How We Approach: Training Pediatric Coagulationists

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Abbreviations:

PHO	Pediatric Hematology/Oncology
HTC	Hemophilia Treatment Center
NHF	National Hemophilia Foundation
QI	Quality Improvement
ABP	American Board of Pediatrics
MOC	Maintenance of Certification
ISTH	International Society of Thrombosis and Haemostasis
HTRS	Hemostasis and Thrombosis Research Society
ASPHO	American Society of Pediatric Hematology/Oncology
MSKUS	Musculoskeletal Ultrasound
ASH	American Society of Hematology
HRSA	Health Resources & Services Administration
ATHN	American Thrombosis and Hemostasis Network
CDC	Centers for Disease Control and Prevention

Abstract

Unique expertise is required for the care of children, adolescents and young adults with bleeding and clotting disorders. A number of Hemophilia Treatment Centers have developed pediatric hemostasis and thrombosis fellowship programs to facilitate sub-specialty training and recruitment and retention in this field. This manuscript reviews an approach to training pediatric coagulationists including a description of current programs, sample curriculum, funding sources, and expected outcomes.

Why do we need to train clinical specialists in hemostasis and thrombosis?

The breadth of knowledge required for an expert in hemostasis and thrombosis is vast and includes disease-specific medical and practice-based knowledge. The required knowledge and skill sets can simply not be obtained in the standard three-year pediatric hematology/oncology (PHO) fellowship program that must cover an ever expanding breadth of specialty topics in addition to scholarly work.[1]

The clinical practice of pediatric hemostasis and thrombosis includes acquired and congenital bleeding and clotting disorders with patients seen from birth through young adulthood in outpatient settings, general inpatient units, intensive care units, and surgical settings. The diagnosis of bleeding and clotting disorders requires specialized knowledge in diagnostic coagulation, genetic testing, and imaging. The care of patients with bleeding disorders requires specialized knowledge in blood products, clotting factor replacement, non-factor hemostatic products, and, now, gene therapy, all of which require attention to individualized prescription and monitoring plus attention to allocation of high-value resources. The care of children with or at risk for thrombosis requires expertise in management of anticoagulation (and reversal). Coagulationists are called upon to develop anticoagulation policies and procedures and lead hospital-wide efforts to prevent hospital-acquired venous thromboembolism[2] and sometimes run a local coagulation laboratory for reliable diagnostics. In addition to the care of patients with bleeding and clotting disorders, coagulationists may lead or participate in Vascular Malformation Clinics and Blood Bank/Transfusion Medicine services.

The management of children with chronic bleeding and clotting disorders requires expertise in multi-disciplinary comprehensive care[3] and understanding of transition

medicine.[4,5] Tools which may improve comprehensive care and transition include telemedicine and mobile health technology (mHealth). Some HTCs are incorporating telehealth to reach patients who live at a distance from the HTC[6] and/or to supplement education provided at annual comprehensive visits. mHealth may be used to track outcomes such as activity and medication adherence. HTC providers should understand how to set-up and utilize such infrastructure.

Leaders in the field must also develop the administrative skill sets for the organization and funding of the Hemophilia Treatment Center (HTC), local collaboration with the National Hemophilia Foundation (NHF) chapter, regional collaboration within the US HTC network, and national collaboration with NHF. Additionally, coagulationists must learn skills to advocate for patient access to care and treatments.

In order to advance the field and produce scholarly work, there is an expectation for bench, translational, or clinical research and the conduct of quality improvement (QI) projects. Each scholarly discipline requires specific training.[7,8] Trainees who plan a career in clinical research may also pursue a Master's Degree in Public Health, Clinical Trials and Statistical Design, or Epidemiology during fellowship. QI training is now available through the US HTC network and through many academic institutions and hospitals.

The field of pediatric hemostasis/thrombosis is fortunate to have a number of laboratory-based physician scientists. These individuals often participate in HTC leadership and clinical care, such that they can also benefit from specialized training

incorporated into their laboratory training. Therefore, the training programs described are not limited to clinicians or clinician scientists.

What are the required competencies?

The American Board of Pediatrics (ABP) is responsible for board certification of pediatric hematology/oncologists. In order to be board-certified, one must pass an initial examination with questions derived from the Subspecialty Content Outline with 11 domains that cover the knowledge required for safe and effective pediatric hematology/oncology practice.[1] Hemostasis/Thrombosis is one of the domains. As of April 1, 2019, 10% percent of questions on the in-training and initial examination are derived from this domain. For subsequent hematology-focused maintenance of certification exam (MOC) the percentage is 16%. The topics in this domain include: normal physiology of coagulation factors and vessel wall; inherited disorders of coagulation; acquired disorders of coagulation; and thrombotic disorders. This basic knowledge is important for any pediatric hematologist/oncologist. However, an expanded knowledge base is necessary to provide expert care to children with bleeding and clotting disorders.

