



# **Heller myotomy is the optimal index procedure for esophageal achalasia in adolescents and young adults**

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## **Abstract**

**Background** There is limited and conflicting data on the optimal intervention for the treatment of achalasia in adolescents and young adults (AYA), Heller myotomy (HM), esophageal dilation (ED) or botulinum toxin injection (botox). The goal of this study is to determine the most appropriate index intervention for achalasia in the AYA population.

**Methods** We completed a longitudinal, population-based analysis of the California (2005–2010) and New York (1999–2014) statewide databases. We included patients 9–25 years old with achalasia who underwent HM, ED or botox. Comparisons were made based on the patients' index procedure. Rates of 30-day complications, long-term complications, and re-intervention up to 14 years were calculated. Cox regression was performed to determine the risk of re-intervention, adjusting for patient demographics.

**Results** A total of 442 AYAs were analyzed, representing the largest cohort of young patients with this disease studied to date. Median follow-up was 5.2 years (IQR 1.8–8.0). The overall rate of re-intervention was 29.3%. Rates of re-intervention for ED and botox were equivalent and higher than HM ( $65.0\%$  for ED,  $47.4\%$  for botox and  $16.4\%$  for HM,  $p < 0.001$ ). Ultimately, 46.9% of ED and botox patients underwent HM. The overall short-term complication rate was 4.3% and long-term, 1.9%. There was no difference in the short-term and long-term complication rates between intervention groups  $(p > 0.05)$ . On adjusted analysis, ED and botox were associated with increased risks of re-intervention when compared to HM (HR 5.9, HR 4.8, respectively,  $p < 0.01$ ). Black patients were found to have a risk of re-intervention twice that of white patients (HR 2.0,  $p = 0.05$ ).

**Conclusions** HM has a similar risk of complications but a significantly lower risk of re-intervention when compared to ED and botox. Based on our findings, we recommend HM as the optimal index procedure for AYAs with achalasia.

**Keywords** Adolescents and young adults · Achalasia · Long-term re-intervention rates · Complication rates

Achalasia is an idiopathic disease of esophageal motility that remains rare in adolescents and young adults (AYA). The incidence rate ranges between 0.1–1.8/100,000 children/

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year [\[1](#page-5-0)[–3](#page-5-1)], with 0.25/100,000 children hospitalized annually [[4\]](#page-5-2). The most common symptoms of achalasia are regurgitation and dysphagia [[5\]](#page-5-3). Almost all AYA patients with achalasia will eventually undergo either Heller myotomy (HM), esophageal dilation (ED) or botulinum toxin injection (botox)  $[2, 6-8]$  $[2, 6-8]$  $[2, 6-8]$  $[2, 6-8]$ .

The limited available literature suggests that HM is superior to ED and botox for the treatment of achalasia in AYAs [[7,](#page-5-7) [9–](#page-5-8)[11](#page-5-9)]. However, these studies are single-institutional with small sample sizes thus making their generalizability unclear. Indeed, a systematic review of the literature on this topic covering the last 30 years included only 164 patients less than 20 years old and showed mixed conclusions, with one favoring ED, two favoring HM, and four reporting inconclusive findings [\[9](#page-5-8)]. Two recently published population-based studies suggest that fewer re-interventions

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are required after HM than ED or botox in adults, however AYAs were excluded from both studies [[12,](#page-5-10) [13\]](#page-5-11). A large randomized controlled trial focusing on therapeutic success using Eckardt and quality of life scores showed equivalent therapeutic success with HM and ED, but this paper also excluded AYA patients [\[14](#page-5-12)]. Additionally, systematic reviews in the adult literature also have reached conflicting conclusions regarding optimal treatment for achalasia [\[15](#page-5-13)[–17](#page-5-14)]. Given the paucity of data in AYAs, and conflicting data in adults, it remains unclear if there is a superior index treatment for achalasia in AYAs.

The goal of this study was to determine the most appropriate index intervention for achalasia in AYAs at a population level. We assessed the re-intervention rates and both short-term and long-term complications rates after Heller myotomy, esophageal dilation, or botox injection.

## **Materials and methods**

A retrospective longitudinal analysis was performed using the California Office of Statewide Health Planning and Development (OSHPD) database from 2005 to 2010 and the New York Statewide Planning and Research Cooperative System (SPARCS) from 1999 to 2014. OSHPD and SPARCS contain all inpatient admissions and outpatient procedures performed in public and private hospitals in the state of California (*n*=70) and New York (*n*=66), excluding US military and Veterans Affairs hospitals. Both inpatient admissions and outpatient procedures were queried. In both databases, all patient data were de-identified with a unique record linkage ID that allows patients to be tracked longitudinally through time and in all in-state hospitals.

