Annual Conference of the Israeli Association of Pediatrics

Tel Aviv, 16 November 2016
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Meir Goldberg MD

Oil on canvas, 70 x 80 cm, 2015

Meir Goldberg studied medicine at the Hebrew University-Hadassah Medical School. He went on to specialize in General and Pediatric Surgery at Hadassah Hospital, Mount Scopus. He then moved to Shaare Zedek Medical Center, where he worked in Pediatric Surgery Unit for 25 years, 20 years of which he served as head of the department. He is presently at the Dana Children's Hospital, Tel Aviv Sourasky Medical Center.

Dr. Goldberg began painting 20 years ago, although from a young age he was already interested in art. His style is figurative and the subject is mostly landscapes, as seen in the painting shown here of the source of the Yarkon river near the town Rosh HaAyin.
Pediatric Practice in Israel 2016: Combining the Art of Medicine and Science

This special issue of the *Israel Medical Association Journal (IMAJ)*, distributed at the annual conference of the Israeli Association of Pediatrics (IAP), 16 November 2016 in Tel Aviv, includes several original and review manuscripts from ambulatory clinics as well as several medical centers across Israel and from different pediatric disciplines. These articles represent some of the broad and continuous scientific work done by members of our association.

Amir et al. [1] review the experience of a tertiary medical center in surgical repair of congenital heart defects and report encouraging results that are quite comparable to those of leading centers in the world. In fact, Israel has been a site for heart surgeries in recent years, not only for local and neighboring countries’ children but also for children arriving from developing countries around the world for repair of heart defects through the ‘Save a Child’s Heart’ fund.

Baram et al. [2] examine the risk for occult bacteremia in the era of routine 13 valent pneumococcal vaccination. As expected, there is a prominent decline in the rate of occult bacteremia; however, even during this era the risk for occult bacteremia is not negligible and should still be considered during the evaluation of the febrile infant.

The "new morbidities" in Pediatrics include several metabolic, nutritional, educational and behavioral disorders demanding increasing attention in routine pediatric care. Several articles in this issue reflect the growing interest in this area. Berman and co-authors [3] did not find an association between Legg-Calvé-Perthes disease and attention deficit hyperactivity disorder (ADHD). Cohen et al. [4], who examined the seasonality of methylphenidate prescriptions during the year, demonstrated a decrease in the number of these prescriptions dispensed during the summer months and Passover and call for attention that due to this phenomenon this chronic illness may be not be managed optimally. Leitner et al. [5] investigated the different diagnostic practices of ADHD and found significant differences among three medical specialties with regard to the clinical evaluation of ADHD. This finding is worrying and may reflect insufficient solid criteria for the diagnosis and treatment of this widespread disorder.

Katz and Rothenberg [6] review the trend of current guidelines for the introduction of solid food to the infant diet, calling for earlier introduction in order to prevent future allergies. The mechanism of this alleged protection is not clear and may be related in part to desensitization of actually allergic children. The authors’ review and interesting perspectives provide encouraging data for the prospects of future decrease in the rate of serious and life-threatening food allergy reactions. However, this review should be analyzed and interpreted cautiously. For example, early introduction of eggs was effective in decreasing egg allergy in only some of the studies, and interventional data on the effectiveness of early cow’s milk introduction are still lacking. It should also be pointed out that changes in dietary guidelines are not arbitrarily made but are derived from the collection and analysis of scientific data.

One of the goals of the Israeli Association of Pediatrics (IAP) has been to coordinate all the subspecialties and disciplines related to child care, and I am pleased to include in this issue articles from our Pediatric Surgery colleagues. Sweed et al. [7] nicely demonstrated the utility and safety of transcatheter arterial embolization for blunt and penetrating abdominal trauma in children when these procedures are performed cooperatively with surgeons and interventional radiologists. Jawdat and team [8] describe their experience with one-stage laparoscopic orchiopexy in the treatment of intraabdominal testis and report results comparable with those of the more conservative surgical repair. Another example of the expansion of laparoscopy in pediatric surgery is reported by Sukhotnik et al. [9] who successfully used laparoscopic surgery instead of conservative laparotomy for the repair of urachal anomalies. Avinadav and colleagues [10] describe how the addition of "bedside" ultrasound as part of the routine care in a pediatrics department has led to quicker diagnoses and quicker administration of the appropriate treatment.

