ABSTRACT

Background: The TIDE (Treatable Intellectual Disability Endeavor) Protocol is a two-tiered evidence-based approach used to screen children for treatable genetic conditions (inborn errors of metabolism) causing intellectual disability. A systematic literature review performed in 2012 identified 81 treatable intellectual disabilities. The TIDE first-tier assessment can be used to identify 52 of these 81 conditions using readily available biochemical tests of urine and blood. The TIDE second-tier assessment takes a more targeted approach to identifying the remaining 29 conditions, and includes single metabolite or primary molecular analysis. Because these analyses can be more expensive and require invasive sampling procedures, the second-tier diagnostic workup is handled by hospital-based specialists.

Methods: The TIDE Protocol was introduced to 19 BC-based pediatricians with the help of a consensus-building workshop and downloadable resources (available at http://tidebc.org/Ph/physicians.html and www.tidebc.org/Ph/Ph/bcmj.html) designed to facilitate the use of the protocol in a community setting: detailed information about the TIDE Protocol, stickers to place on laboratory requisitions, and forms for referral to the Biochemical Diseases Clinic at BC Children's Hospital. To evaluate knowledge, acceptance, and use of the protocol, participating pediatricians were asked to respond to a web-based survey 18 months after the workshop was held.

Results: Of the 19 participating community pediatricians, 13 responded to the survey (68.4%). Respondents demonstrated knowledge of the TIDE first-tier tests and recognized the indications for referral to BC Children's Hospital. All respondents said that the protocol made a change in their clinical practice.

Conclusions: The acceptance of the TIDE Protocol by community pediatricians surveyed suggests there is a solid basis for implementing the protocol throughout BC. Because performing TIDE first-tier tests captures 65% of currently known treatable conditions causing intellectual disability, expanding the use of the protocol could lead to improvements in early diagnosis and treatment of inborn errors of metabolism, and prevention of brain damage.

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Introduction of the TIDE Protocol to screen children for treatable intellectual disability: First evaluation of protocol use by community pediatricians in British Columbia

Findings from a survey of BC pediatricians indicate that expanding the use of a two-tiered evidence-based approach to screening children for treatable genetic conditions could lead to improvements in early diagnosis and treatment.

This article has been peer reviewed.

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Introduction of the TIDE Protocol to screen children for treatable intellectual disability

Background

Intellectual disability (ID) is a lifelong condition with onset before the age of 18 years; it is characterized by limitations in cognitive functioning (IQ below 70) and adaptive behavior. For children younger than 5 years with a delay in two or more developmental domains (e.g., fine/gross motor skills, speech, and interaction), the term global developmental delay (DD) is used. Unless otherwise stated, however, the term ID is used in this article for both DD and ID.

ID affects 2% to 3% of the pediatric and adult populations worldwide. Based on BC 2013 population estimates, this means that 18,000 to 27,000 children are affected by ID, and 880 to 1,300 newborns present with ID in the province each year. Individuals with ID have a high number of comorbidities, including neurological conditions, systemic problems, and behavioral abnormalities. Medical costs associated with ID exceed those for cardiovascular disease and cancer combined. Medical costs associated with ID exceed those for cardiovascular disease and cancer combined.

ID causes are extremely heterogeneous and include environmental causes (e.g., infection, exposure to teratogens), genetic causes, and multifactorial causes. In developed countries, more than 50% of ID causes are deemed genetic, ranging from chromosomal to single gene abnormalities.

Current practice for evaluating children with ID prioritizes cytogenetic testing, which has a high diagnostic yield. However, the conditions identified are not all amenable to causal treatment—that is, interventions targeting the pathophysiology of the condition at a cellular level. This can lead to neglect of inborn errors of metabolism (IEMs), genetic conditions causing ID for which causal treatment is available.

In a systematic literature review performed in 2012, we identified 81 treatable inborn errors of metabolism that cause ID. Of these, 52 conditions (65%) are detectable by biochemical testing of blood and urine, while the rest can be diagnosed by considering specific clinical symptoms and ordering appropriate biochemical or single gene tests. Early diagnosis of a treatable ID is essential because medical diets, vitamin supplements, substrate inhibitors, stem cell transplantation, gene therapy, and other treatments can prevent irreversible brain damage and optimize developmental outcomes.

