Narrative Review

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The patient admitted without a clear diagnosis to intensive care

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The ICU patient without a clear diagnosis

Summary

Dealing with an uncertain or missed diagnosis is commonplace in the Intensive Care Unit (ICU) setting. Affected patients are subject to a decrease in quality of care and a greater risk of a poor outcome. The diagnostic process is a complex task that starts with information gathering, followed by integration and interpretation of data, hypothesis generation and, finally, confirmation of a (hopefully correct) diagnosis. This may be particularly challenging in the critically ill patient where a good history may not be forthcoming and/or clinical, laboratory and imaging features may be non-specific. The aim of this review is to analyse and describe the common causes of diagnostic error in the ICU, highlighting the multiple types of cognitive bias. Clinicians should be cognisant as to how they formulate diagnoses and utilise debiasing strategies. Multidisciplinary teamwork and more time spent with the patient, supported by effective and efficient use of electronic healthcare records and decision support resources, should improve the quality of the diagnostic process and patient care.

"Medicine is a science of uncertainty and an art of probability" Sir William Osler.

Reaching a diagnosis represents a key moment in the doctor-patient relationship. It allows clinicians to administer the correct treatment, establish a prognosis and, hopefully, influence the outcome. [1] A diagnosis is also used to communicate with the patient and their relatives, to give a label to the patient's condition, and an idea of the challenges and the likely outcome the patient is facing. Despite its importance, making a correct diagnosis represents one of the most complex tasks confronting clinicians. This is particularly pertinent in the Intensive Care Unit (ICU) setting. ICU clinicians are often obliged to work at multiple levels, trying to stabilize a rapidly deteriorating patient while establishing a diagnosis. [2] Moreover, the acutely deteriorating patient often presents with concomitant organ dysfunction and non-specific signs and symptoms, leading to a syndromic diagnosis (such as sepsis, acute kidney injury, acute respiratory distress syndrome) rather than a specific disease. [3]

However, dealing with an unclear – or even erroneous - diagnosis is more frequent than commonly realised. Bhise et al suggest an unclear diagnosis or diagnostic uncertainty is the subjective perception of an inability to provide an accurate explanation of the patient's health problem. [4] Diagnostic error, sometimes referred to as misdiagnosis, has been defined by Graber as a diagnosis that is '*missed, wrong, or delayed, as detected by some subsequent definitive test or finding*'. [5] Broadly, it has been estimated that between 40-80,000 ICU patients in the United States die annually as a result of diagnostic errors or misdiagnosis and the mortality rate of patients with improperly classified diseases can be twice as high. [6] The magnitude of misdiagnosis in ICU is also higher than expected; for example Winters et al showed that 28% of autopsied ICU patients had at least one misdiagnosis. [7]

Thus, patients with an unclear diagnosis represent a complex, heterogenous group requiring considerable effort to increase their quality of care. With the increasing use of electronic health records (EHR), more precise estimates can be made of the size of this problem. [8] Such

patients are usually admitted to hospital through the Emergency Department (ED), and quickly escalated to the ICU because of acute physiological derangement and the need for organ support. Lim et al reported an incorrect diagnosis in 13.3% of patients admitted from the ED. [9] In a large Danish population-based observational study of 264,265 acute medical patients, 28.7% were admitted to hospital with a non-specific diagnosis. [10] Abe et al. showed in a multicentre prospective cohort study on 1060 patients with a suspected infection, that 81 patients (7.6 %) were eventually found to be without infection and that in 113 patients (11.6 %) the initial location of the infection was misdiagnosed. [11] Of 2579 patients admitted to two Dutch ICUs with an admission diagnosis of sepsis, 13% had a post-hoc likelihood of infection of “none”, and 30% of only “possible”. [12]

Missing diagnoses in ICU are a much more complex problem than expected. This review aims to guide ICU and non-ICU clinicians to understand the main reasons leading to missed diagnosis, misdiagnosis and diagnosis delay, provide a better understanding of the cognitive processes underlying diagnostic reasoning, and suggest a pragmatic method to overcome the main causes of diagnostic bias.