The International Society on Thrombosis and Haemostasis (ISTH) developed the Clinical Core Curriculum of required competencies for clinical specialists in thrombosis and hemostasis. The Curriculum was based on a global survey to establish required competency levels required for someone to practice independently in the field. There are 27 specialty areas with multiple sub-areas. The curriculum lists associated competency levels: knows how; shows how; and does. The competencies are listed in Table 1.

Trainee Workshops and Resources

In the early to mid-2000s, the shortage of specialty trained physicians in hemostasis and thrombosis was recognized.[9,10] Increased training in these areas was called for, particularly in light of new therapeutic options and expansion of prophylaxis for patients with hemophilia.[9] The one week International Course in Hemophilia through Lund University in Malmö, Sweden was established to provide clinical training and professional development for clinical coagulation specialists. More recently, similar training has focused on von Willebrand disease. The Hemostasis and Thrombosis Research Society (HTRS) has established a number of resources and training programs to facilitate training of the next generation of specialists in hemostasis and thrombosis. The HTRS Fellows Network aims include the following: establish and enhance communication among fellows/trainees interested in careers in hemostasis and thrombosis; establish a network of peers to provide support and advice; provide information and resources to encourage and assist fellows to pursue a successful career in hemostasis and thrombosis; provide access to the expertise of established physicians and researchers working in hemostasis and thrombosis; and collaborate with ConECCTOR (the HTRS Junior Faculty Network) and HTRS members to develop and retain physician investigators in hemostasis and thrombosis. HTRS Trainee Workshops have been ongoing since 2010. Other programs that provide specialized training are listed in Table 2.

Training Programs

Advanced fellowship training in pediatric hemostasis and thrombosis was first made possible through the NHF-Shire (now Takeda) Clinical Fellowship Award that has funded >20 HTCs to train fellows since 2002.[11] The impact of this program has been significant with 34 fellows trained to date. Goldenberg et al. conducted a nested case-control survey study to evaluate the impact of the award on early career

outcomes. Graduates of the award had higher rates of hematology-related careers, peer-reviewed publications, and grant funding.[12] In review of the current listings for the NHF-Shire Clinical Fellowship Award, fourteen pediatric hematologists completed the NHF-Shire Clinical Fellowship between 2011 and 2019. Of the two 2019 graduates, one is completing a transfusion medicine fellowship and one has an instructor position. Of the 12 other graduates, all have an academic faculty position at the Assistant Professor or higher level and provide specialty care in pediatric hemostasis and/or thrombosis. Ten of the 14 graduates remain at the same institution where they completed their fellowship. Four are an HTC Director or Associate Director.

A number of HTCs are now offering advanced fellowship training in hemostasis and thrombosis, typically an additional 1-2 years of training, either integrated within the three year pediatric hematology/oncology fellowship or following the initial fellowship. Table 3 lists programs that are currently recruiting through HTRS and/or the American Society of Pediatric Hematology/Oncology (ASPHO).[13,14] These and other fellowship programs are targeted towards physicians who aim to have an independent, academically-oriented, career dedicated to the comprehensive care of children with bleeding and clotting disorders. Fellows are typically recruited during their 3rd year of PHO fellowship. In addition to appointment as a trainee in Graduate Medical Education, some fellows are appointed as an Instructor with attending privileges. Fellowship funding is commensurate with trainee level and benefits are program specific. Funding sources include institutional and philanthropic funding and training grants (Table 4).

The fellowship programs have some key components of training including clinical work, didactics, clinical/translational research, and QI. In regard to the clinical

training, fellows participate in outpatient comprehensive and continuity clinics and may participate in specialty clinics focused on anticoagulation management, stroke, young women with bleeding and clotting disorders, and vascular malformations. Inpatient service includes participation in hematology service and sometimes a dedicated coagulation or cardiac intensive care unit service. Electives include Coagulation Laboratory, Blood Banking/Transfusion Medicine, Vascular Medicine, and Neuroimaging. A growing number of HTCs are using point-of-care musculoskeletal ultrasound (MSKUS) such that trainees have the opportunity to learn this skill for the evaluation of joint health.[15,16] Hay et al. recently identified training in the aged population and global hematology as two keys components of advanced hematology training that have previously been neglected and are urgently needed.[17] Training in these areas may be accomplished through exposure to adult hemophilia career in a lifespan center or in a collaborating adult-focused HTC and by participation in a twinning program sponsored by the World Federation of Hemophilia.