To translate these findings into clinical practice, we established TIDE-BC, the Treatable Intellectual Disability Endeavour (www.tidebc.ca), in 2011. TIDE-BC is the first Collaborative Area of Innovation initiative funded by the BC Children's Hospital Foundation (www.bcchf.ca) to improve outcomes for children with rare diseases by way of enhanced diagnosis and treatment.

Based on the evidence summarized in our 2012 review, we created the two-tiered TIDE Protocol to place screening for treatable IEMs at the forefront of the diagnostic evaluation process for children with unexplained ID. The TIDE Protocol can be viewed at www.tidebc.ca/Ph/If/bcmj.html.

The TIDE protocol for evaluating children with unexplained intellectual disability involves two tiers. The first tier involves readily available biochemical tests of urine and blood with the potential to identify 52 of 81 treatable IDs. These first-tier tests can be ordered by community pediatricians in BC, even though ordering metabolic/biochemical genetic tests is generally not regarded as a community pediatrician’s responsibility. Most of the tests are offered by the Biochemical Genetics Laboratory at BC Children’s Hospital (BCCH) and are funded by the medical services plan for a total cost of approximately $528 per patient.

The next step in the diagnostic evaluation of a child with unexplained ID requires considering current diagnostic guidelines, which recommend investigations such as vision and hearing tests, chromosome microarray, and, in selected cases, fragile X testing and neuroimaging.

At this stage, the TIDE second-tier screening process for identifying the remaining 29 treatable IDs begins. The second-tier process involves a targeted workup, including single metabolite or primary molecular analysis. Because these tests can be expensive and can require invasive sampling procedures (e.g., spinal tap to collect cerebrospinal fluid, skin biopsy to cultivate fibroblasts), hospital-based specialists are needed to facilitate an efficient diagnostic workup.

The TIDE Protocol is supported by an app (available at https://itunes.apple.com/us/app/treatable-id/id634757831?mt=8) that provides information on symptoms, diagnostic approach, and management of each treatable ID.

In a 2.5-year study conducted at BCCH in the divisions of biochemical diseases, pediatric neurology, and medical genetics, more than 500 children with unexplained ID were screened with the two-tiered TIDE Protocol. Of the children screened, 5% were diagnosed with a treatable IEM. Furthermore, a retrospective analysis showed that the protocol was cost- and time-effective, and that it reduced unnecessary diagnostic testing and delay.

To expand the use of the TIDE Protocol in the community practice setting and to simplify a process that usually involves hospital-based subspecialists, we started a provincial pilot project in collaboration with BC pediatricians and Child Health BC. We then conducted a formal qualitative evaluation 18 months after introducing the protocol.
Introduction of the TIDE Protocol to screen children for treatable intellectual disability

Methods
Our study was conducted through BC Children’s Hospital, the only tertiary/quaternary care centre in BC that provides specialized services for children with inborn errors of metabolism. Children diagnosed with a treatable IEM are seen at the Biochemical Diseases Clinic within the BCCH Department of Pediatrics, and laboratory samples collected from these children are analyzed by the Biochemical Genetics Laboratory at BCCH.

We invited community pediatricians and health care professionals from different regions (Lower Mainland, Interior, Northern BC, and Vancouver Island) who had expressed special interest in the TIDE Protocol to be part of a consensus-building workshop that was organized under the umbrella of Child Health BC—the network linking the province’s health authorities, the three child-serving ministries, the University of British Columbia, and other health professional organizations such as BC Pediatric Society to support equitable access to high-quality health services. A summary of the workshop (TIDE Workshop Report) is available at www.tidebc.org/Ph/Ph/bcmj.html.

Implementation of TIDE
The workshop had three main objectives:
1. To identify the impact of the TIDE Protocol on clinical practice, specifically from the perspective of community pediatricians.
2. To develop a step-by-step process for using the protocol, which includes defining and recognizing the target patient group, ordering laboratory tests, following up test results, and understanding referral indications.
3. To develop consensus among community-based pediatricians for the use of the TIDE first-tier tests.

