Economic burden of acute steroid-refractory graft-versus-host disease in commercially insured pediatric patients

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What is already known about this subject

- Acute graft-versus-host disease (aGVHD) is a potentially life-threatening complication of hematopoietic stem cell transplantation (HSCT) often treated with steroids, but there is no standard of care for the more than 50% of patients who become steroid refractory.
- Steroid-refractory (SR) aGVHD is associated with significantly worse pediatric health outcomes and with economic burden thought to be greater than that seen with steroid-responsive aGVHD.

What this study adds

- A retrospective analysis of commercial insurance claims data provides insight into the economic burden and health care resource utilization (HCRU) of these pediatric patients across multiple treatment centers.
- Pediatric patients with SR aGVHD experienced more frequent complications and incurred significantly higher HCRU and direct medical costs within the 12 months following allo-HSCT than controls who had no claims for GVHD.
- Within 12 months of transplant, the costs incurred by patients with SR aGVHD who ultimately died were significantly higher than for those who survived.

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ABSTRACT

BACKGROUND: Acute graft-versus-host disease (aGVHD), a potentially life-threatening complication of hematopoietic stem cell transplantation (HSCT), often occurs within 100 days of HSCT. While steroids are typically used as first-line treatment, there is no consensus on second-line steroid-refractory (SR) treatments. SR aGVHD is associated with significantly worse pediatric health outcomes, but less is known about its economic impact.

OBJECTIVE: To evaluate the economic burden of SR pediatric aGVHD in a commercially insured US patient population.

METHODS: Retrospective analyses were conducted using medical and pharmacy claims data from the HealthCore Integrated

Research Database (study period January 1, 2006-May 31, 2019). Included patients had at least 1 claim for allogeneic HSCT (earliest HSCT claim set as index date), no claims for autologous HSCT, and no pre-index GVHD. Patients were aged less than 18 years with no minimum pre- or post-index continuous enrollment. The GVHD cohort included patients with at least 1 claim for aGVHD over 100 days from index with at least 1 claim for any steroid and at least 1 claim for second-line therapy, both on or after the date of the first aGVHD claim. Patients post-HSCT with no GVHD claims over follow-up formed the comparison cohort. Health care resource utilization and costs over 12 months from the index date were calculated and compared between cohorts using parametric testing.

RESULTS: 38 patients with SR aGVHD and 184 controls were included. Mean age and sex were similar for aGVHD (8.6 years, 50% female) and control (8.2 years, 45% female). During the 12-month post-index follow-up, SR aGVHD patients had higher rates of complications vs controls (* for $P < 0.05$): anemia (79% vs 68%), drug-induced anemia* (53% vs 34%), neutropenia (63% vs 53%), thrombocytopenia (58% vs 42%), gastrointestinal complications* (95% vs 65%), and infections* (95% vs 79%). Mean inpatient length of stay was longer by 31.6 days ($P < 0.01$) with a total average of 96.0 days for those with SR aGVHD vs 64.3 days for the controls. More SR aGVHD patients required inpatient total parenteral nutrition (71% vs 58%), readmission within 12 months of discharge from index hospitalization* (89% vs 60%), ER visits

(34% vs 24%), and outpatient visits (100% vs 86%). Total 12-month mean medical costs were higher in aGVHD patients: \$1,212,944 vs \$673,491 ($P < 0.001$), mostly because of complication-related costs: \$868,966 vs \$396,757 ($P < 0.001$). Among patients with SR aGVHD, mean total costs were higher by about \$1.8 million (\$2,609,445 vs \$812,385; $P = 0.014$) for those who died compared with those who were alive within 12 months.

