

## INVITED COMMENTARY

**The charm of “small data”**

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experience with intestinal transplantation”

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The manuscript by Ceulemans *et al.* [1] in this issue reports results of a multicentric Belgian survey on their experience with  $n = 23$  intestinal transplantations (IT) over a period of 15 years. The authors report 1- and 5-year patient and graft survival rates of 71.1% and 62.8% as well as 58.7% and 53.1%, respectively, which is well in line with the previously reported data from the Intestinal Transplant Registry (ITR) [2] and data presented on the International Small Bowel Transplant Symposium in Buenos Aires, in June 2015. The authors concluded that IT has come of age in Belgium as a valuable means of treating patients with irreversible intestinal failure and stage IV portomesenteric thrombosis by providing a life-saving therapeutic option and improving quality of life.

The question is: Is there more to learn?

Despite its retrospective nature and although the number of described procedures is very low in comparison with the recent report of the ITR [2], there is extra value by this paper. Some arguments supporting this statement are going

to be highlighted exemplarily in the following by addressing the current state and challenges in the field of intestinal failure and transplantation.

Grant *et al.* recently demonstrated that the approval of IT as the standard of care for complicated, irreversible intestinal failure in the United States in 2000 resulted in the establishment of IT programs and increase of activities throughout developed countries, with South America experiencing the highest growth rates most recently. Annual transplantation volumes have recently declined [1], partly due to progress in pediatric and adult intestinal rehabilitation. The ITR report demonstrated actuarial patient survival rates of 76%, 56% and 43% at 1, 5 and 10 years, respectively. Whereas both *per se*, inclusion of the colon and the liver, as well as not-being inhouse patient at the time of transplant, use of induction immunosuppression, and maintenance therapy with an m-TOR inhibitor were associated with improved outcome, the long-term outcome, particularly the outcome after the first year, has not

improved substantially over the last decade [3]. The latter represents the most important challenge in the field of IT and, on first sight, is equally reported by the Belgian multicentric analysis.

Several reasons account for this fact. The most evident and likely being chronic allograft damage for several reasons. Donor-specific antibodies were shown to contribute significantly [4]. Infectious complications, chronic renal insufficiency, nonadherence, and other side effects of immunosuppression do further contribute as documented for other solid-organ transplants.

However, there is some truth behind big data, which may be hidden from perception. Here lies one strength of the Belgian multicenter report which, of course, covers a by far smaller cohort. First of all, there is a substantial heterogeneity of data in the Belgian data set which is composed of several smaller centers and on patient cohort of  $n = 16$  patients which revealed markedly better long-term outcome. Particularly, this very heterogeneity uncovers important details.

It may be old hat to say that center size matters, but a complex field such as intestine transplantation is in urgent need of dedicated programs which engage in intestinal failure treatment, intestinal rehabilitation, and IT as well. However, the difference in survival rates may not just be due to sample size, but also due to innovative approaches to reduce initial allograft damage caused by ischemia reperfusion, strict donor selection, a mitigation of alloimmune responses by modulation of the recipient immune system, such as donor-specific transfusions, and the insight that “less may be more” with regard to immunosuppression [5]. Interestingly, the occurrence of donor-specific antibodies was not reported to be a major problem in this cohort of patients, eliciting the question whether the development of DSA is really inevitable and whether a certain composition of induction and maintenance immunosuppression as well as immunomodulatory [6] or cell-based interventions would decrease the long-term risks of DSA.

As a matter of fact, there are some promising and innovative approaches worldwide to improve overall outcome of intestine transplantation. As only very few centers transplant more than 10 intestines per year [2], progress is often limited to single center initiatives lacking enough statistical

power to create strong evidence. Hence, the intestinal transplant community should cooperate internationally to homogenize their approaches and create multicentric consensus on various aspects of intestinal transplant care, such as immunosuppressive and immunomodulatory protocols, and allograft monitoring, as well as the assessment of appropriate biomarkers.

Thus, the presented analysis is a good example for urgently needed steps to analyse the data in a multicentric fashion to obtain more insight into the field and create knowledge. The analysis of heterogeneity of data sometimes creates more insight into complex processes by uncovering single important findings.

In summary, more and broader initiatives are needed particularly with regard to multicentric prospective approaches, a more targeted data collection through the ITR, as well as prospective clinical and scientific cooperations throughout the intestinal transplant community to join efforts.

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