Precision Medicine: the Future of Critical Care

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Critically ill patients are considerably heterogeneous. The common ICU conditions like sepsis and acute respiratory distress syndrome have protean manifestation and course.[1] If we consider the patients with sepsis, the patients can vary significantly with regards to the underlying etiology (bacterial, parasitic, viral, etc), state of immunological response to infection (ranging from inflammation-induced organ injury to profound immune suppression to a mixture of the two) and extent of organ dysfunction (early fluid responsive vasodilated hypotensive state with hyperdynamic ventricles to late sepsis induced myocardial dysfunction causing hypotension unresponsive to fluid boluses).[2] The situation can be further complicated by the multiple comorbidities, rapidly changing physiological state of the patient and complex interaction between concurrent managements. It is clearly evident that the concept of "one-size-fits all" and applying protocolized management for these heterogeneous patients can be fairly imprecise and can be potentially harmful.[1,3,4]

"Precision medicine" involves considering unique individual characteristics like genetics and environment, while treating and preventing the disease, to maximize effectiveness and to minimize harm.[5] The concept of precision medicine largely originated from oncology, where personalized strategy based on genomics and biomarkers have improved outcome and decreased toxicity.[6] Clearly, applying precision medicine in critically ill patients can improve outcome. Patient management guided by information obtained from clinical examination, bedside monitoring, genomics, biomarkers and big data can be the ways to find precision in critically ill patients.

Considering the rapidly changing clinical scenario and complex interaction of various interventions and treatment strategies, the tools to be applied to practice precision, should consider these unique properties of ICU patients and should prefer the investigation tools and monitoring modalities, that can guide the management in real time, with a short time lag, to allow the intervention to be of maximal benefit.[7] The current designs of randomized trials, which enroll a large group of heterogeneous patient population may not be helpful to guide precision management in future. Current trials usually miss the hidden unique group of population that my actually be benefited by the intervention and in the other end, it may fail to show another group that may be harmed by the intervention. In a trial comparing warfarin and aspirin in patients with heart failure and sinus rhythm, there was no overall difference in primary outcome of ischemic stroke, intracerebral hemorrhage or death. However, in patients receiving warfarin, there was reduced risk of stroke, which was offset by an increased risk of major bleeding.[8] The future trial designs should incorporate large data registry, so called registry-based randomized controlled trials and the trial that would test the effectiveness of various simultaneous interventions, called response-adaptive platform trials. These trial designs may provide justice to the heterogeneous patient population and would foster evidence in favor of precision. However, it needs a lot of collaboration between centers and demanding high level of funding.[1]

"Omics" technology, involving genomics, epigenomics, proteomics and metabolomics have been increasingly used to identify the subtypes or endotypes among the heterogenous patient population to individualize management. Use of prognostic enrichment to identify high risk patient populations and the use of predictive enrichment to identify the subgroup that would respond to the selective intervention has been proposed and the initial trials have shown promising outcomes.[9] Incorporating the wealth of data from data rich environment into the computerized system, multicentric collaboration, creating big databases and using machine learning modules can help to streamline and better use the data for both effective prognostication and for individualizing patient management in ICU. Significant amount of funding, collaboration and close synchrony with data scientists is of utmost importance.

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Though challenging, the world has been marching in the path to precision for salvaging more critically ill patients. Rather than extrapolating the findings from resource rich environment to low income countries in the future (that may sometimes prove to be ineffective or even harmful),[4] considering the large burden of critical illness and the big population of sick ICU patients in low income countries, the researchers striving for precision in ICU should not forget this big population who equally deserve precise and improve care and who equally deserve to survive salvageable critical illness. Bedside clinical examination, which is often forgotten and disregarded, can be a potential tool, which is cheap and practical even in places in resource limitations, can be a viable armamentarium while we long for precision in low resource settings.[10] The future expensive trials should search for clinical surrogates (applicable in poor countries) to the expensive tools for precision.

REFERENCES

1. Maslove DA, Lamontagne F, Marshall JC, Heyland DK. A path to precision in the ICU. Crit Care. 2017;21:79.

2. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. Lancet Infect Dis. 2015;15:581-614.

3. Klein HG, Flegel WA, Natanson C. Red blood cell transfusion: Precision vs imprecision medicine. JAMA. 2015;314:1557-8.

4. Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, et al. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: A randomized clinical trial. JAMA. 2017;318:1233-40.

5. Hudson K, Lifton R, Patrick-Lake B, Burchard EG, Coles T, Collins R, et al. The precision medicine initiative cohort program: building a research foundation for 21st century medicine. Bethesda: National Institutes of Health; 2105. https://acd.od.nih.gov/reports/DRAFT-PMI-WG-Report-9-11-2015-508.pdf. Accessed 18 Oct 2017

6. Schwaederle M, Zhao M, Lee JJ, Eggermont AM, Schilsky RL, Mendelsohn J, et al. Impact of precision medicine in diverse cancers: A meta-analysis of phase II clinical trials. J Clin Oncol. 2015;33:3817-25.

7. Shrestha GS. Point-of-care ultrasonography: a practical step in the path to precision in critical care. Crit Care. 2017;21:215.

8. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med. 2012;366:1859-69.

9. Wong HR, Atkinson SJ, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, et al. Combining prognostic and predictive enrichment strategies to identify children with septic shock responsive to corticosteroids. Crit Care Med. 2016;44:e1000-3.

10. Mer M, Scultz MJ, Adhikari NK. Core elements of general supportive care for patients with sepsis and septic shock in resource-limited settings. Intensive Care Med. 2017; doi: 10.1007/s00134-017-4831-z (Epub ahead of print)