Directed readings and didactic lectures as well as the external training programs listed in Table 2 supplement the clinical training. The curricula are typically customizable based on the fellow's prior experience and career goals; an example is provided in Supporting Information Table S1. Fellows are expected to contribute to education of other trainees and to the development of clinical protocols. Importantly, fellows are provided with protected time to participate in research and QI activities with the expectation to present and publish data. Given the limited time frame, a research study using existing data or a limited translational research project are usually most feasible. Given the critical role of clinical trials for pediatric drug development, fellows should have the opportunity to learn about ongoing trials and

even participate in recruitment, consent, and other study procedures. As part of this training, trainees can learn about the importance of "team science" in the development and conduct of clinical trials as well as collaborative investigator-initiated research for a successful academic career.

A key aspect is mentorship and the development of long-term collaborative relationships. All of these programs allow for additional mentoring and experience in patient-oriented clinical research. Burns et al. evaluated the effect of an intense mentoring program as part of the American Society of Hematology (ASH) Clinical Research Training Institute.[18] In the first seven years of the program, graduates had high rates of publications and grant awards as well as retention in hematology-related jobs. The program HTC Director will mentor the fellow in regards to administration of the HTC 340B Drug Pricing Program,[19] the Regional HTC network, and collaborations with and data reporting to Health Resources & Services Administration (HRSA), the American Thrombosis and Hemostasis Network (ATHN), and the Centers for Disease Control and Prevention (CDC). The mentor will work with the fellow on a career development plan including funding opportunities (Table 4) and identification of the first faculty position. The mentor can help facilitate networking with other HTC Directors who may be hiring and provide guidance regarding negotiations.

PHO Sub-specialty Training and the Workforce

Advanced training after pediatric hematology/oncology fellowship is not unique to hemostasis and thrombosis. In fact, a survey of PHO Division Directors published in 2017 cited that 25% of graduates continued in a trainee-level of subspecialty fellowship position, increasing from 16% in 2010 to 37% in 2015.[20] The ASPHO website lists a number of other post-PHO fellowship programs for further

specialization. The areas with highest number of programs are neuro-oncology, bone marrow transplantation/cellular therapy and blood banking/transfusion medicine. Other programs include Adolescent Young Adult, survivorship, non-malignant hematology, developmental therapeutics, clinical research, leukemia, solid tumor, neuroblastoma, hemangioma and vascular malformations, bone marrow failure/myelodysplastic syndrome, and global pediatric medicine. Of these, only Blood Banking/Transfusion Medicine has a separate board certification. Ultimately, the goal is for the fellow to be hired as a junior faculty member. As noted above, the job market is competitive and the search will likely need to start early and be open-ended. APSHO, ASH and HTRS all have annual meetings that are excellent for networking and they post positions on their respective websites. Workforce is currently a top 5 priority for ASPHO and there is a great challenge to ensure that highly trained pediatric hematologists/oncologists are recruited into a career pathway where they can deliver their much needed expertise. One of the challenges of extended training is delay in faculty-level salary and ability to pay off loans. In order to offset this risk, trainees may apply for the NIH Loan Repayment Program (LRP) which was established to retain health professionals in biomedical or biobehavioral research careers. Alternatively, fellows may be recruited to a faculty position after PHO fellowship and try to accomplish “on the job” training in their desired field.

Summary

There remains a critical need for advanced training in hemostasis and thrombosis such that pediatric hematologists with the necessary expertise can be recruited and retained to provide comprehensive care for children with bleeding and clotting disorders. Fortunately, there are excellent resources to train the next generation of pediatric coagulationists including post-PHO fellowship coagulation fellowships and

workshops. These training programs should continue to play a central role in training and initiation of mentored and peer collaborations for long-term success. Additional work is needed to track and report recruitment into post-PHO fellowships and the impact of the training programs on attainment of post-fellowship faculty position and the nature of those positions plus academic productivity.