CONCLUSIONS: SR aGVHD in pediatric patients following HSCT is associated with incremental 12-month medical costs of greater than \$500,000, driven largely by complications.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for children with serious hematologic conditions, including malignancies (eg, acute myeloid leukemia, acute lymphoblastic leukemia, and myelodysplastic syndromes) and nonmalignant disorders (eg, aplastic anemia, sickle cell disease, and thalassemia).¹⁻³ However, after allo-HSCT, many patients develop acute graft-versus-host disease (aGVHD), a potentially life-threatening complication that typically occurs within 100 days of transplantation.⁴

aGVHD is an immunologically mediated response that occurs when donor T-cells recognize antigens on host cells and target them for attack.⁵ Disease manifestations largely involve the skin, gastrointestinal (GI), and liver organ systems.^{4,6} The most commonly occurring symptoms are maculopapular rash, GI disturbances (eg, diarrhea and GI pain), cholestatic hepatitis, and elevated hepatic enzymes, which reflect the tissue damage in these 3 organ systems.^{4,6,7} The complications associated with aGVHD result in substantial morbidity, reduced quality of life, and increased risk of mortality for patients.^{6,8,9}

In the United States, 106,112 allo-HSCTs were performed between 2013 and 2017, of which 35%–50% of patients were estimated to have developed aGVHD.^{4,10} The incidence of aGVHD varies based on the degree of human leukocyte antigen (HLA)-disparity between the donor and transplant recipient and increases with greater levels of disparity.^{6,7} In children receiving HLA-matched HSCT, the incidence of aGVHD has been reported at 31%.¹¹ In transplant recipients with 1 antigen mismatch, an incidence rate of 75% has been reported, rising to 90% in those with 2–3 antigen mismatches.⁶

Over 50% of patients who develop aGVHD following allo-HSCT are refractory to first-line treatment with steroids, and up to 75% of patients require additional therapy.^{6,7} Steroid-refractory (SR) aGVHD is associated with greater symptom severity and poorer outcomes.¹² Mortality rates

as high as 90% have been reported in adults and pediatric patients with SR aGVHD, who fail to respond to initial steroid therapy.¹³ While first-line treatment with steroids is well established in clinical guidelines, there is no consensus for the second-line treatment for SR aGVHD in adult and pediatric patient populations.^{7,14-16} Therapies used in the second-line setting vary in clinical practice; while patients may undergo extracorporeal photopheresis or may receive drugs such as antibodies targeting tumor necrosis factor alpha or interleukin-2 receptor, inhibitors of mammalian target of rapamycin, mycophenolate mofetil, or alemtuzumab, their use is supported by limited evidence.^{7,14,15} To date, ruxolitinib is the only treatment approved in the United States for SR aGVHD, which is indicated for patients aged 12 years and older, although the clinical trial included only adults.¹⁷

The economic burden of aGVHD is high. A systematic literature review reported health care costs in the United States ranging from \$114,698 to \$224,000 per year in pediatric patients with aGVHD post-HSCT, which were driven by hospitalizations.^{9,18,19} Compared with allo-HSCT pediatric patients without aGVHD, those who developed aGVHD incurred significantly higher incremental health care costs by approximately US\$200,000 and had a longer inpatient stay by 41.5 days ($P = 0.004$) during the first year after transplant.²⁰ Preliminary data also suggest that health care costs may be substantially higher in pediatric patients with aGVHD who are refractory to first-line treatment with steroids, similar to the trend seen in adults.^{9,21} However, there is limited evidence on the health care costs and resource utilization of aGVHD in this SR pediatric patient population.

Given the lack of economic data available, we conducted a retrospective analysis of medical and pharmacy claims from a US commercial insurance database to evaluate the economic burden of SR aGVHD in pediatric patients.

Methods

Retrospective analyses were conducted using medical and pharmacy claims data from the HealthCore Integrated Research Database (HIRD) from January 1, 2006 to May 31, 2019. Claims for aGVHD were assessed using the *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (ICD-9/10-CM) codes. ICD-9/10-CM, Generic Product Identifier, *Current Procedural Terminology*, and Healthcare Common Procedure Coding System codes were also used for allo-HSCT, autologous stem cell transplant, GVHD, infectious and noninfectious stem cell transplant complications, medications, and total

TABLE 1 Demographic and Clinical Characteristics on Date of allo-HSCT in Commercially Insured Pediatric Patients (<18 Years) with SR aGVHD vs Controls Without GVHD^a