To facilitate the use of the TIDE Protocol in a community setting, we also provided the following materials (all available for download at http://tidebc.org/Ph/physicians.html):
- The essentials of the TIDE Protocol to serve as a memory aid for the pediatrician during assessment of a child with unexplained ID.
- Stickers to place on laboratory requisitions when ordering TIDE first-tier tests.
- Forms for referral to the Biochemical Diseases Clinic at BCCH for follow-up of abnormal TIDE first-tier test results, further evaluation of symptoms, or both.

Survey design and analysis
To evaluate implementation, we administered a web-based questionnaire 18 months after introducing the TIDE Protocol in the community. Survey questions were designed to collect knowledge, behavior, demographic, and opinion/attitude information, and were based on a guide developed by Taylor-Powell and Marshall. Respondents were asked about their identification of target populations for screening, lab test ordering practices, referral practices, and satisfaction with the protocol. Multiple-choice and open-ended questions were used to capture as much information as possible. A copy of the survey questionnaire (TIDE Protocol Survey) is available at www.tidebc.org/Ph/Ph/bcmj.html.

The survey was voluntary and confidential and was designed using REDCap (Research Electronic Data Capture) software. The questionnaire was distributed to community pediatricians who were using the TIDE Protocol in a primary care setting.

To encourage participation, the questionnaire included a short introduction outlining the survey’s purpose and the approximate time needed to complete it (15 minutes). To obtain an optimal response rate we sent regular reminders to the recipients and provided an incentive ($20 coffee/pastry gift card).

We approached 19 community-based pediatricians from all health authorities in British Columbia. Of these, 16 had taken part in the consensus-building workshop and 3 had used the TIDE Protocol after they heard about it from families or fellow pediatricians. The survey was conducted over 3 weeks and was completed at the end of March 2014. Responses were analyzed using descriptive statistics and content analysis. Ethics approval to conduct this research was obtained from the University of British Columbia—Children’s and Women’s Health Centre of British Columbia Research Ethics Board.

Results
Of the 19 community pediatricians contacted, 13 (68.4%) responded to the survey. The majority of respondents were from the Lower Mainland (8/13; 66.7%), followed by Vancouver Island (3/13; 23.1%), and the Interior (2/13; 15.4%). No pediatricians from Northern BC responded. Pediatricians’ professional experience ranged from 4 to 25 years of practice, with 6 of 13 (46.2%) having more than 20 years of experience.

ID types targeted with TIDE first-tier tests
ID occurs in various forms: isolated (unspecific ID) or ID combined with various visceral, neurological, or psychiatric manifestations such as epilepsy, movement disorder, and/or autism. We wanted to know which types of ID community pediatricians were targeting with the TIDE Protocol (Table 1).

All pediatricians reported using TIDE first-tier tests for children with...
unspecific DD (13/13; 100.0%), and almost all reported using it for unspecific ID (12/13; 92.0%). Many pediatricians (10/13; 76.9%) screened patients with ID and autism, while some (4/13; 30.3%) screened patients with autism irrespective of the presence of ID. None of the pediatricians screened patients in the absence of developmental delay or intellectual disability.

Knowledge of TIDE first-tier tests
The TIDE first-tier process involves eight lab tests. Results for the four tests analyzed by the Biochemical Genetics Laboratory at BCCH (plasma amino acids, blood spot acylcarnitines, urine organic acids, urine purine/pyrimidine/creatine metabolites) are reported with a full interpretation, and the pediatrician does not have to consider the single numeric results. For the other three tests analyzed in provincial clinical chemistry labs (ammonia, copper, ceruloplasmin) and the single test analyzed at a central lab at Vancouver General Hospital (plasma total homocysteine), the pediatrician has to interpret the significance of flagged results and decide how to follow up.

We wanted to determine whether pediatricians know which tests are TIDE first-tier tests, which are non-TIDE tests, and which tests require interpretation and follow-up (Table 2).

