Exploring the Healthcare Resource Utilization (HCRU) Associated with Rare Diseases (RD) in the United States (US): A Systematic Literature Review (SLR) across Six Disease Areas

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Introduction and Objective

- RD is defined by the Orphan Drug Act as a condition that affects less than 200,000 people in the US[1]. While RD individually have a low prevalence, the large number of RD being diagnosed means more than 30 million Americans are affected in total[1].
- RD tend to be complex, and the multifaceted care required often results in a heavy burden on HCRU and costs. Since each RD is associated with distinct manifestations, symptoms, and treatment approaches there are likely to be different cost drivers for HCRU within each disease.
- Therefore, this study aimed to explore the burden of and drivers for HCRU in six different RD in the US: Huntington's disease (HD), dystrophic epidermolysis bullosa (DEB), hereditary angioedema (HAE), transthyretin amyloidosis (ATTR), Stargardt disease (SD), and alpha-1 antitrypsin deficiency (A1AT).

Methods

- A broad SLR was conducted in Embase in March 2023 to evaluate the direct and indirect costs associated with the six RD.
- Studies of interest were full text papers published 2008-2023 or conference proceedings published 2020-2023 presenting data on HCRU or disease-related direct or indirect costs. This sub-analysis was focused on data relating to HCRU in the US.
- Studies were screened by two reviewers and reconciled by a third. Data was extracted by a single reviewer, with data number-checked by a second reviewer.
- The SLR yielded 54 papers with data on HCRU in the US. Full citations of all papers are included in the supplementary document.

Embase hits: 1,238
(HD: 238, DEB: 63, HAE: 622, ATTR: 128, SD: 16; A1AT: 171)

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Included economic studies: 189
(HD: 62, DEB: 13, HAE: 55, ATTR: 25, SD: 3, A1AT: 31)

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HCRU studies: 54
(HD: 17, DEB: 2, HAE: 10, ATTR: 8, SD: 1, A1AT: 16)

Results

Overall healthcare costs

- Annual healthcare costs were highest in HAE ($363,795)[2], A1AT (up to $167,935)[3], and ATTR ($64,066)[4] (Table 1).
- For A1AT, annual healthcare costs were between $122,936[5] and $167,935[3] in patients receiving augmentation therapy, and $14,185[5] in patients not receiving augmentation therapy.
- For HD, lower annual costs were reported in one study with late-onset HD[11] and a study that looked specifically at healthcare costs in Medicaid beneficiaries with HD in the year prior to their death (end-of-life costs)[10].

Table 1: Mean annual healthcare costs by RD (USD$)

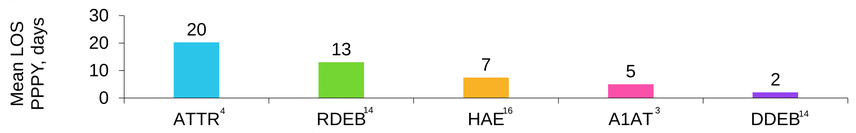
RD	Annual healthcare costs ($)
HAE[2]	363,795
A1AT[3,5,6]	14,185 - 167,935
ATTR[4]	64,066
HD[7-12]	27,120 - 41,631
DEB overall[13]	32,352
DDEB[14]	31,836
RDEB[14]	29,995

Note: Costs reported by month have been multiplied by 12 to give an annual cost. **Abbreviations:** DDEB: dominant dystrophic epidermolysis bullosa; RDEB: recessive dystrophic epidermolysis bullosa; RD: rare disease; USD: United States dollar

Inpatient visits

- The percentage of patients with at least one inpatient visit over a 12-month period varied across diseases, from 6% in DDEB[14] to 33% in RDEB[14] (HAE: 7.8%[15]-12.8%[16], ATTR: 24.9%[4], HD: 26.8%[17], A1AT: not reported).
- The mean length of stay for inpatient visits per year varied from 2 days (DDEB)[14] to 20 days (ATTR)[4] (Figure 1) .
- Annual costs per patient of inpatient visits were highest in HAE at $80,464[2] and lowest in A1AT at $4,912[5] (HD: $5,762-$12,235[7-9,12], ATTR: $34,461[4], DEB: not reported).