	SR aGVHD n=38	Control (no GVHD) n=184
Female, n (%)	19 (50)	83 (45)
Age at index (years), mean (SD)	8.6 (5.97)	8.20 (5.57)
Age categories (years), n (%)		
0-5	15 (39)	61 (33)
6-11	10 (26)	58 (32)
12-17	13 (34)	65 (35)
Geographic region, n (%)		
Northeast	5 (13)	44 (24)
Midwest	4 (11)	49 (27)
South	16 (42)	46 (25)
West	12 (32)	39 (21)
Unknown	1 (3)	6 (3)

^aDemographic characteristics were assessed on index HSCT procedure claim. aGVHD=acute graft-versus-host disease; HSCT=hematopoietic stem cell transplant; SR=steroid refractory.

parenteral nutrition ([Supplementary Tables 1 to 8](#), available in online article). Revenue codes were used to assess intensive care unit costs and length of stay ([Supplementary Table 9](#), available in online article).

Patients included in this study had at least 1 claim for allo-HSCT (earliest HSCT claim set as index date) in an inpatient setting, no claims for autologous HSCT at any time, and no pre-index GVHD. Patients were aged less than 18 years on the index date and were commercially insured, with no minimum pre- or post-index continuous health plan enrollment. Two patient cohorts were evaluated: those with aGVHD and those without GVHD. The aGVHD cohort included patients with SR aGVHD, defined as those with at least 1 claim for aGVHD over 100 days from the index date and at least 1 claim for any steroid on or after date of first aGVHD claim and at least 1 claim for any second-line therapy ([Supplementary Table 7](#), available in online article) or extracorporeal photopheresis on or after date of the first aGVHD claim.

The comparison cohort included post-HSCT patients without any GVHD claims over their entire available follow-up period. Complications, health care resource utilization (HCRU), and per-patient costs over 12 months from the

index date were calculated based on claims and compared across cohorts. Selected cost data were also reported in a per-patient per-month (PPPM) format. Outcomes were also assessed over 24 months. Costs are presented as the combined amount paid by the health plan and the patient. Patient out-of-pocket costs included all coinsurance, deductible, copayment, or other patient outlays. Costs were adjusted to 2018 US dollars (USD), using the medical care component of the Consumer Price Index provided by the Bureau of Labor Statistics.²² Mortality data from the National Death Index (NDI) were linked to claims for a subset of patients.

STATISTICAL ANALYSIS

Descriptive statistics including means and SDs were reported for continuous variables, and absolute/relative frequencies were reported for categorical variables. At follow-up, categorical outcomes were compared across the 2 cohorts using chi-square or Fisher's exact tests (without adjustment for differential follow-up time). Generalized linear model regressions with gamma distribution and log-link, weighted for follow-up time, were used to compare continuous variables (hospital length of stay and costs). This study took an exploratory approach, and no adjustment for confounding was conducted.

Results

PATIENT POPULATION

A total of 38 pediatric patients who developed SR aGVHD following allo-HSCT and 184 controls without GVHD were included in this study. In 53% of aGVHD patients, medical claims with codes for chronic GVHD were present during follow-up.

Patient demographics on index date were generally similar between the 2 cohorts. The mean age was 8.6 years for patients with SR aGVHD and 8.2 years for controls without GVHD. Across both cohorts, 33%-39% of patients were aged 0-5 years, and approximately half were female (45%-50%; Table 1).

In patients with SR aGVHD, 63% underwent peripheral blood HSCT compared with 45% for controls. Median length of follow-up health plan enrollment was 20.5 months and 14.9 months for SR aGVHD patients and controls, respectively. Of the SR aGVHD patients, 25 (66%) had an enrollment time of at least 12 months, and 15 (39%) had an enrollment time of at least 24 months. Of the control group, 101 (55%) had an enrollment time of at least 12 months, and 61 (33%) had an enrollment time of at least 24 months. Approximately 40% of patients (n=16 SR aGVHD, n=64

TABLE 2 Post-HSCT Complications Over 12 Months in Pediatric Patients (<18 Years) with SR aGVHD vs Controls Without GVHD

	SR aGVHD n=38	Control (no GVHD) n=184	P value ^a
Anemia total, n (%)	30 (79)	126 (68)	0.925
Drug induced ^b	20 (53)	62 (34)	0.028
Nondrug induced	24 (63)	112 (61)	0.792
Neutropenia total, n (%)	24 (63)	97 (53)	0.239
Drug induced ^b	5 (13)	13 (7)	0.203
Nondrug induced	23 (61)	95 (52)	0.317
Thrombocytopenia total, n (%)	22 (58)	77 (42)	0.070
Liver diseases, n (%)	6 (16)	31 (17)	0.873
GI diseases, n (%)	36 (95)	119 (65)	<0.001
Infections, n (%)	36 (95)	146 (79)	0.025

^aChi-square test or Fisher test.