Conflict of Interest Statement

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References

1. American Board of Pediatrics. Pediatric Hematology-Oncology Content Outline. https://www.abp.org/sites/abp/files/pdf/pediatric_hemo_content_outline_updated.pdf. Accessed June 20, 2019.
2. Jaffray J, Mahajerin A, Young G, et al. A multi-institutional registry of pediatric hospital-acquired thrombosis cases: The Children's Hospital-Acquired Thrombosis (CHAT) project. Thromb Res 2018;161:67-72.
3. Pai M, Key NS, Skinner M, et al. NHF-McMaster Guideline on Care Models for Haemophilia Management. Haemophilia 2016;22 Suppl 3:6-16.
4. Young G. From boy to man: recommendations for the transition process in haemophilia. Haemophilia 2012;18 Suppl 5:27-32.
5. Brand B, Dunn S, Kulkarni R. Challenges in the management of haemophilia on transition from adolescence to adulthood. Eur J Haematol 2015;95 Suppl 81:30-35.
6. Kulkarni R. Use of telehealth in the delivery of comprehensive care for patients with haemophilia and other inherited bleeding disorders. Haemophilia 2018;24(1):33-42.
7. Thornburg C, Lane H, Farrow K, Brooks R, Jahan M, Scopelliti M. Increasing quality improvement capability in a hemophilia treatment center. Blood 2016;5908a.
8. Drayton Jackson M, Bartman T, McGinniss J, et al. Optimizing patient flow in a multidisciplinary haemophilia clinic using quality improvement methodology. Haemophilia 2019. doi.org/10.1111/hae.13768

9. Berntorp E, Gomperts E, Hoots K, et al. The next generation of hemophilia treatment specialists. Semin Thromb Hemost 2006;32 Suppl 2:39-42.

10. Todd RF, Gitlin SD, Burns LJ, et al. Subspeciality training in hematology and oncology: results of a survey of training program directors conducted by the American Society of Hematology. Blood 2004;103(12):4383-4388.

11. NHF-Shire Clinical Fellows. https://www.hemophilia.org/Researchers-Healthcare-Providers/Research-Grant-Programs/NHF-Shire-Clinical-Fellowship-Program/NHF-Shire-Clinical-Fellows. Accessed April 29, 2019.

12. Goldenberg NA, Kruse-Jarres R, Frick N, et al. Outcomes of mentored, grant-funded fellowship training in haemostasis /thrombosis: findings from a nested case-control survey study. Haemophilia 2012;18(3):326-331.

13. Hemostasis and Thrombosis Research Society. Fellowship Listings. https://www.htrs.org/HTRS/Jobs--Resources/Fellowships. Accessed May 1, 2019.

14. American Society of Pediatric Hematology/Oncology. Post-PHO Fellowship Training Directory. http://aspho.org/career-development/post-pho-fellowship-program-directory. Accessed May 1, 2019.

15. von Drygalski A, Moore RE, Nguyen S, et al. Advanced hemophilic arthropathy: sensitivity of soft tissue discrimination with musculoskeletal ultrasound. J Ultrasound Med 2018;37(8):1945-1956.

16. Nguyen S, Lu X, Ma Y, et al. Musculoskeletal ultrasound for intra-articular bleed detection: a highly sensitive imaging modality compared with conventional magnetic resonance imaging. JTH 2018;16(3):490-499.

17. Hay D, Hatton CS, Weatherall DJ. The future of academic haematology. BJH 2017;176(5):721-727.

18. Burns LJ, Clayton CP, George JN, et al. The effect of an intense mentoring program on junior investigators' preparation for a patient-oriented clinical research career. Acad Med 2015;90(8):1061-1066.

19. Malouin RA, McKernan L, Forsberg A, et al. Impact of the 340B Pharmacy Program on Services and Supports for Persons Served by Hemophilia Treatment Centers in the United States. Matern and Child Health J 2018;22(9):1240-1246.

20. Leavey PJ, Hilden JM, Matthews D, et al. The American Society of Pediatric Hematology/Oncology workforce assessment: Part 2-Implications for fellowship training. Pediatr Blood Cancer 2018;65(2). doi:10.1002/pbc.26765.

TABLE 1 ISTH Clinical Core Curriculum

Topics	Number of Subtopics
Role of the thrombosis and hemostasis specialists	13
Laboratory practice	4
Clinical trials and research	7
Bleeding disorders	7
Platelet disorders	7
Hemophilia A and B	20
Von Willebrand disease (VWD)	7
Rarer bleeding disorders	5
Immune-mediated acquired bleeding disorders	5
Thrombotic disorders-hypercoagulable states	6
Clinical aspects of venous thromboembolism (VTE)	8
Clinical aspects of arterial thrombosis	2
Antithrombotic agents	7
Plasma-derived and recombinant therapeutic agents	6
Obstetrics and gynecology	10
Intensive care	4
Oncology	1
Hematological diseases	2
Neurology	4
Nephrology	2
Infectious diseases	1
Gastroenterology and liver disease	2
Cardiology and cardiovascular surgery	4
General and orthopedic surgery	3
Traumatology	1
Blood transfusion	6
Pediatrics	1