More than half of the pediatricians surveyed (9/13; 69.2%) recognized six of the eight TIDE first-tier lab tests (ammonia, blood spot acylcarnitines, plasma amino acids, total homocysteine, urine organic acids, urine purine/pyrimidine/creatine metabolites) in a list including non-TIDE lab tests such as thyroid stimulating hormone and array comparative genomic hybridization (CGH). Only two pediatricians (15.4%) recognized that total homocysteine results require direct interpretation and follow-up.

Table 1. Types of intellectual disability (ID) that survey respondents reported targeting with TIDE first-tier screening tests.

<table>
<thead>
<tr>
<th>Type of intellectual disability (ID)</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unspecific ID</td>
<td>12/13</td>
<td>92.3</td>
</tr>
<tr>
<td>Unspecific DD (global developmental delay)</td>
<td>13/13</td>
<td>100.0</td>
</tr>
<tr>
<td>Familial ID</td>
<td>9/13</td>
<td>69.2</td>
</tr>
<tr>
<td>ID+ dysmorphic features</td>
<td>11/13</td>
<td>84.6</td>
</tr>
<tr>
<td>ID+ failure to thrive/poor somatic growth</td>
<td>8/13</td>
<td>61.6</td>
</tr>
<tr>
<td>ID+ multiple congenital anomalies</td>
<td>8/13</td>
<td>61.5</td>
</tr>
<tr>
<td>ID+ neurological deficits</td>
<td>11/13</td>
<td>84.6</td>
</tr>
<tr>
<td>ID+ autism</td>
<td>10/13</td>
<td>76.9</td>
</tr>
<tr>
<td>ID+ organomegaly/systemic involvement</td>
<td>8/13</td>
<td>61.5</td>
</tr>
<tr>
<td>Autism</td>
<td>4/13</td>
<td>30.8</td>
</tr>
<tr>
<td>Learning disabilities</td>
<td>1/13</td>
<td>7.7</td>
</tr>
<tr>
<td>No established ID or DD</td>
<td>0/13</td>
<td>0.0</td>
</tr>
<tr>
<td>Other</td>
<td>0/13</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 2. Knowledge of TIDE first-tier screening tests demonstrated by survey respondents.

<table>
<thead>
<tr>
<th>Tests identified correctly</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIDE first-tier tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonia</td>
<td>9/13</td>
<td>69.2</td>
</tr>
<tr>
<td>Copper</td>
<td>8/13</td>
<td>61.5</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>8/13</td>
<td>61.5</td>
</tr>
<tr>
<td>Blood spot acylcarnitine profile</td>
<td>9/13</td>
<td>69.2</td>
</tr>
<tr>
<td>Plasma amino acids</td>
<td>9/13</td>
<td>69.2</td>
</tr>
<tr>
<td>Total homocysteine</td>
<td>9/13</td>
<td>69.2</td>
</tr>
<tr>
<td>Urine organic acids</td>
<td>9/13</td>
<td>69.2</td>
</tr>
<tr>
<td>Urine purine/pyrimidine/creatine metabolites</td>
<td>9/13</td>
<td>69.2</td>
</tr>
<tr>
<td>Non-TIDE first-tier tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>4/13</td>
<td>30.8</td>
</tr>
<tr>
<td>Fragile X</td>
<td>2/13</td>
<td>15.4</td>
</tr>
<tr>
<td>Chromosome</td>
<td>3/13</td>
<td>23.1</td>
</tr>
<tr>
<td>Array comparative genomic hybridization</td>
<td>2/13</td>
<td>15.4</td>
</tr>
<tr>
<td>TIDE first-tier tests requiring direct interpretation by pediatrician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonia</td>
<td>11/13</td>
<td>84.6</td>
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</tr>
<tr>
<td>Total homocysteine</td>
<td>2/13</td>
<td>15.4</td>
</tr>
</tbody>
</table>
interpretation by the pediatrician, and only four pediatricians (30.9%) used the downloadable TIDE stickers on lab requisition forms. Non-users were either unaware the stickers were available or indicated they had memorized the tests needed and preferred to write these on the lab requisition by hand.