^bBased on ICD-9/10-CM coding. Real-world physician behavior may deviate in some cases, so misclassification is possible.

aGVHD=acute graft-versus-host disease; GI=gastrointestinal; HSCT=hematopoietic stem cell transplant; ICD-9/10-CM=International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification; SR=steroid refractory.

controls) were eligible for mortality linking to the NDI. Over 12 months, all-cause death was observed for 25% of SR aGVHD patients and 30% of controls. Over 24 months, all-cause death reached 38% for SR aGVHD and 33% for controls.

Patients with SR aGVHD had higher complication rates than controls over the 12-month follow-up period. Significantly higher rates were seen for drug-induced anemia (53% vs 34%; $P<0.05$), GI manifestations (95% vs 65%; $P<0.001$), and infection (95% vs 79%; $P<0.05$; Table 2).

Similar clinical characteristics and complication rates were observed after 24 months follow-up in both cohorts.

HEALTH CARE RESOURCE UTILIZATION

Length of stay for the inpatient episode surrounding allo-HSCT was approximately 60 vs 50 days for SR aGVHD patients vs controls, and readmissions over 12 months after discharge occurred significantly more frequently in the aGVHD cohort (89% vs 60%; $P<0.001$). Across all hospitalizations, a similar proportion of patients in both cohorts (45%-46%) stayed in the intensive care unit. Patients with SR aGVHD had a numerically longer mean length of stay in intensive care than controls by 16.2 days over 12 months

(36.5 vs 20.3 days) and significantly longer overall hospital length of stay of 31.6 days (96.0 vs 64.3 days; $P<0.001$).

Likewise, emergency room (ER) and outpatient visits occurred more frequently in the SR aGVHD cohort (34% vs 24% and 100% vs 86%, respectively; no statistical significance testing was conducted).

Outpatient parenteral nutrition (39% vs 20%; $P<0.01$) occurred more frequently in SR aGVHD patients compared with controls.

Within the SR aGVHD cohort, 95% required second-line treatment over 12 months. Biologic and branded small molecule therapies (etanercept, infliximab, rituximab, ruxolitinib, and tocilizumab) were used by 21% of patients as second-line options, and 87% used traditional immunosuppressants, including methotrexate and everolimus.

Similar HCRU and patterns of medication use were observed over the 24-month follow-up period.

DIRECT MEDICAL COSTS

Mean total 12-month direct medical costs (including the transplant) incurred by patients with SR aGVHD were nearly twice as high compared with controls (\$1,212,944 vs \$673,491, USD 2018; $P<0.001$; [Supplementary Figure 1](#), available in online article), equating to an incremental difference of over \$500,000. Inpatient costs accounted for the vast majority of these costs: \$1.02 million vs \$576,581 ($P<0.001$), followed by outpatient and emergency costs. The total direct medical costs were largely driven by costs associated with complications, which remained significantly higher in patients with SR aGVHD (\$868,966 vs \$396,757; $P<0.001$). PPPM medical costs were also significantly higher by \$38,130 ($P<0.01$).

Of the HSCT-related complications, SR aGVHD patients incurred significantly higher health care costs than controls relating to anemia, neutropenia, thrombocytopenia, and infection, as shown in Table 3 ($P<0.05$ for all comparisons).

Mean costs for ER visits were approximately twice as high in patients with SR aGVHD than controls (\$1,979 vs \$826; $P=0.033$), as were the majority of outpatient management costs, except for durable medical equipment costs, which were higher in the control cohort ($P<0.05$ for all; Figure 1). Medication costs were not significantly different between the 2 cohorts over either the 12- or 24-month follow-up period (approximately \$8,900 per patient in each cohort over 12 months).