Two articles deal with management of acute pain in children. The challenges of pain assessment and treatment in the pediatric emergency department are illustrated in a review by Jacob and Shavit [11]. This short review provides an update of the recent literature on acute abdominal pain and appendicitis-related pain in the pediatric emergency department. Rimon et al. [12] examined the effect of medical clowns on biochemical and expression analysis of pain in the emergency department. While there was no evidence for decreasing cortisol level in children assisted by clowns, the pain score was significantly lower in the intervention group. This study should encourage more research to define the role of medical clowns in pediatric services.

Neonatology research is represented in this issue by the study of Bin Nun et al. [13] who investigated the role of prophylactic heparinization and propose optimal dosing and a practical clinical aid for the neonatologist.
The abstract session of the annual conference includes high quality clinical studies in various aspects of pediatric emergency medicine. Jacob et al. [14] examined factors associated with the administration of emergency department (ED) analgesia in patients with acute appendicitis and observed a low rate of administration of analgesia, with no ethnic differences. Gelernter et al. [15] assessed the prevalence of significant traumatic brain injury on computerized tomography in infants with head trauma and found no difference in the incidence of significant brain injury between children presenting to the ED less than 24 hours after the injury and children with late presentation. Aronson-Schinas and team [16] developed and evaluated a simulation-based workshop for pediatrics residents on the disclosure of medical errors and found that through this workshop providers gained experience in error disclosure. Erell et al. [17] reported that although shivering was a common symptom in febrile children presenting to the ED, it was not associated with an increased risk for serious bacterial infection. Allon et al. [18] showed that the pediatric Canadian Triage and Acuity Scale (CTAS) demonstrated good validity in categorizing patients’ acuity levels in an Israeli pediatric ED.

The second part of this issue includes original articles and case reports from our colleagues that had been submitted to IMAJ prior to the time of call for articles for this special issue. We chose to include these in order to further emphasize the fruitful scientific work done by Israeli pediatricians.

The scientific work presented in this issue of IMAJ is conducted in addition to the clinical work and the involvement of Israeli pediatricians through the IAP in child health care issues and national public health measures. Examples from recent years include the direct and prominent involvement of the IAP in the national campaign of wild poliovirus elimination, renewal of water fluoridation administration, regulation of food, and shaping the future of “milk drop” clinics across Israel. The IAP includes more than 2500 pediatricians. While the number of pediatricians per population in Israel is comparable to several Western countries, the demography in Israel is different and therefore the work load on Israeli pediatricians is quite heavy. For example, the percentage of children < 14 years old in Israel is double that of Germany (28% vs. 14% respectively). The annual fertility rate and population growth rate in Israel are two to three times higher than the average in Europe [19]. In spite of these data, and in spite of a relatively low health expenditure as a percentage of the gross domestic product (GDP), several indices such as neonatal and infant mortality are low and vaccination coverage is relatively high in Israel. All these figures reflect the critical role of Israeli pediatricians in shaping the health and the future of children and the future of Israeli society in general.

References

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“So many books, so little time”
Frank Zappa (1940-1993), American musician, songwriter, composer, guitarist, record producer, actor and filmmaker
Neonatal Cardiac Surgery in the New Era: Lessons Learned from 1000 Consecutive Cases

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ABSTRACT: Background: Neonatal cardiac surgery has evolved over the last 50 years with a large percentage of the patients achieving complete physiological repair in the neonatal period. The remaining patients achieve staged palliation with an increasing amount of success.

Objectives: To report our experience with 1000 neonatal cardiac surgical procedures performed in the last 10 years.

Methods: We conducted a retrospective analysis of surgical outcome in all neonatal patients who underwent cardiac surgery between January 2007 and July 2016 at Schneider Children’s Medical Center of Israel.