TABLE 2 Trainee Workshops

Name	Sponsor	Eligibility	Curriculum
HTRS Trainee Workshops	HTRS	1st and 2nd year fellows and 3rd year residents	Various topics related to hemostasis and thrombosis
The Hematology Fellows Consortium	HTRS with Dr. Kessler, Georgetown University	Fellows	Focus on networking and collaboration
Center for Advance Training in Inhibitor Management (CATHIM)	Nationwide Children's Hospital/The Ohio State University School of Medicine	Fellows	Care of patients with hemophilia and inhibitors
Haemophilia Academy	Novo Nordisk Health Care AG	Fellows from invited institutions	Management of hemophilia and other bleeding disorders, career development
VWD-From Theory to Clinical Practice	Octapharma USA	Fellows and junior faculty	Von Willebrand Disease
ISTH Academy	ISTH	All	Online education on various topics related to hemostasis and thrombosis
Partners in Bleeding Disorders Education	Indiana Hemophilia & Thrombosis Center	All	Online education on various topics related to bleeding disorders
Clinical Research Training Institute	ASH	Fellows and junior faculty	Patient Oriented Clinical Research
Translational Research Training in Hematology	ASH and European Hematology Association	Fellows and junior faculty	Translational Research

TABLE 3 Pediatric Hemostasis and Thrombosis Training Programs Currently Recruiting through HTRS and ASPHO

Program Name and Training Site(s)
Fellowship Program in Hemostasis and Thrombosis at The University of Michigan Pediatric Hemophilia and Coagulation Disorders Program and the Indiana Hemophilia and Thrombosis Center
Pediatric Hemostasis and Thrombosis Fellowship at Rady Children's Hospital San Diego
Medical College of Wisconsin and Versiti-Blood Research Institute
The Joan Fellowship in Pediatric Hemostasis-Thrombosis at Nationwide Children's Hospital
Pediatric Hemostasis and Thrombosis Fellowship at Children's Hospital Los Angeles
Fellowship in Pediatric Coagulation Medicine at Children's Mercy Hospital
Fellowship at Emory University School of Medicine, Hemophilia of Georgia Center for Bleeding & Clotting Disorders, Atlanta, GA
Special Coagulation Fellowship at the University of Rochester/Mayo Clinic
Hemostasis/Thrombosis Clinical Research Fellowship at Children's Hospital of Orange County
Fellowship at Hospital for Sick Children Toronto

TABLE 4 Funding Resources for Hemostasis and Thrombosis Research*

Sponsor	Eligibility	Award amount
NHF-Shire (now Takeda) Clinical Fellowship Program	Candidate must submit application to work at approved institution	Up to $100,000/year (for up to two years)
CSL Behring Heimburger Award	Candidate must hold a medical degree. Applicants with less than 5 years of faculty experience in hemostasis will be preferred.	$20,000 euros
HTRS/NovoNordisk Clinical Fellowship Awards in Hemophilia and Rare Bleeding Disorders	Candidate must be mentored by experience physician at an established US HTC	Up to $119,600, or $80,000 salary/fringe benefits and up to $39,600 to support salary/fringe benefits for the primary mentor for up to 1 year
NHF Judith Graham Pool Postdoctoral Research Fellowships	Must apply from a doctoral, postdoctoral, internship or residency training program.	Up to $52,000 annually for up to 2 years for pre-clinical or basic science research
NHF/Novo Nordisk Career Development Award	No more than 6 years of postdoctoral years of experience in hematology and no more than 6 years since completion of medical training	Up to $70,000 annually for up to 3 years
HTRS Mentored Research Award	Fellow in training for a career in hemostasis and/or thrombosis or junior faculty within 7 years of completing training for a career in hemostasis and/or thrombosis (or related)	Up to $162,000 over a two year period

HTRS/ATHN Dataset Research Engagement and ATHN Mentorship (DREAM) Award	2nd or 3rd year fellow in US based PHO fellowship or Junior faculty within 7 years of completing PHO fellowship	Up to $100,000 over a two year period
ASH Junior Investigator Research Training Award for Fellows	2nd or 3rd year fellow with less than 5 years of research experience whose research has been initiated but has not generated preliminary data	Up to $70,000 for one year; may apply for a 2nd year of support
Fellow ASH Scholar Award	Must be in mentored postdoctoral training position	Up to $100,000 over a two- to three-year period
Fellow to Junior Faculty ASH Scholar Award	Must be in mentored postdoctoral training position	Up to $125,000 over a two- to three-year period
Junior Faculty ASH Scholar Award	Must hold independent faculty level positions (Assistant Professor or equivalent	Up to $125,000 over a two- to three-year period
US Hemophilia Aspire Award (Pfizer)	Early-career or established investigator	Up to $125,000 annually for up to 2 years

*See individual award eligibility for more details