DIAGNOSTIC PROCESS

Diagnosis in Intensive Care Medicine

Diagnosis is defined as “*the act of discovering or identifying the exact cause of an illness or a problem*”. [13] The diagnostic process is the method by which health professionals select one disease over another, identifying one as the most likely cause of a person’s signs, symptoms and investigations. Diagnosis and diagnostic process are related but in different terms.

The clinician faces many probabilistic questions trying to make sense of signs, symptoms and parameters. [14] Multimodal approaches and tools including laboratory tests and imaging exist to assist physicians during the diagnostic process. Despite the proliferation of monitors

and diagnostics, obtaining a thorough history and a comprehensive physical examination of the patient should remain the cornerstone in intensive care medicine, though this is not uniformly performed. [15] Laboratory testing provides relevant diagnostic benefits, however the potential of obtaining misleading results, inducing iatrogenic anaemia and encouraging therapeutic interventions of uncertain benefit should always be considered. [16] Point-of-care testing may be helpful when rapid turn-around times, facilitating rapid diagnosis, are crucial for patient management. [17,18] Imaging modalities such as conventional x-ray, computed tomography and magnetic resonance are commonly used to support ICU clinicians in the diagnostic process. [19,20] In recent years, critical care ultrasound (e.g. point-of-care ultrasound [POCUS]) has emerged as an useful, important and relevant adjunct measure for diagnosis, monitoring or to guide invasive procedures, [21,22] and increasingly employed by ICU clinicians directly (Zieleskiewicz2015). [23] For hemodynamic diagnosis and monitoring, a wide modality of invasive and noninvasive tools are in widespread use across ICUs. [24,25]

In brief, the process of gathering information represents the first step of a complex circular process whereby data are integrated, interpreted and hypotheses generated. [26] The whole process can be negatively influenced by inadequate knowledge, faulty data gathering, or faulty information processing . [27] Graber et al suggest gaps in medical knowledge are seldom responsible for misdiagnosis, but mistakes are mainly driven by faulty data processing. [5] Therefore, clinicians should be familiar with cognitive processes underlining diagnostic decision-making in order to avoid common mistakes.

Thinking of a diagnosis

During the last 40 years, the field of cognitive psychology has studied how our mind approaches complex problems. The dual-process theory, described by Daniel Kahneman in his book “Thinking Fast and Slow”, suggests there are two parallel cognitive systems, named

System 1 and System 2, that humans use to process information and for making decisions. [28,29]

System 1 is fast, automatic, unconscious and based on pattern recognition. Clinicians, based on intuitive thinking and past experiences, create heuristics, i.e. mental shortcuts to rapidly assist in dealing with complex problems. [2] The reason why heuristics perform so well is that they ignore some information, thereby reducing cognitive workload. [30] System 1 decision-making is utilised for immediate life-saving decisions. To overcome an emergency intervention and stabilize a critical patient, an experienced clinician usually relies on System 1. Following rapid assessment of clinical signs, with an often incomplete history and with little time to analyse the situation in depth, the doctor will instinctively treat the patient using intuitive reasoning. [2]

In contrast, System 2 is a slow, controlled, conscious and analytical decision-making process. It requires effort but allows the clinician to proceed in a logical systematic manner. It usually takes over from System 1 in unexplored situations, for example when the clinician is facing unexpected complications or uncertain symptoms.