The inclusion criteria were patients between age 9 and 25 with a diagnosis of achalasia who underwent HM, ED or botox. To ensure that the index procedure we identified was the first that the patient received, we included a run-in period of at least one year. This method ensures that the patient has not undergone any procedure within one year prior to our index intervention. We excluded patients who had an esophagectomy or esophageal cancer prior to the index procedure.

Achalasia was defined by International Classification of Procedures, Ninth Revision, Clinical Modification (ICD-9) diagnosis code 530.0. HM included ICD-9 procedural codes of esophagomyotomy (42.7) and Current Procedural Terminology (CPT) codes 43330, 43279, 43331, 32665 and S2079. ED included ICD-9 procedural code 42.92 and CPT codes 43220, 43226, 43458, 43453, and 43233. Botox was defined by ICD procedural code 99.29 and CPT code 43236.

Re-intervention for recurrent symptoms of achalasia was defined as a second HM (with or without fundoplication), ED, botox or fundoplication after the index operation.

Fundoplication was defined as a fundoplication without a concurrent HM and included ICD-9 codes 44.66 and 44.67, and CPT codes 43280 and 43327. All subsequent HM, ED or botox were considered re-interventions despite the understanding that some may be part of a planned series of treatments [[14](#page-5-12)]. We included both planned or unplanned treatment because either reasons contributes to the morbidity experienced by AYAs with achalasia and thus is not clinically insignificant.

Short-term, 30 day post-operative complications, were captured for the index intervention only and included operative repair for surgical complications, intraoperative iatrogenic injury, infection, wound complication (including nonhealing wound), hemorrhage and esophagectomy. Long-term complications included operative repair for surgical complications and esophagectomy between 30-days and up to 14 years after the index procedure.

Operative repair for surgical complications was defined by the following ICD-9 codes: insertion of permanent tube into esophagus (42.81), suture of laceration of esophagus (42.82), closure of esophagostomy (42.83), repair of esophageal fistula, not elsewhere classified (42.84), repair of esophageal stricture (42.85), production of subcutaneous tunnel without esophageal anastomosis (42.86), other graft of esophagus (42.87), and other repair of esophagus (42.89). Intraoperative iatrogenic injury included ICD-9 diagnosis codes of accidental puncture or laceration during a procedure (998.2). Infection was defined by the following ICD-9 diagnosis codes: infected postoperative seroma (998.51), other postoperative infection (998.59), mediastinitis (519.2), empyema with fistula (510.0), empyema without fistula (510.9). Wound complications included ICD-9 diagnosis codes of, disruption of wound, unspecified (998.30), disruption of internal operation (surgical) wound (998.31), disruption of external operation (surgical) wound (998.32), non-healing surgical wound (998.83), and seroma complicating a procedure (998.13). Hemorrhage included ICD-9 diagnosis codes of hemorrhage complicating a procedure (998.11), hematoma complicating a procedure (998.12) and ICD-9 procedural codes of suture of unspecified blood vessel (39.30), suture of artery (39.31), suture of vein (39.32), and hemorrhage control (39.98). Esophagectomy was defined by ICD-9 codes 42.40, 42.41, 42.42, 42.51, 42.52, 42.53, 43.54, 42.55, 42.56, 42.58, 42.59, 42.61, 42.62, 42.63, 42.64, 42.65, 42.66, 42.68, and 42.69.

Re-intervention and complication rates were calculated using the Kaplan Meier failure function. Unadjusted analysis included Student's *t* test, Chi square test and log-rank test. Adjusted analysis was performed using Cox proportional hazards regression to predict risk of re-intervention, adjusting for index intervention, age, race, operative setting and insurance types. Statistical analysis was performed with Stata SE statistical software, version 13.1 (StataCorp LP,

College Station, TX). IRB approval was granted from the state of California (IRB identifying number: 16-05-2558) and from the state of New York (IRB identifying number: 2017P001211).

# **Results**

We identified a total of 442 AYAs with achalasia who had surgical interventions. Approximately three-fourths of the index procedures were HM (75.8%) with one-fifth of patients undergoing ED (18.3%), and far fewer undergoing botox (5.9%). The average age at index intervention was 19.1  $(\pm 4.3)$  years old (Table [1](#page-2-0)).

On unadjusted comparison, there was no difference in age or gender between intervention groups  $(p > 0.05)$ . However, there was a significant difference in the index intervention between races. Black patients underwent HM less frequently  $(60.4\%)$  when compared to other races ( $p < 0.01$ ). In addition, compared to patients with private insurance, patients with Medicaid or who were self-pay had HM less frequently (67.6% for Medicaid, 60.7% for Self-pay versus 80.5% for private insurance;  $p < 0.01$ ) (Table [2](#page-2-1)).