Total medical costs and costs for outpatient management, ER visits, and HSCT-related complications remained significantly higher in SR aGVHD patients than controls over the 24-month follow-up period ($P<0.05$ for all comparisons; [Supplementary Table 10](#), available in online article).

TABLE 3 Post-HSCT Complication Costs Over 12 Months in Pediatric Patients (<18 Years) with SR aGVHD vs Controls Without GVHD (USD, 2018 Cost Year)

	SR aGVHD n=38	Control (no GVHD) n=184	P value
	Mean	Mean	
All complications	\$868,966	\$396,757	<0.001
Anemia total	\$411,470	\$142,913	<0.001
Drug induced	\$176,753	\$44,818	<0.001
Nondrug induced	\$250,433	\$106,338	0.006
Neutropenia total	\$171,799	\$58,886	0.002
Drug induced	\$30,014	\$10,314	0.175
Nondrug induced	\$141,815	\$48,579	0.006
Thrombocytopenia total	\$97,106	\$36,221	0.011
Liver diseases	\$26,904	\$37,311	0.780
GI diseases	\$86,483	\$48,425	0.130
Infections	\$542,286	\$202,125	<0.001

Note: Complication cost categories are not mutually exclusive. Differences in mean costs were modeled using a generalized linear model with gamma distribution and log-link, weighted for follow-up time.

aGVHD=acute graft-versus-host disease; HSCT=hematopoietic stem cell transplant; SR=steroid refractory; USD=US dollars.

Among patients with SR aGVHD, mean total costs were higher by about \$1.8 million for those who died compared with those who were alive within 12 months (Figure 2). Among the control cohort without GVHD, mean total costs were also higher for patients who died, with a difference of about \$298,000. Mean total costs were significantly higher for the SR aGVHD cohort vs the control cohort among the subgroup that died ($P=0.002$) and among those who survived for 1 year ($P=0.014$).

Discussion

aGVHD in pediatric patients is a serious and life-threatening complication of allo-HSCT that often occurs within 100 days of transplantation.^{4,8} It is associated with substantial morbidity, decreased quality of life, and increased risk of mortality.^{6,8,9} Over half of patients with aGVHD do not respond to first-line treatment with steroids, yet there is no consensus on the second-line treatment of SR aGVHD.^{6,7,14-16} Furthermore, the economic burden of aGVHD is high, yet there is little evidence of the economic impact of SR aGVHD on pediatric patients. A single-cohort retrospective

study evaluated costs and HCRU among pediatric patients with aGVHD and found increased inpatient days and costs for patients with SR aGVHD relative to those with steroid-responsive aGVHD.²⁰ We believe that our retrospective study of commercially insured US patients aged less than 18 years with SR aGVHD is the first to assess economic burden and HCRU in the pediatric SR aGVHD population across multiple treatment centers.

Our findings showed that pediatric patients with SR aGVHD incurred significantly higher HCRU and direct medical costs within the 12 months following allo-HSCT than controls who had no claims for GVHD. These results are consistent with recent findings on economic burden and HCRU among adult US patients with GVHD, which analyzed a cohort of patients with SR/high risk GVHD and found significantly longer median lengths of stay, higher median total costs, higher readmission rates, and higher inpatient mortality vs patients who underwent transplant but did not develop GVHD.²¹ Similarly, a retrospective review of adult patients in the United Kingdom found that patients with severe (grade 3/4) GVHD had higher readmission rates, mean number of inpatient days, and total cost of treatment relative to those with grade 1/2 GVHD. Overall, patients with GVHD had higher HCRU and costs than those without GVHD.²³

Hematologic, GI, and infectious complications occurred more frequently in patients with SR aGVHD than controls (Table 2). Correspondingly, SR aGVHD patients had higher HCRU, hospital readmission rates (89% vs 60%; $P<0.001$), outpatient parenteral nutrition rates (39% vs 20%; $P<0.01$), and longer inpatient stay (by 31.6 days) compared with controls.