System 1, even if effective most of the time, is more subject to bias due to its instinctive nature. However cognitive error can also originate from System 2, albeit less commonly. Here the clinician may apply flawed rules or start from a false premise, and this may compromise the diagnostic process. [28,31]

Almost all mental processes are a combination of the two systems. It is important to emphasize that both systems are complementary. Nonetheless, clinical decision-making often remains a complex process with many factors influencing the balance between the two processes. The equilibrium between Systems 1 2 can be altered, usually towards System 1 overuse, by individual factors such as affect, fatigue, cognitive load, distractions, sleep deprivation and burnout. [31]

Cognitive bias

A bias is defined as a predictable deviation from rationality. [32] While not a negative term *per se*, bias and error are often associated together. Some experts prefer the phrase "*Cognitive disposition to respond*" (CDR). [33]

More than 30 clinically relevant recognized biases or CDR have been identified (fig.1). [34] As some examples, there is availability bias, defined as the tendency to believe that some diagnoses are more probable if they can easily come to mind. [35] During the recent pandemic, clinicians failed to rapidly identify other causes of respiratory distress as COVID-19-related disease immediately sprang to mind. Experience may not necessarily overcome this; Mamede et al. demonstrated that second-year residents were more prone to availability bias than first-year residents, possibly because reliance on non-analytical reasoning tends to increase with experience. [36] Patients were often labelled as likely to have COVID by triaging; this also determined the place of care, a bias known as triage cueing bias. This particular bias is associated with the maxim "*geography is destiny*". [37] Clinicians may anchor themselves to the first piece of information gathered during initial presentation, and fail to change opinion even after acquiring subsequent information. This "*first impression bias*" is named anchoring bias [38] while failure to integrate the new data results in a diagnostic momentum bias, i.e. accepting a previous diagnosis without sufficient scepticism. [39] This often happens when a diagnostic label is stuck to the patient by different healthcare workers in different clinical settings, or by colleagues handing over between shifts. Clinicians are more likely to accept prior labels without necessarily challenging them, and this may be exacerbated by a lack of time, being preoccupied by other patients, and a fear of accepting diagnostic uncertainty. [40] Confirmation bias is defined as the tendency to seek, interpret and favour evidence in a way that supports prior beliefs. [41] Confirmation bias can lead to a "*tendency to prematurely stop the decision-making process, accepting a conclusion before it has been fully verified*". [42]

SOLUTIONS

The problem of unclear or misdiagnosis is extremely complex. Even if not properly characterized, several solutions have been proposed to assist healthcare workers. The National Academy of Medicine has proposed a long list of possible implementations to improve the safety of the diagnostic process. [43] We will discuss below the most relevant implementations for the ICU setting. A multidisciplinary teamwork approach should be encouraged to reach a diagnosis. Debiasing strategies that decrease cognitive errors can be taught and then adopted by clinicians. Clinicians should also spend more time with the patient with appropriate implementation of electronic medical records and decision support resources. [43]

Multidisciplinary approach

Multidisciplinary teamwork represents a group of professionals from one or more clinical disciplines (both medical and allied healthcare professionals) who make shared decisions regarding investigations and treatment regimens for individual patients. [44] This approach is fundamental in the ICU and its implementation improves the quality of care delivered. [45] Team training focused on team-building exercises and improvement in clinical skills (differential diagnosis and procedural skills) significantly reduced adverse events and mortality in both surgical settings and intensive care units. [46]

The National Academy of Medicine identified that the paternalistic model of care is associated with a 10% greater incidence of diagnostic error. They proposed a team-based, patient-centric model. [43] Both patients and their families/friends are potential solutions to reducing diagnostic errors as they can often provide important history. Engaging families during ICU rounds and increasing visiting hours may improve data gathering and therefore the diagnostic process. [26] The intensivist should maintain leadership yet integrate other allied healthcare professionals into the diagnostic team in appropriate circumstances. [45] The leader should

promote a democratic and accessible workplace so that everybody can contribute. Creating a culture of collaboration encourages participation and feedback; the greater variety of information and perspectives will likely decrease both diagnostic errors and cognitive overload. [26]

