alert fatigue [45]. Alert fatigue is thought to be a result of cognitive overload due to uninformative alerts and desensitization to alerts over time [46]. It is an increasingly recognized issue with electronic alerts and is a major contributor to their inappropriate dismissal and ineffectiveness [47-52]. The magnitude of its impact can be realized from the fact that among drug safety alerts, over 90% are ignored or overridden [47]. This area is thus gaining increasing attention in Clinical Informatics. Non-interruptive alerts, that stay at a strategically visible location in a patient's chart and alert clinicians without disrupting their workflow are a potential alternative to this shortcoming of interruptive alerts [10], but require further research.

CURRENT CHALLENGES IN CRITICAL CARE INFORMATICS

While Clinical Informatics has made significant strides in improving healthcare delivery in Critical Care Medicine, there are still important challenges in its implementation, particularly concerning how it interfaces with Critical Care Medicine team-members--

1. **Usability and User Experience:** One of the primary challenges in Clinical Informatics is ensuring that systems are user-friendly for health care professionals. Majority of electronic health records suffer from complex interfaces and cumbersome workflows [53] leading to frustration and burnout among end-users.
2. **Interoperability:** The lack of seamless interoperability among various electronic health records is another major obstacle in Clinical Informatics [54]. This translates into clinicians having to navigate multiple platforms and interfaces to access patient data which can be both cumbersome and error prone. Improving interoperability between different electronic health records systems is thus an important challenge to further enhance the role of Clinical Informatics in Critical Care Medicine.
3. **Alert Fatigue:** As we have discussed above, alert fatigue is an important challenge. Though electronic alerts can be helpful for clinicians and improve the delivery of care, they can also overburden Critical Care team-members with notifications leading them to overlook critical warnings. Development and implementation of electronic alerts that improve workflow of clinicians is an important challenge in Clinical Informatics.
4. **Security and Privacy Concerns:** The inherent digital nature of Clinical Informatics raises obvious security and privacy concerns. Safeguarding patient data from unauthorized access and ensuring compliance with data protection regulations is critical. This is one of the key challenges in Clinical Informatics and before healthcare organizations in general.
5. **High Implementation Costs:** Implementing and maintaining Clinical Informatics systems can be expensive, especially for smaller healthcare organizations with limited resources. The initial investment, ongoing maintenance, and training costs can be significant barriers to its effective implementation.

FUTURE DIRECTIONS

As we can see, Clinical Informatics plays a ubiquitous role in Critical Care Medicine. With rapid technological advancements, the role of Clinical Informatics will continue to increase to further optimize data gathering, data display, and augment real-time clinical decision making at point of care. Majority of current ICUs are already equipped with devices that are readily interconnected. From bedside monitors to ventilator and dialysis machines, they all have some degree of interconnectivity built in where they communicate with and export their data into the electronic health record. However, one of the limitations of the majority of current electronic health records is their inability to capture high resolution physiological waveform data. The waveform data provides valuable information, such as pulse pressure variation, ventilator dys-synchrony, etc., that is used by Critical Care Medicine clinicians to provide care at the bedside. In recent years, machine learning algorithms have identified novel uses for these waveform data, such as predicting hyperkalemia from electrocardiogram waveforms [55], hypotension from arterial waveforms 15 minutes before it happens [56], and automated screening for acute respiratory distress syndrome using ventilator waveforms [22]. These techniques have great potential to be deployed for real-time clinical decision support in ICUs. Additionally, so far the majority of focus in Clinical Informatics has been on effective utilization of structured data to augment clinical decision making. Recent advancements in natural language processing have unlocked new horizons for growth by capturing the vastly underutilized unstructured data to develop clinical decision support systems.

Another area of where the role of Clinical Informatics will continue to grow is in providing CDSS, not just for diagnosis but also for management of critically ill patients. Machine learning algorithms can develop predic-

Table 1. The Five Rights of Clinical Decision Support Systems (CDSS)

The Rights	Explanations
Right Information	Information presented in the CDSS should be evidence based, accurate and just sufficient for the end user to take action
Right Time	CDSS should be presented at the appropriate time in the end user's workflow
Right Channel	CDSS can be delivered through electronic health record, pager, text or a smartphone app
Right Format	CDSS can be implemented as an alert (interruptive/non-interruptive), order set or checklist
Right Person	CDSS should be directed only to the appropriate end users

tive models for CDSS with increasing accuracy. As low positive predictive value of CDSS can contribute to alert fatigue, it is expected that CDSS based on these newer models will help minimize alert fatigue and increase their impact. A limitation for developing CDSS that provide personalized management guidance for patients has been the reliance on best practice guidelines that are not specific to a given patient. Machine learning and reinforcement learning techniques have made impressive headways in this area in the last few years [39] and will be crucial in the development of prescriptive CDSS for critically ill patients.

Building CDSS in such a way as to enhance clinician workflow and further reduce alert fatigue is another aspect of CDSS that is attracting interest. The importance of this issue can be realized from the fact that the Leapfrog Group now includes alert fatigue as an evaluation metric in their CPOE evaluation tool [57]. It is recommended to build CDSS using the five core principles or the five rights of CDSS, as they are called [58] (Table 1). By following these five rights we were recently able to develop an electronic alert for AKI detection that showed over 83% acceptance rates by end users 6 months after implementation and over 94% acceptance rates 12 months after implementation [10]. More studies are needed, however, in this area.

CONCLUSIONS AND OUTLOOK

Health information technology plays an essential role in providing care in ICUs. Though there have been many technological advancements in the last few decades that have positively impacted the practice of Critical Care Medicine, much still needs to be done. Healthcare lags behind other industries in utilization of technology. The reasons for this are multifaceted and include a large variety of data (eg, structured data, unstructured notes, physiological waveforms, etc.), issues with interoperability of among systems and users, and concerns with security, privacy, and confidentiality of healthcare data. Standardization of messaging standards across different platforms will help to continue to optimize interoperability across them and allow for better utilization of data for point of care decisions. Finally, the advancements in machine learning and their careful integration with CDSS hold promise to transform the field of Critical Care Medicine and Clinical Informatics.

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