The median follow-up time was 5.2 years (IQR 1.8–8.0). Overall re-intervention rate was 29.3%. The re-intervention rates for ED and botox were similar  $(p=0.43)$  but significantly higher than HM  $(p < 0.001)$  $(p < 0.001)$  $(p < 0.001)$  (Fig. 1). The rate of repeat ED within 6 months was 13.9%.

The overall unadjusted 30-day complication rate was 4.3%, (HM 4.5%, ED 3.7%, and botox 3.9%) and there was no difference in the 30-day complication rates between index

<span id="page-2-0"></span>**Table 1** Demographics of the study population

Variables	Mean $(SD)$ or N $(\%)$ (n=442)
Index procedure	
HM	335 (75.8%)
ED	81 (18.3%)
<b>Botox</b>	$26(5.9\%)$
Age	19.1 $(\pm 4.3)$
Female	241 (54.5%)
Race	
White	$165(44.1\%)$
<b>Black</b>	48 (12.8%)
Hispanic	71 (19.0%)
Asian	$9(2.4\%)$
Other	81 (21.7%)
Insurance	
Private	302 (68.6%)
Medicaid	$108(24.6\%)$
Self-pay	28 (6.4%)

<span id="page-2-1"></span>**Table 2** Unadjusted analysis of the dataset

Variables	HM $(n=335)$	$ED (n = 81)$	Botox $(n=26)$	<i>p</i> Value
Age	19.5 $(\pm 4.2)$	17.2 $(\pm 4.4)$	19.9 $(\pm 4.0)$	0.77
Female	181 (54.0%)	47(58.0%)	13 (50.0%)	0.72
Race				
White	142 (86.1%)	19 (11.5%)	$4(2.4\%)$	0.002
<b>Black</b>	29 (60.4%)	14 (29.2%)	$5(10.4\%)$	
Hispanic	51 (67.1%)	14 (19.7%)	6(8.5%)	
Asian	$9(100\%)$	$0(0\%)$	$0(0\%)$	
Other	59 (72.8%)	20 (24.7%)	$2(2.5\%)$	
Insurance				
Private	243 (80.5%)	46 (15.2%)	13 (4.3%)	0.004
Medicaid	73 (67.6%)	25(23.2%)	$10(9.3\%)$	
Self-pay	17(60.7%)	$9(32.1\%)$	$2(7.1\%)$	

procedures  $(p=0.95)$ . The most common complications were operative repair of surgical complications (2.7%), followed by iatrogenic injuries (2.3%). The long-term complication rate was 1.9% with 1.3% of patients requiring operative repair of surgical complications and two patients (0.6%) ultimately undergoing esophagectomy. Similar to short term complication rates, there is no difference in the long-term complication rates between index procedures  $(p=0.64)$ (Table [3](#page-3-0)). Notably, the complication rate of Botox may be elevated because of its small sample size (*n*=26). The 3.9% complication rate of Botox represents one patient who developed a short-term complication, and similarly one who developed a long-term complication (these complications occurred in two different patients).

On adjusted analysis, ED and botox had a higher risk of re-intervention when compared to HM (HR 5.9, HR 4.8, respectively,  $p < 0.01$ ). In addition, the risk of re-intervention in black patients was two times that of white patients, even after adjusting for index intervention, age, operative settings and insurance types (OR 2.0,  $p = 0.05$ ) (Table [4](#page-4-0)).



<span id="page-2-2"></span>**Fig. 1** Overall re-intervention rate

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<span id="page-3-0"></span>**Table 3** Rates of re-interventions and complications at 14 years