Referral practices
Some of the TIDE first-tier test results and symptoms require immediate referral to the Biochemical Disease Clinic, whereas others can be referred on a non-urgent basis or followed up locally. We wanted to understand the community pediatricians’ course of action after ordering first-tier TIDE tests and their practices and reasons for referral to hospital-based specialists.

Most pediatricians (11/13; 84.6%) correctly identified all of the “alert symptoms” that warrant immediate referral to BCCH. “Alert symptoms” include unexplained/progressive cognitive deterioration/neurologic manifestations; refractory seizures; recurrent vomiting, hypoglycemia, (keto) acidosis; dysmorphic features, dysostosis; organomegaly; and unexplained death of a sibling (see the TIDE Fact Sheet at www.tidebc.org/Ph/Ph/bcmj .html). Many (8/13; 61.5%) reported that they wait for lab results before deciding on follow-up visits in their own practice or referral to a subspecialist. Most pediatricians (11/13; 84.6%) said they arranged a follow-up visit in their clinics even if the TIDE first-tier tests did not reveal abnormalities. If one or more of the TIDE first-tier tests revealed abnormalities, almost all pediatricians (12/13; 92.3%) referred to the Biochemical Diseases Clinic at BCCH for further evaluation, and some (4/13; 30.8%) arranged for a repeat visit to their own clinics first.

Satisfaction with TIDE Protocol
The TIDE Protocol is designed to help identify treatable inborn errors of metabolism. We wanted to determine whether community pediatricians were satisfied with the TIDE Protocol and whether they found the protocol made a change to their clinical practice.

All survey respondents (13/13; 100.0%) were satisfied and reported that the TIDE Protocol presented an improvement in their diagnostic evaluation of children with ID. Almost all (12/13; 92.3%) agreed that the TIDE Protocol is a useful and systematic method for testing children with ID for treatable underlying conditions. Of the pediatricians surveyed, most (10/13; 76.9%) felt that the protocol increased their awareness of standard diagnostic evaluation recommendations and the causes of ID, specifically of treatable IEMs, and most (10/13; 76.9%) reported that the TIDE Protocol reduced waiting time, improved the referral process, and made communication with specialists more efficient. Some (6/13; 46.2%) reported having more confidence in their approach to the diagnostic assessment of ID when using the TIDE Protocol, while only two pediatricians (15.4%) felt that the use of the protocol increased their workload. No survey respondents reported dissatisfaction with the use of the protocol in their community practice.

Conclusions
The goal of introducing the TIDE Protocol in a community setting was to raise awareness of treatable IDs across BC and to increase community capacity to perform TIDE first-tier tests capable of capturing 65% of currently known treatable IDs. The results of this survey indicate that the preliminary implementation process has resulted in excellent awareness and knowledge of the protocol. The promising behavior changes and opinions/attitudes reported by survey respondents suggest a solid basis for successful expansion of the TIDE Protocol throughout BC. TIDE has the potential to improve screening of treatable IEMs and to enhance pediatrician knowledge of IEMs and referral practices.

Benefits of TIDE Protocol identified by study
While most cases of treatable ID present with neurological or psychiatric comorbidities, or both, and 69% of cases present with systemic manifestation, the only diagnostic hint in an early disease state is often mild unspecific ID without concomitant signs and symptoms. For example, progressive cognitive decline, vision and hearing loss, spastic tetraparesis, seizures, and adrenal insufficiency are characteristic of advanced stages of X-linked adrenoleukodystrophy (X-ALD). However, subtle loss of cognitive functions with behavioral disturbances in late infancy is often the first manifestation. Recognition of the diagnosis at this early disease stage provides an opportunity for stem cell transplantation, which is currently the only causal treatment for X-ALD and which is not effective at a later disease stage. Screening patients with unspecific and mild/moderate ID with the TIDE Protocol can allow diagnosis and treatment at early disease states and thus improve outcomes.

