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Delayed graft function—more than just a kidney transplant complication?

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Introduction and objectives

- There is no universal definition of delayed graft function (DGF). The United Network for Organ Sharing (UNOS) definition is the most commonly used and is the recommended choice by the US Food and Drug Administration (FDA). Based on UNOS, DGF refers to the acute kidney injury (AKI) that occurs in the first week of kidney transplantation and necessitates dialysis intervention.
- There are no clinical guidelines or approved treatments for DGF; off-label treatments (with limited evidence base) are currently used to prevent DGF, commonly referred to as background therapies. While the same type of treatment is used across markets, treatment patterns vary between individual countries.
- The objective of this study was to characterize and highlight the disease burden of DGF including epidemiology, clinical, humanistic, and economic outcomes, and identify unmet needs and gaps in current knowledge.

Methods

- A targeted review and synthesis of the current literature on epidemiology, clinical, economic, and humanistic burden was conducted to identify relevant articles published between Jan 2013 and Aug 2023 in the following scope markets: the US, the UK, Germany, France, China, and Japan. Kidney transplants obtained from deceased donors were only included. Searches on clinical guidelines, randomized controlled trials (RCTs) related to standard of care (SoC), and health technology assessments (HTAs) outcomes were also conducted to understand the landscape situation in DGF.

Results

1. DGF occurs in around a quarter of all kidney transplants.

- In total, 41 studies were deemed relevant and used in the analysis on the epidemiology burden.[1-41] The majority of studies were retrospective cohort studies conducted in the USA (n=23). Other countries included China (n=9), Germany (n=5), France (n=2), and the UK (n=2).
- Incidence rates of DGF were reported higher for adult vs pediatric patients. Considerable variation was reported in the incidence of DGF across studies:

Adult

35 studies reported adult incidence rates related to DGF, ranging from[1-35]:
14% to 55%

The median total incidence reported across 21 studies was[1-21]:
24.3% (IQR 9.25)

Pediatric

6 studies reported pediatric incidence rates related to DGF, ranging from[36-41]:
5% to 25%

Based on US data only

- Adult studies reporting incidence rates in the lower range (<15%) were always single-center studies whereas those reporting incident rates in the higher range (>39%) had either high proportions of donation after cardiac death (DCD) or were also single-center studies.

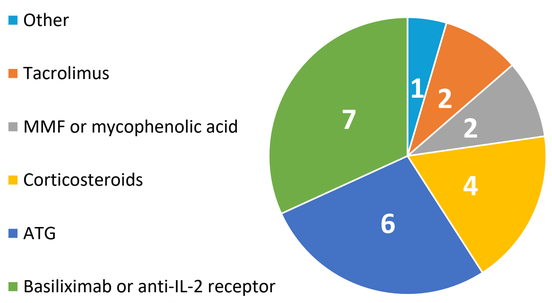
The following factors were associated with increased incidence rates of DGF across patients:

- A longer CIT before transplantation (adults)
- Grafts from donors with AKI (adults); AKI stage also affected DGF rates
- DCD kidney transplants (adult and pediatric)
- Recipients of grafts from ECD (adults)

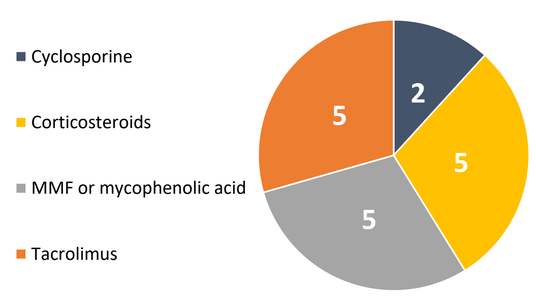
2. DGF is associated with increased risk of graft survival loss, influenced by donor characteristics. Literature is limited on the clinical burden in pediatric patients.

- Treatment patterns of off-labeled therapies varied between induction and maintenance treatments for DGF.