Results: A total of 1003 neonates aged <30 days underwent surgery for congenital heart defects at our center. Neonatal surgery accounted for 22.5% of all cardiac surgeries. Neonatal operative mortality was 7.3%. Operative mortality for individual lesions were: simple aortic coarctation (CoA) (198 patients, 2.5%), CoA with hypoplastic arch (24, 4%), CoA with ventricular septal defect (VSD) (84, 2.3%), transposition of the great arteries (TGA, simple and complex, 185, 6.3%), TGA with VSD (37, 0%), truncus arteriosus (26, 3.8%), interrupted aortic arch (25, 4%), Norwood Sano (71, 19.7%), neonatal tetralogy of Fallot (41, 0%), and shunt (131 patients, 12%).

Conclusions: Neonatal surgical capabilities have improved substantially over the last decades. Excellent results can be expected for lesions that can be repaired to create biventricular circulation. Improved results can be attributed in part to the evolution of surgical strategies and assistive technologies, but essential is the collaborative effort of surgeons, cardiologists, anesthesiologists, and intensive care specialists acting as a cohesive team whose performance far exceeds the sum of its individual members’ contributions.

KEY WORDS: neonate, cardiac surgery, mortality, cardiac team

Many factors are responsible for the improved results: improvement in diagnostic abilities and surgical techniques, innovation in cardiopulmonary bypass, and the creation of specialized intensive care units. Over the past 10 years, we have been committed to the improved care of neonatal patients with congenital cardiac malformations, striving to achieve the best possible results. We report our experience with 1003 consecutive neonatal cardiac surgical procedures performed in the last 10 years.

PATIENTS AND METHODS

We conducted a retrospective analysis of all neonatal patients who underwent cardiac surgical procedures at Schneider Children’s Medical center of Israel between January 2007 and July 2016. Patients were enrolled if age at operation was less than 30 days. Operative mortality was defined as occurring prior to discharge from the hospital. Preoperative and operative diagnosis was determined by the cardiology team and operating surgeon.

RESULTS

Between January 2007 and June 2016, 1003 neonates under 30 days of age underwent surgery for congenital heart defects at Schneider. During the same period, 4450 pediatric patients underwent surgery for congenital heart defects. Overall operative mortality for the whole cohort of patients was 2.96%. Neonatal surgery accounted for 22.5% of all cases performed at our center. The most prevalent operation performed was the repair of aortic coarctation (CoA, 198 patients) and transposition of the great arteries (TGA, 185 patients). Figure 1 depicts the distribution of operative diagnosis of all patients who underwent surgery. Neonatal out-of-hospital postoperative mortality was 7.3%. Table 1 presents the operative mortality for each of the main neonatal diagnoses and operations, compared with results obtained from international databases and leading centers worldwide.

DISCUSSION

The care for patients with congenital heart disease has evolved over the last decades and has changed significantly. Neonatal cardiac surgery is the most demanding field among surgeries.
for congenital heart disease due to the high surgical complexity and the fragility of the immature systems [12]. The exposure to surgical trauma and to the effects of heart and lung machines provokes an intense inflammatory response accompanied by hemodilution and hypothermia [13].

Since the first pioneering neonatal surgeries performed on patients with transposition of the great arteries in the 1970s [14], surgical techniques evolved and were gradually standardized, allowing complex repairs and palliation for lesions such as hypoplastic left heart syndrome that were previously considered inoperable [15]. With time, even symptomatic neonates with tetralogy of Fallot were repaired in the neonatal period rather than being subject to palliative shunts [16,17]. Recent advances in the treatment of these patients, e.g., the introduction of the RV-to-PA shunt (the Sano shunt) for patients with hypoplastic heart syndrome, further improved results [18].

**OVERALL PEDIATRIC CARDIAC SURGERY RESULTS**

During the past decade, 4450 pediatric patients underwent cardiac surgery at our institution, of whom 1003 (22.5%) were neonates. We sought to assess our results and compare them with the results of leading centers in the world.

Surgical results can be evaluated using formulated complexity scores, the most recent being the Aristotle Complexity Score (ACS), which is based on the primary procedure of a given operation. Huge databases have been created. In 2005, the American Society of Thoracic Surgeons (STS) database accounted for 18,928 patients, and the European database (EACTS) added 21,916 patients [19]. For the whole patient cohort, operative mortality at our institution was 2.96%. This is substantially lower than the mortality reported in the American STS database (4.5%) and in the European EACTS database (5.4%). Moreover, our complexity scores (measured annually), 7.2–7.4, were higher than the STS mean complexity score (7.1) and the European score (6.5).