Of the SR aGVHD cohort, nearly all patients (95%) escalated to second-line therapy with traditional immunosuppressants or biologics. A number of biologics were used in the second line (Supplementary Table 7, available in online article), and the variation in their use in clinical practice seen in this study underscores the lack of consensus on the second-line treatment of SR aGVHD.^{7,14-16}

During the 12 months after HSCT, total direct medical costs for patients with SR aGVHD were significantly higher and nearly double that of controls (\$1,212,944 vs \$673,491; $P<0.001$). Medical costs for SR aGVHD were driven by post-HSCT complications, which accounted for \$868,966 of costs. When assessed by complication type, significantly higher costs were seen for anemia and infection (Table 3), which reflects the higher rate of these complications reported in SR aGVHD patients and may result from current second-line agents used. The rate of complications, HCRU, and medical costs seen over 24 months were consistent with those observed over 12 months.

FIGURE 1 Outpatient Costs Over 12 Months After HSCT in Pediatric Patients (<18 Years) with SR aGVHD vs Controls Without GVHD (USD, 2018 Cost Year)

Note: Differences in mean costs were modeled using a generalized linear model with gamma distribution and log-link, weighted for follow-up time.

^aP < 0.05.

^bP < 0.01.

aGVHD=acute graft-versus-host disease; HSCT=hematopoietic stem cell transplant; OV=office visits; PT/OT/ST=physical therapy/occupational therapy/speech therapy; SR=steroid refractory; USD=US dollars.

This study also found that costs are very high for patients with a poor outcome in SR aGVHD. Within 12 months of transplant, the costs incurred by patients with SR aGVHD who ultimately died were substantially higher (mean cost difference ~\$1.8 million, $P=0.014$) than for those who survived. This difference was far less pronounced among the control cohort, in which a mortality outcome was associated with a mean total cost of about \$298,000 more than for those who survived.

LIMITATIONS

This study is subject to several limitations. First, we are not aware of validated algorithms to identify steroid-refractory aGVHD patients in claims. Our study definition is consistent with clinical literature; however, we did not conduct validation. Second, our analyses were strictly exploratory; for example, the presence of confounding by baseline characteristics was not examined. Third, data were derived from medical and pharmacy claims, which may have contained undetected coding errors. Moreover, all patients included in the study were enrolled in US commercial health insurance plans and satisfied all the inclusion/exclusion criteria. The results may not be generalizable to patients not selected, with other types of health insurance or who are uninsured, or to those outside the United States.

Another limitation of this work is that the comparator cohort was composed of patients who underwent HSCT and did not have any GVHD claims, rather than patients with steroid-responsive aGVHD. However, given that steroid responsiveness is generally established within 1 week of treatment and based on the relatively low cost of steroids, the cost burden of steroid-responsive aGVHD is likely to be only modestly higher than that of patients undergoing HSCT who do not develop GVHD. Some patients may have prolonged steroid treatment for mild to moderate symptoms of aGVHD, but this treatment is not likely to incur substantial additional costs. Thus, our reported cost difference between the cohorts of patients with SR aGVHD and no GVHD is likely to represent the upper range of the actual cost difference between patients with steroid-responsive and SR aGVHD. Because this was an exploratory study, future research could focus on developing an algorithm to identify steroid-responsive patients.

Conclusions

Our study indicates that within 1 year after HSCT, pediatric patients who develop SR aGVHD incur over half a million dollars in medical costs beyond costs incurred by those

FIGURE 2 Mean Total Per-Patient Medical Costs for Patients With or Without All-Cause Mortality Within 12 Months

aGVHD=acute graft-versus-host disease; SR=steroid refractory.

who do not develop GVHD, a difference largely driven by complications. Likewise, complication rates after HSCT and HCRU are higher in patients with SR aGVHD. These findings help to explain the high economic burden of pediatric patients with SR aGVHD and will help researchers to assess the value of novel therapeutic options for pediatric aGVHD.

DISCLOSURES

This research was sponsored by Mesoblast, Inc. Grabner is an employee of HealthCore, Inc., which acted as consultants to Mesoblast, Inc., during the conduct of this research. Strati is an employee of Mesoblast, Inc. Sandman and Forsythe are employees of Purple Squirrel Economics, which acted as consultants to Mesoblast, Inc., during the conduct of this research.

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