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Risk Factors for Delirium: Are Systematic Reviews Enough?

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Delirium is one of the most important predictors of poor long-term outcomes in critically ill patients. Delirium has been associated with higher mortality,(1) functional disability,(2) and cognitive decline,(3, 4) and may occur in up to 80% of patients at some point during their ICU stay.(5) Since effective treatment of delirium has proven difficult, ICU-based prevention efforts are critical. In this context, rigorously defining risk factors for delirium would allow clinicians to more accurately identify high-risk patients and target them for focused delirium prevention, while also allowing researchers to better understand the relevant pathophysiology underlying delirium.

In this issue, Zaal et al.(6) describe a rigorous systematic review of risk factors for delirium in critically ill adults. The authors identified 33 cohort studies or randomized controlled trials that examined associations between putative risk factors and a validated measure of critical-care delirium. Using a systematic approach of evaluating the number, quality, and consistency of studies providing relevant evidence, eleven risk factors were identified as having either strong or moderate evidence of association with ICU delirium. Of these eleven risk factors, only three—use of dexmedetomidine, length of mechanical ventilation, and coma—are potentially modifiable.

The results of this systematic review highlight the challenge of identifying risk factors for ICU delirium by simply reviewing available data. The authors' original intent was to statistically pool the available data for each risk factor, but substantial heterogeneity between published studies precluded that possibility. Such heterogeneity stems from the difficulty of measuring delirium in the first place [with even validated tools being assessor-dependent (7)]; the diversity of critically ill populations (with potentially different pathophysiologic mechanisms of delirium depending on the reason for critical illness, e.g., medical versus surgical); and delirium-prevention protocols, participant recruitment

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practices, and scientific goals that vary substantially from one study to the next. As evidence of this heterogeneity, even among medical ICU populations using a single instrument for delirium assessment (the Confusion Assessment Method, CAM-ICU), the incidence of delirium ranged from 22–78% in studies included in this review. Given such wide diversity in delirium assessment, patient populations, and study designs, it seems likely that the strength of evidence for an association between any risk factor and ICU delirium will reflect study practices (for example, preferential collection of certain data) as much as any underlying causal link.

Thus, we should view the admirable efforts of Zaal et al. not as a definitive assessment of risk factors for ICU delirium, but rather as a reflection of severe limitations in our current understanding that are driven by heterogeneity in methodologies and outcome measurement. This challenge is not unique to ICU delirium; many other fields also struggle to standardize methodologies and effectively combine the results of disparate studies.(8, 9) In this regard, there is growing recognition of the importance of standardized outcome measures (including delirium) (10) and increasing momentum to synthesize diverse studies through collaborative analysis rather than relying on systematic review. As an example, the Core Outcome Measures in Effectiveness Trials (COMET; (<http://www.cometinitiative.org/>)) initiative was launched to facilitate development of core outcome datasets across a wide range of health areas, with the goal of allowing the results of trials and other studies to be compared, contrasted, and combined as appropriate. There are several examples of COMET initiatives focused on critical care outcomes, including mechanical ventilation and rehabilitation outcomes. As yet, there are no initiatives focused on delirium.

How might we use collaboration to extend and strengthen the findings of this review? An essential first step would be the development of minimum data collection sets and agreement on essential elements of the delirium assessment with accurate reporting on how the assessment was operationalized. For example, 70% of the studies reviewed used the CAM-ICU as an assessment tool; if those studies operationalized the CAM-ICU assessment in comparable fashion and also collected risk factor data (severity of illness scores, sedation measurements, etc.) using similar instruments, combined collaborative analyses could be performed that would provide standardized, large-sample-size evidence for the comparative importance of those risk factors for CAM-ICU delirium. Similar analyses have been used to investigate the associations between early antiretroviral therapy and survival after HIV infection (11), and between kidney function and all-cause mortality (12), with important implications for both policy and clinical practice. Both the American Delirium Society and European Delirium Association are vibrant groups with large annual meetings, and would be well-suited to facilitate such an initiative. Collecting and measuring a common set of important variables and standardizing the methods and reporting of delirium assessment would be a major advance. Further, creating a collaborative network would facilitate sharing of data with similar analytic approaches to allow much stronger evaluation of risk factors and lend insight into the pathophysiology and optimal clinical management of delirium.

In summary, Zaal et al. should be applauded for their exhaustive review of risk factors for delirium. However, the authors' most important contribution may not be the methodology of their review, but rather their elucidation of the limitations in our current approach to

delirium research. In doing so, the authors demonstrate the need for collaborative standardized research approaches if we are ultimately to understand the importance of risk factors for ICU delirium and prevent the complications of delirium among critically ill patients.

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