Nevertheless, comparing results is a difficult task. There is a complex relationship between cardiac surgical case volumes and mortality rates [11]. Overall mortality in centers performing more than 350 cases annually was 3.2%, while in centers performing 250–350 cases annually the mortality was 3.7%, and in smaller centers 4.1%. This difference is more pronounced in high complexity cases, where mortality was found to be 7.2%, 8.4%, and 13% respectively [11]. Comparisons aside, this sends a clear message, namely, that in this field one must create a few, high volume centers of excellence rather than focus on patient convenience and geographic distribution.

**NEONATAL CARDIAC SURGERY RESULTS**

Neonatal cardiac surgical mortality was also evaluated using these large databases. The STS reported neonatal operative mortality of 12.2%, and the EACTS reported 13.3% [19]. More recently, the EACTS reported their results in 14,843 neonates operated on between 1999 and 2009 [3]. For this cohort of patients, out-of-hospital postoperative mortality was 10.7%. Out-of-hospital mortality at our institution for neonates was only 7.2%, which compares favorably with the international results.

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**Table 1. Neonatal surgical mortality**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sub-diagnosis</th>
<th>No. of patients</th>
<th>Schneider (No. %)</th>
<th>mortality</th>
<th>STS / EACTS / selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>Total</td>
<td>185</td>
<td>12, 6.4%</td>
<td>6% [1]</td>
<td>11% [1]</td>
</tr>
<tr>
<td></td>
<td>TGA VSD</td>
<td>37</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TGA CoA</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TGA VSD CoA</td>
<td>11</td>
<td>1, 9%</td>
<td>3, 20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taussig Bing</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoA</td>
<td>Total</td>
<td>338</td>
<td>5, 2.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simple</td>
<td>198</td>
<td>2, 2.3%</td>
<td>16% [2]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CoA CoA</td>
<td>85</td>
<td>1</td>
<td>1, 6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoplastic arch</td>
<td>24</td>
<td>2, 1, 4%</td>
<td>3, 4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single ventricle</td>
<td>7</td>
<td>1</td>
<td>5, 2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CoA AVSD</td>
<td>4</td>
<td></td>
<td>2, 3%</td>
<td></td>
</tr>
<tr>
<td>Shunt</td>
<td>Total</td>
<td>131</td>
<td>16, 12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PA IVS</td>
<td>40</td>
<td>5, 12.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TOF</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOF</td>
<td>Complete repair</td>
<td>41</td>
<td>0</td>
<td>6% [7]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shunt</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Truncus</td>
<td>26</td>
<td>1, 3.8%</td>
<td>15.4% [2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IAA VSD</td>
<td>25</td>
<td>1, 4%</td>
<td>14.5% [2]</td>
<td>19.2% [3]</td>
<td></td>
</tr>
<tr>
<td>TAPVR</td>
<td>Total</td>
<td>39</td>
<td>2, 5.1%</td>
<td>10.7% [2]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infra-cardiac obstructed</td>
<td>10</td>
<td>2, 20%</td>
<td>16.5% [3]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>29</td>
<td></td>
<td>14% [10]</td>
<td></td>
</tr>
</tbody>
</table>

Neonatal surgical mortality by diagnosis for patients operated. TGA = transposition of great arteries, VSD = ventricular septal defect, IAA = interrupted aortic arch, TAPVR = total anomalous venous repair, TOF = tetralogy of Fallot, CoA = coarctation, PA IVS = pulmonary atresia intact septum.
RESULTS FOR SPECIFIC LESIONS IN THE NEONATAL GROUP
In order to further scrutinize our results, we sought to compare surgery for specific important lesions with published results of leading international cardiovascular centers. Transposition of the great arteries (TGA) is a congenital cardiac malformation in which both great vessels emerge from the “wrong” ventricle; consequently, the systemic circulation and the myocardium receive deoxygenated blood while the lungs recirculate oxygenated blood. Survival of the neonate is only possible due to mixing of oxygenated and deoxygenated blood via communication between the two circulations. Operative repair is achieved by “switching” back the great arteries and the coronary arteries, the arterial switch operation (ASO). There is a wide spectrum of anatomic variants that make the operation much more complex, as reflected in the operative results of the different subgroups [20]. Complex transpositions include associated ventricular septal defects (VSD), coronary anomalies, malposition of the great vessels and aortic coarctation (CoA). In 2010, the group from Ann Arbor Michigan published results for their complete cohort of ASOs. Their demographics are similar to ours, and their operative mortality was 6%, similar to our result of 6.2% [20]. Taking a closer look at the various subgroups of the complex transpositions, we had no mortality in the complex group of TGA VSD (37 patients), and only one patient died in the TGA VSD CoA group (11 patients). Taussing-Bing anomaly is one of the most complex anomalies within the transposition spectrum. In this anomaly, both great vessels arise from the right ventricle alongside each other, making the operative reconstruction extremely difficult. In this challenging subgroup of patients we lost 3 of the 15 patients.