14 years follow up	All $(n=442)$		HM $(n=335)$		$ED (n = 81)$		Botox $(n=26)$		$p$ Value
	Kaplan Meier 95 CI		Kaplan Meier 95 CI		Kaplan Meier 95 CI		Kaplan Meier 95 CI		
Overall re-intervention rate	29.3%	23.5–36.3 16.4%		11.8-22.6 65.0%		44.3-84.8 47.4%		$30.1 - 68.3$	< 0.01
Median follow-up time $(year)^a$	5.2	$1.8 - 8.0^{\rm a}$	5.5	$2.3 - 8.1$ <sup>a</sup>	1.9	$0.4 - 6.6^a$	3.6	$0.8 - 8.4^a$	
Re-intervention type									
HM	9.2%	$5.4 - 15.5$	4.0%	$2.2 - 7.1$	23.0%	10.4–46.3 23.9%		$11.5 - 45.6$	
Fundoplication	1.3%	$0.5 - 3.0$	0.7%	$0.2 - 2.7$	2.6%	$0.7 - 10.0$	3.9%	$0.6 - 24.3$	
ED	7.4%	$5.2 - 10.6$	3.4%	$1.7 - 6.6$	23.4%	15.4-34.5 8.9%		$2.3 - 31.6$	
<b>Botox</b>	11.9%	$8.2 - 17.0$	8.6%	$5.2 - 14.1$	20.4%	11.1-35.7 20.7%		$9.1 - 43.1$	
Complication rates									0.95
30-day complication rates <sup>b</sup>	4.3%	$2.8 - 6.7$	4.5%	$2.7 - 7.3$	3.7%	$1.2 - 11.0$	$3.9\%$ <sup>d</sup>	$0.6 - 24.3$	
Infection	0.9%	$0.3 - 2.4$	$0.9\%$	$0.3 - 2.8$	1.2%	$0.2 - 8.4$	$0.0\%$	NA.	
Iatrogenic	2.3%	$1.2 - 4.2$	3.0%	$1.6 - 5.5$	$0.0\%$	<b>NA</b>	$0.0\%$	<b>NA</b>	
Wound complication	0.0%	<b>NA</b>	0.0%	<b>NA</b>	0.0%	<b>NA</b>	$0.0\%$	<b>NA</b>	
Hemorrhage	0.2%	$0.03 - 1.6$	0.3%	$0.04 - 2.1$	$0.0\%$	<b>NA</b>	$0.0\%$	<b>NA</b>	
Esophagectomy	0.0%	<b>NA</b>	0.0%	<b>NA</b>	0.0%	<b>NA</b>	$0.0\%$	NA	
Operative repair of sur- gical complications	2.7%	$1.6 - 4.7$	3.0%	$1.6 - 5.5$	1.2%	$0.2 - 8.4$	3.9%	$0.6 - 24.3$	0.64
Long-term complication rates <sup>b</sup>	1.9%	$0.9 - 3.9$	1.9%	$0.8 - 4.5$	1.2%	$0.2 - 8.4$	3.9%	$0.6 - 24.3$	
Esophagectomy	0.6%	$0.1 - 2.2$	0.4%	$0.1 - 3.1$	1.2%	$0.2 - 8.4$	$0.0\%$	<b>NA</b>	
Operative repair of sur- gical complications	1.3%	$0.5 - 3.1$	1.1%	$0.4 - 3.5$	1.2%	$0.2 - 8.4$	3.9%	$0.6 - 24.3$	

a Interquartile range

<sup>b</sup>Some patients may have more than one complication

c 13.9% within 6 months

<sup>d</sup>One patient developed a short-term complication and a different patient developed a long-term complication

## **Discussion**

This study reports a large, multi-institutional population review of re-intervention rates and complication rates in AYA patients with achalasia. The overall re-intervention rate was 29.3%. Overall short-term and long-term complication rates were low (4.3% and 1.9% respectively) and no difference was found in the short-term and long-term complication rates between different index interventions (all  $p > 0.05$ ). The high rates of patients requiring HM after ED (23.0%) and botox (23.9%) suggest that the longevity of therapeutic success for ED and botox is limited. This study shows that the risk–benefit ratio of HM is superior to ED and botox, and thus should be recommended as the index procedure for AYA patients with achalasia.

In this study, HM was found to have the lowest reintervention rate. Our findings are consistent with prior literature in both adults and children [[2](#page-5-4), [7,](#page-5-7) [12,](#page-5-10) [13,](#page-5-11) [15,](#page-5-13) [17](#page-5-14), [18](#page-5-15)], and similar to a large systematic review of pediatric HM (16.4% vs. 15%) [[19](#page-5-16)]. In the calculation of re-intervention rate for ED, some clinicians may argue that planned sequential ED should not be counted as re-interventions. However, we argue that sequential ED repeatedly exposes patients to the morbidity of anesthetic exposures and invasive procedures whether the procedure is planned or unplanned. Notwithstanding, if all dilations occurring within 6 months of the index procedure are excluded, the overall rate of re-intervention for ED remains higher than that of HM (51.1% vs. 16.4%). In addition, anecdotal observations have suggested that botox may increase the technical difficulty of subsequent HM, despite conflicting results in the literature [[20](#page-5-17)–[23\]](#page-5-18). However, given the poor performance and high complications rates of botox seen in this cohort, physicians should only consider botox for AYA patients that have strong medical contraindications to HM. The rates of severe complications, such as esophageal perforation or esophagectomy, were extremely low in our study and in the literature [[12](#page-5-10), [14\]](#page-5-12). Overall, our complication rates may be more representative of the AYA population when compared to the current literature given our

