Iatrogenic anemia: an underestimated and solvable problem in the intensive care unit

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The amount of blood collected for diagnostic purposes at intensive care units leads to significant anemia and continues harming far too many critically ill patients all over the world. This is once more confirmed in a recently published admirable study by Jackson Chornenki *et al.* (1).

Diagnostic blood sampling is associated with anemia in critically ill patients

Whereas healthy persons can easily tolerate a 550 mL whole blood donation, critically ill patients may develop anemia after losing smaller volumes of blood. A large international study performed in the 80-ties of the last century showed that 45% of the patients had about five phlebotomies at their first day of admission in the intensive care unit and on average 41 mL blood taken during following days at the intensive care (2). These figures have been confirmed in numerous studies from various countries (3-5). Jackson Chornenki *et al.* recently quantified blood volume taken for laboratory testing among 7,273 patients who had been admitted for at least 48 hours to four medical-surgical intensive care units between 2012 and 2015 in Hamilton, Ontario, Canada (1). At admission to the intensive care patients had a mean hemoglobin concentration of 107 g/L (standard deviation 25 g/L). The mean total volume of blood loss due to phlebotomies during the whole intensive care stay was 337 mL (standard deviation 411 mL); the

mean daily volume was 32 mL (standard deviation 27 mL). Higher volume of blood loss due to phlebotomies was associated with the development of anemia. The number of patients with severe anemia (hemoglobin of 90 g/L or less) increased from 40% at intensive care admission to 67% during intensive care stay. One cannot deduce that all newly developed cases of anemia are explained by phlebotomies at the intensive care, because critical illness itself is also associated with the development of anemia. So, the question remains: how many cases of anemia were explained by phlebotomies? Or, more clinically relevant: how many cases of anemia could have been prevented with preventive measures such as limiting testing and using small volume tubes?

Volumes for diagnostic testing unavoidable or needlessly high?

Diagnostic testing is obviously done to support therapeutic choices and ultimately to improve clinical outcomes. One thus needs to balance disadvantages of blood loss and anemia due to phlebotomy against the diagnostic value and positive effects of it on clinical outcomes of critically ill patients. Yet, the larger part of the blood drawn for laboratory testing is discarded (6).

Modern lab-analyzers need about 100 to 200 μL of blood. Standard volume tubes collect about 4 to 6 mL of

blood. Thus, when standard volume tubes are used more than 90% of blood is thrown away (7). For the cohort of Jackson Chornenki *et al.* we calculated that approximately 1,964 L of blood collected for diagnostic testing was thrown away (0.3 L × 7,273 patients × 0.9). We conclude that, even without reducing the number of diagnostic tests, patients in the intensive care unit would be better off if the volume of blood collected for testing would be reduced to the volume that is needed for the tests.

Diagnostic blood sampling harms critically ill patients

Diagnostic blood sampling might lead to unintentional harm in critically ill patients, given that it might lead to severe anemia. Anemia is a common problem in critically ill patients and can severely affect their recuperation (8). Since anemia can lead to a decreased oxygen delivery capacity and thus decreased oxygen delivery to vital organs (5,9), critically ill patients with severe anemia receive red blood cell transfusions to improve the tissue oxygenation. As early as in the 80-ties, it was described that the total diagnostic blood sampling volumes in critically ill patients unintentionally can cause anemia and result in red blood cell transfusions (2,10). Jackson Chornenki *et al.* showed that 47.5% of the anemic critically ill patients needed blood cell transfusion, receiving a median of 3 units (1). These results concur with results from previous studies (5,11). Cumulative blood loss due to laboratory testing from day 2 to 7 of intensive care unit admission was independently associated with red blood cell transfusions (hazard ratio 2.28 for each 150 mL increment; 95% confidence interval, 2.02–2.59) (1). However, the efficacy of red blood cell transfusions in improving oxygen delivery capacity is not established; reviews on the topic suggest no improvement (12,13). Since the results of the Transfusion Requirements in Critical Care trial (14), many studies have looked into the hemoglobin range that would yield most improvement in tissue oxygenation, while minimizing the harm of red blood cell transfusions. A recent systematic review and meta-analysis found that red blood cell transfusion in critically ill patients with a hemoglobin level of 7–8 g/dL or lower (restrictive strategy) was associated with reduced risk of 30-day mortality, length of hospital stay, number of transfusions, and reduced risk of stroke than in critically ill patients receiving red blood cell transfusions with a liberal strategy (hemoglobin trigger 9–10 g/dL) (15). An earlier meta-analysis had shown that the outcomes of patients

did not differ between liberal and restrictive transfusion trigger strategies (16). These differences could be due to heterogeneity of the population, study design and outcome measurements. Furthermore, administration of red blood cell transfusions has been associated with increased risk of nosocomial infections, infectious complications, multi-organ dysfunction syndrome and acute respiratory distress syndrome in critically ill patients (17), next to the increased risk of transfusion-related acute lung injury, transfusion-associated circulatory overload, transfusion-related immunomodulation, and substantial costs ($522 per unit of blood) (18).

What can be done to stop harming vulnerable patients at the intensive care unit?

Needles blood drawing can be reduced with various technical solutions. Blood-conserving arterial systems were associated with 59% less blood loss compared with conventional arterial line systems (19). Small-volume tubes with phlebotomies have been shown to reduce both volume of blood loss and anemia (20). Improved laboratory analysis techniques have led to more efficient analyses using ever smaller blood volumes. New developments in the field of blood collection and analysis should be encouraged to further reduce the amount of blood wasted in the process of diagnostic testing.

Finally, behavioral changes of intensive care professionals are needed to stop unnecessary laboratory testing in critically ill patients. Testing in response to specific diagnostic questions rather than at regular intervals has been advocated in the Critical Care Choosing Wisely Campaign published in 2014 (21). The results of Jackson Chornenki *et al.* suggest the problem of unnecessary testing is still ongoing. It has been shown that standard blood sampling adds little benefit to patient management (22). This is corroborated by the results of a study showing that physicians only considered 49% of the daily blood tests as essential in critically ill patients (23). Accordingly, the general agreement is that routine daily diagnostic blood sampling, including arterial blood gas sampling, need careful evaluation and reasoning to maximize the clinical and cost benefit and minimize the risks associated with diagnostic blood sampling (24). Suggested strategies to reduce unnecessary diagnostic blood sampling are changes in blood sampling ordering (25), diagnostic blood sampling guidelines (26), and education. Some have presented the effects of these strategies in reduction of routine diagnostic

blood sampling (27,28). One of the studies found that a combination of educational sessions, reminders for the need of routine blood-test and specification for ordering routine tests, led to a 13–15% decrease in routine blood sampling, which saved 11,200 Canadian dollars per year (27).

We conclude that anemia and red cell transfusions in critically ill patients are at least in part due to needless diagnostic blood sampling. Efforts to optimize both the frequency and the volume of tests will prevent wasting huge amounts of blood and improve clinical outcomes of patients in intensive care units all over the world.

Acknowledgments

Footnote

References

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