Analysis of the nine studies[1, 4, 7-9, 13, 28, 29, 43] that included induction treatments for adults



Analysis of the five studies that included maintenance treatments for adults[7, 9, 13, 28, 43]



- Twelve studies were identified to report on the clinical burden of DGF in post-transplant patients, with only two of these studies conducted on pediatric patients.[1, 4, 5, 7-9, 13, 28, 29, 39, 40, 43]

	Graft survival				Patient survival		Patient mortality	
	1 year	3 years	5 years	10 years	1 year	3 years	1 year	3 years
Adult	96.2% (mean)	89%*	89%*	33.2% to 67%*	97.7% (mean)	94.5%*	1.6% to 7.5%	2% to 11%*
Pediatric	89%*	78%*	73%*	NR	NR	NR	NR	NR

*% obtained from a single study.

- AKI, time from transplant and treatment in a non-specialized center correlates with decreased graft survival/increased graft loss in adults.

Two studies[1, 9] reported that **rehospitalization rates for DGF patients are higher** than in non-DGF kidney transplant patients.

Duration of hospitalization is linked with time to last dialysis post-transplant. Extensive dialysis within 7 days post transplantation negatively impacted 10-year graft survival.[1]

Only two US studies were identified to report on the economic burden of DGF, both reporting only on the total cost of hospitalization. DGF is associated with a 9.9%-11% cost increase. Total hospitalization costs were reported to be US$142,927.

3. Despite the lack of humanistic and economic data, the largest burden of DGF is expected to be between the social and financial burden in patients and healthcare systems.

- No data on HRQoL for patients with DGF were identified in literature across all markets.
- It is likely that DGF has a considerable impact on HRQoL, as patients are dependent on dialysis which causes physical symptoms such as pain and fatigue, emotional stress such as anxiety and depression, and overall, diminishes the daily functioning of patients.

- There is a lack of economic data for long-term outcomes due to graft loss, such as long-term dialysis and re-transplantation.
- The extended treatment and care for managing DGF can lead to substantial financial strain on both patients and healthcare systems.
- Understanding the long-term costs associated with graft loss will be the key to demonstrate cost savings.

4. Gap analysis

Epidemiology	USA	• China • France • Germany • UK	• Japan • European (regional) • Asian (regional) • Global
Clinical burden	NA	• Graft survival/loss • Patient survival/mortality • Hospitalization rates	• Pediatric survival/mortality
Humanistic burden	NA	NA	• Physical symptoms • Quality of life • Emotional impact
Economic burden	NA	• Total hospitalization costs	• Direct costs • Indirect costs • Pharmacy costs

High data availability | **Moderate data availability** | **No data available**

Conclusions

- The absence of clinical guidelines and approved treatments alongside some notable gaps in data, particularly in the humanistic and economic impact of DGF, warrants further attention from payers and healthcare providers.
- There are many evidence gaps in characterizing the burden of DGF, which means that the value of new treatments in this disease area may be underestimated and emphasizes the need for additional research to better inform treatment strategies and support payer decisions.

Financial support: This study and poster development were funded by argenx BVBA (Ghent, Belgium).

Disclosures: The material in this poster has not been previously presented or published. Francesca Barion and Glenn Phillips are employees of argenx. Vasileios Pardalidis, James Beggs, Ally Robert, and Catherine Kielar are employees of Avalere Health and serve as paid consultants for argenx.

Abbreviations: Ab, antibody; AKI, acute kidney injury; ATG, anti-thymocyte globulin; CIT, cold ischemia time; CD, cluster of differentiation; DCD, donation after cardiac death; DGF, delayed graft function; ECD, expanded criteria donor; FDA, Food & Drug Administration; HRQoL, health-related quality of life; HTA, health technology assessment; IL, interleukin; IQR, interquartile range; mAb, monoclonal antibody; MMF, mycophenolate mofetil; NA, not available; NR, not reported; RCT, randomized controlled trial; SoC, standard of care; UNOS, United Network for Organ Sharing.

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