The TIDE first-tier tests allow identification of various disease groups, including disorders of amino acid, fatty acid, and organic acid metabolism, urea cycle defects, vitamin-dependent conditions, and disorders of creatine and nucleotide metabolism. Careful interpretation of results for mild and atypical disease variants
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characterized by subtle deviation from normal is crucial. While most disorders are characterized by the accumulation of specific metabolites, which can be safely detected by the analytic technologies employed in the TIDE first-tier screening, some disorders are characterized by the reduction of specific metabolites. For example, AGAT deficiency, a treatable disorder of creatine synthesis, is characterized by a reduction of guanidinoacetate (GAA). In the TIDE first-tier screening process, urinary GAA levels are part of urine purine/pyrimidine/creatine screening, although accurate detection of levels below the normal range is challenging. This might be the reason why fewer than 20 patients have been diagnosed worldwide since AGAT deficiency was first described in 2001. Thus, in the TIDE second-tier process, careful analysis of apparently unspecific results is a prerequisite, particularly in the recognition of mild and atypical variants of treatable ID and disorders characterized by lower-than-normal metabolite levels.

In 2000 to 2009, prior to implementation of the TIDE Protocol, 31 patients were diagnosed with a treatable ID at BC Children’s Hospital. Retrospective analysis of time intervals associated with a final diagnosis showed that for those treatable conditions identifiable by way of first-tier tests, significant diagnostic delay (mean 9 months; range 1 to 29 months) could have been avoided in nine patients had the TIDE Protocol been used along with the Treatable-ID app, which allows for specific searches based on signs and symptoms. For example, in the case of a 6.5-year-old boy presenting with developmental delay and challenging behaviors, the diagnosis of cerebral creatine transporter deficiency was made only after more than 4 years of extensive diagnostic evaluation, indicating a missed opportunity for earlier treatment as well as unnecessary costs of more than $3000. Using the TIDE first-tier tests could have established this diagnosis at the initial referral. This example illustrates how using the protocol in the community could help pediatricians avoid delay in diagnosis and improve the diagnostic yield of treatable ID in the future.

The goal of introducing the TIDE Protocol in a community setting was to raise awareness of treatable IDs across BC and to increase community capacity to perform TIDE first-tier tests.

The recognition of treatable ID is particularly important for community-based pediatricians, whose first aim is to provide early and effective therapies. For patients who undergo extensive evaluation yet remain without a diagnosis, the multidisciplinary TIDE Complex Diagnostic Clinic (CDC) was established in 2011. Of the 24 patients evaluated in seven CDC clinics held during a 16-month period, causal diagnoses were firmly established in 9 cases (38%). An interim evaluation revealed a high degree of patient and specialist satisfaction. Biochemical and medical geneticists, neurologists, developmental pediatricians, and psychiatrists particularly appreciated the CDC as an effective mechanism for enabling a quicker diagnosis. This is yet another example of how the TIDE first-tier process supports community pediatricians in their role as gatekeepers for diagnostic assessments of children with unexplained ID, and how the TIDE second-tier process helps specialists in the multidisciplinary assessments that follow in some cases.

Limitations of study
The small number of community-based pediatricians who used the TIDE Protocol and responded to the survey was the chief limitation of our study. Another limitation was the qualitative process evaluation. While this allowed us to obtain the views of pediatricians on their experiences using the TIDE Protocol, an evaluation of the test results and diagnoses among the children screened is currently underway.

Future of TIDE Protocol
The number of treatable IDs is increasing constantly because of genetic discoveries and the development of new treatments. Since the publication of our systematic review on treatable intellectual disability, our own group has discovered one new treatable ID and launched a new treatment for a known IEM.

Teaching about TIDE by way of webinars, digital modules, and collaborative patient consultation during joint clinics or telehealth sessions can be expected to improve knowledge of the protocol and promote province-wide dissemination and uptake.

Increasing awareness of the potential impact of earlier diagnosis and treatment on patient outcomes could lead to further adoption of TIDE both nationally and internationally. Development of a modified TIDE Protocol for children with cerebral palsy and adults with ID might also be considered.

Competing interests
None declared.

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References