Multidisciplinary teamwork can be affected by several factors including lack of familiarity between team members, team size and professional composition. The specific characteristics describing the 'perfect' team composition are not well established in the literature and more research is needed. [47]

Re-thinking how we think: debiasing strategies

Cognitive bias can deeply affect the diagnostic process. Clinicians should be aware of the risk of bias and thus be able to recognize and guard against them. The negative consequences of an excessive reliance on intuition should be highlighted. [5,31] Becoming familiar with some debiasing strategies is important even if their efficacy is difficult to test in everyday clinical practice. [48] The main approach to helping clinicians at present is called Metacognition. This is the ability to self-monitor and assess our decision-making reasoning, and to identify and override heuristics as and when needed. [33] A metacognition time slot could be inserted during diagnostic timeouts to implement general principles to decrease errors, for example ruling out the worst-case scenario in specific acute conditions. The implementation of differential diagnosis checklists can improve diagnostic performance in high difficulty cases (Fig.2). [49]

Time spent with patients

"The complexity of medicine now exceeds the capacity of the human mind". [50] Clinicians in the modern ICU face a considerable challenge linked to the huge amount of data now being generated by computerised systems, and the time being spent scrutinising the data, rather

than with the patient themselves. Using wearable sensors, physicians spent only 13.7% of their day shift time in patient rooms and 40.6% in their work area. [51] The use of electronic health care record systems is linked with increased burnout among clinicians, and this will exacerbate the overall problem. [52] Despite having more data, clinicians have less confrontation with their colleagues. They often do not have enough time to focus on the patient directly. Allocating appropriate time to communicate with patients and family is fundamental for accurate data gathering and will reduce the risk of relying on second-hand information. A good relationship between patient and caregiver will also reduce burnout risk. This is associated with an excessive workload that compromises cognitive performance and increases reliance on System 1 thinking, leading to more diagnostic bias. [31]

Artificial intelligence (AI) and Machine Learning (ML) technology may potentially assist. It can support the clinician in disease identification, perhaps even before the development of acute deterioration and complications. It may also help in predicting disease evolution and provide insights into the patient's peculiarity. [53] New advanced analytical models and clinical tools are published at very regular intervals [54] but none have yet provided a viable and validated solution to the problem. There is an urgent need to rethink the AI interface and how it should best be implemented. A more user-friendly and human interface is needed to rationalize and simplify the work of clinicians and healthcare workers. AI does not represent the magic bullet but, with the right approach, it can help overcome human limitations and give back time to the clinicians.

CONCLUSIONS

Managing patients with unclear diagnoses in the ICU represents a big challenge for clinicians. Missed diagnosis, diagnostic delays and errors are surprisingly common and may determine adverse outcomes. The diagnostic process is characterized by multiple cognitive steps with mistakes potentially occurring at any stage. However, errors due to faulty reasoning are more

common than errors due to faulty knowledge. Moreover, working under time pressure, burnout, stress and fatigue – common characteristics of the ICU environment – can negatively impact cognitive tasks. Low-quality bedside assessment and information gathering, cognitive bias and lack of time may be the main determinants of a low-quality diagnostic performance.

It is time to rediscover the importance of bedside clinical examination and increase time spent with the patient to improve information gathering and patient satisfaction. Clinicians should have insights into their reasoning processes and maintain the healthy scepticism that should characterise the medical profession. However, being aware of cognitive bias is not enough it itself. Implementation of debiasing strategies and differential diagnostic checklists can improve diagnostic accuracy. Finally, a patient-oriented development of the working environment, electronic medical records and decision support resources can help clinicians to overcome some human limitations and extend the time at the bedside.

Competing Interests

WP, PA, DH, MS - no competing interests declared.

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Figure Legends

Figure 1 Cognitive biases. Adapted from Campbell et al., 2007. (Ref. 37)

Figure 2 The diagnostic process and metacognition. The diagnostic process phases (in blue) are interspersed with metacognitive timeouts (in orange).