Figure 1: Mean LOS per RD for patients with an inpatient visit, PPPY

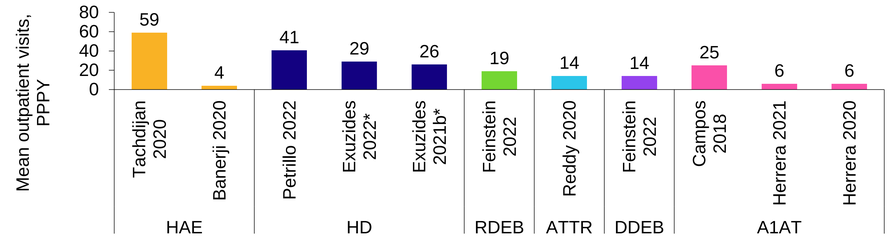


Abbreviations: RD: rare disease; LOS: length of stay; PPPY: per patient per year

Outpatient visits

- The highest mean number of outpatient visits PPPY was reported in one study involving patients with HAE (59 visits PPPY [all-cause])[18] (Figure 2).
- The percentage of patients with at least one outpatient visit over a 12-month period varied across the disease areas from 27% (4 visits PPPY) in HAE[16] to 98% in RDEB[14] and 100% in DDEB[14] (not reported for other RD).
- Annual outpatient costs per patient were highest in ATTR ($23,853)[4] and lower in HD ($10,213-$15,456[7-9,11,12]). Lower costs were reported in A1AT where only physician visits were included in costs ($5,969[5]). Outpatient costs were not reported for the other RD.

Figure 2: Mean number of annual outpatient visits by RD, PPPY

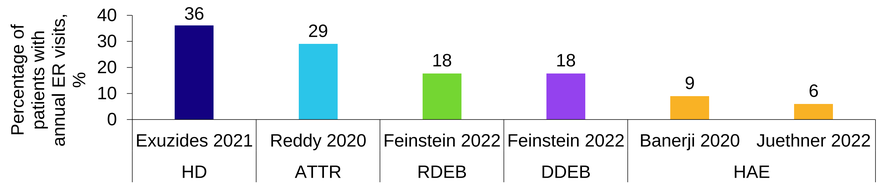


Note: ***Reported per month and multiplied by 12 to estimate yearly values. Banerji 2020 recorded visits to the GP, internist, or family or primary care physician only. **Abbreviations: GP: general practitioner; RD: rare disease; PPPY: per patient per year

Emergency Room (ER) visits

- The percentage of patients visiting the ER at least once over a 12-month period ranged from 6%-9% (HAE)[4] to 36% (HD)[7] (Figure 3).
- Annual costs per patient associated with visiting the ER were highest in HAE ($45,499)[2] and lowest in HD ($1,141)[9] (A1AT: $7,776[5], not reported for other RD).

Figure 3: Percentage of patients with annual ER visits by RD



Abbreviations: ER: Emergency room; PPPY: per patient per year

Conclusions

- Patients with RD incur considerable HCRU due to a variety of different cost drivers. For both ATTR and HAE inpatient visits were a key driver of HCRU burden, with ER visits due to HAE attack being extremely costly to treat. In contrast, for A1AT total costs varied more based on if a patient received augmentation therapy, with much lower costs required for inpatient care.
- Although some RD reported lower total costs, they were often still associated with significant HCRU. For example, HD presented substantial burden in terms of number of outpatient and ER visits each year, indicating high use of healthcare resources. Similarly, RDEB was associated with a high need for lengthy inpatient treatment in a third of patients, with almost all patients with RDEB and DDEB requiring annual outpatient visits and in some cases ER visits.
- Only one paper presented data for SD, which was not comparable to other studies identified, indicating that important research gaps still exist in understanding the economic burden of RD.
- Overall, future treatments addressing the unique drivers of HCRU in each RD are needed to generate improvements in allocation of healthcare system resources.

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