<span id="page-4-0"></span>**Table 4** Adjusted analysis: re-intervention risk in adolescents and young adults

	Hazard ratio	95% CI		<i>p</i> Value	
Index procedure (ref: HM)					
ED	5.94	3.54	9.94	< 0.01	
<b>Botox</b>	4.78	2.12	10.79	< 0.01	
Age group (ref: $21-25$ )					
$9 - 11$	0.94	0.42	2.09	0.88	
$12 - 14$	0.63	0.30	1.30	0.21	
$15 - 17$	1.01	0.54	1.91	0.97	
$18 - 21$	0.69	0.34	1.40	0.31	
Female (ref: male)	1.41	0.88	2.23	0.15	
Race (ref: white)					
<b>Black</b>	1.95	1.00	3.81	0.05	
Hispanic	1.58	0.83	3.01	0.16	
Asian	NA				
Other	1.50	0.79	2.86	0.22	
Insurance (ref: private)					
Medicaid	0.86	0.51	1.45	0.57	
Self-pay	0.41	0.13	1.27	0.12	

large sample size, multi-institutional data and long-term follow up [[2,](#page-5-4) [7](#page-5-7)–[9,](#page-5-8) [24](#page-5-19)–[27\]](#page-5-20).

Interestingly, we found that both the black and Medicaid populations had higher rates of index ED and botox compared to patients with private insurance. Additionally, after accounting for differences in index interventions and insurance types, we found that only black patients had a significantly higher risk of receiving a second intervention, while the effect of insurance was no longer significant. Often these types of disparities are attributable to lack of access to care, provider treatment preferences, or cultural perceptions of medical interventions. However, assessing the contribution of these factors in the outcomes of AYA patients with achalasia was beyond the scope of the study.

Our study has several strengths. First, it is generalizable and less biased than single institution studies as we included a heterogeneous population across multiple socioeconomic, ethnic and geographic domains. As our study tracked patients up to 14 years and across hospitals, it is also more representative of the true rates of reinterventions and complications than the current literature. Furthermore, while most literature only reported major complications such as esophageal perforation, we reported a more granular list of complications. The use of large population datasets introduces some limitations to our analysis, such as the accuracy of the coding of complications. Although data relying on pre-determined codes can potentially underestimate true complication rates because of variance in physician reporting, the alternative approach of chart review also introduces some bias. For example, chart review can be influenced by a single person who reviews the charts, while a population database is collected by people from multiple institutions and thus mitigates the bias introduced by a single reviewer. In addition, people may be concerned that our definition of ED includes a mixture of pneumatic dilation, endoscopic balloon dilation or bougies and thus may affect rates of complication and re-intervention. As pneumatic dilation is the routine method for endoscopic treatment of achalasia, it would be unexpected for other treatments to comprise a significant proportion of the captured ED procedures. However, there are no ICD-9 codes to differentiate methods of dilation, therefore it is possible that the ED re-intervention and complication rates might change if pneumatic dilation could be examined alone. If a large portion of the ED patients do not undergo pneumatic dilation, then it is possible that we could have over-estimated the re-intervention rate but under-estimated that complication rates. However, given that the hazard ratio for re-intervention for the ED group relative to HM group is 5.9, unless the re-intervention rate for ED decreases by more than 80%, then HM would still have a more favorable risk benefit ratio. Lastly, neither SPARCS nor OSHPD captured patients who received procedures in surgi-centers or outpatient offices and this may contribute to the low number of Botox patients. However, we do not expect a difference in outcomes between those who are captured versus who are not captured.

In conclusion, we provide important data for physicians and families regarding the risks and benefits of the treatment options for achalasia in AYAs. The outcomes of this study support HM as the initial intervention for AYAs with achalasia.

**Author contributor** Dr. Kelleher conceptualized the study, critically reviewed the data and drafted the initial manuscript, and reviewed and revised the final manuscript. Dr. Hung and Dr. Chang conceptualized the study, collected the data and carried out the initial data analysis, critically reviewed the data and drafted the initial manuscript, and reviewed and revised the final manuscript. Dr. Westfal critically reviewed the data, reviewed and revised the initial and final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

### **Compliance with ethical standards**

**Disclosures** ML Westfal is financially supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (Award Number: T32 DK007754) and by the Massachusetts General Hospital Department of Surgery Marshall K. Bartlett Fellowship. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Y-C Hung, DC Chang, CM Kelleher have no conflicts of interest or financial ties to disclose.

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