EARLY COMPLETE REPAIR VS. MULTI-STATE STRATEGIES
Single-stage repair and complete and early physiological correction are the hallmarks of modern neonatal cardiac surgery. As neonatal cardiac surgery evolved, however, it became apparent that early surgical correction is also beneficial to palliation; benefits include promotion of normal growth and development of organs, and the elimination of hypoxemia. These benefits had to outweigh the surgical risks at an early age. Improved surgical results have been made possible by meticulous surgical techniques and improved cardiopulmonary bypass protocols and hardware.

Surgical treatment of tetralogy of Fallot (TOF) has changed dramatically since the first palliation was performed by Alfred Blalock in 1945; palliative procedures have been replaced with complete repair in infancy, but treatment of symptomatic neonatal patients is still controversial. Advocates of neonatal palliation claim that it reduces the need for future trans-annular patching and decreases the risk of early mortality, while advocates of neonatal complete repair claim that mortality is lower and the avoidance of cyanosis and chronic right ventricular overload beneficial to the patient in the long run. A multicenter analysis published just recently reports that of 845 patients with ductal-dependent TOF, 41% underwent complete repair, while 59% underwent initial palliation [7]. Operative mortality was found to be similar for the first operation (7.8% vs. 6%), though the staged palliative approach was associated with higher morbidity [7]. Our approach has been towards early complete repair; although it is more technically challenging, in our opinion it yields better results. Of 45 patients presenting with clinically symptomatic neonatal TOF who required surgery, 4 patients (10%) were palliated while complete neonatal repair was performed in 41 patients. There was no operative mortality, which is comparable with contemporary leading cardiosurgical centers (1.6% [8], 0% [9]). Such low mortality in the complete repair of neonatal TOF is a clear reflection of the sum ability of all teams caring for the neonate with complex congenital heart disease.

Another lesion that demonstrates the advantage of complete early correction is coarctation of aorta in conjunction with a hemodynamically significant VSD (CoA VSD). The optimal surgical strategy has been controversial [21]. There are three surgical options: the first and most conservative is the two-stage repair, in which the coarctation is repaired through a left thoracotomy and a band is placed around the pulmonary artery through the same incision; the VSD is closed when the child is older and bigger. The second option is a single-stage repair with two incisions, whereby the coarctation is repaired through a left thoracotomy incision, followed by a VSD closure through a sternotomy. The third strategy is concomitant repair of the arch and the VSD through sternotomy using regional cerebral perfusion. The latter is our preferred strategy.

NEUROLOGICAL IMPLICATIONS
With the significant advances achieved in the repair of complex congenital heart defects and the consistent reduction in mortality, focus was directed towards preservation of the neurological status. One of the most important technical modifications was the use of selective cerebral perfusion when performing arch reconstruction [22]. Historically, repair of complex congenital heart defects was associated with a high incidence of clinical and subclinical seizures (28% and 67% respectively in patients with TGA VSD) [23]. In our neonates the rate of postoperative seizure is well under 2% over the last 5 years. Clearly, further evaluation and follow-up are required to assess the issue of neurological outcome of neonatal cardiac surgery, which is beyond the scope of this paper.

Cardiopulmonary bypass is initiated by cannulating the innominate artery and lowering the core temperature to 28°C. Once the target temperature has been reached, total body circulatory arrest is initiated and the brain is selectively perfused through the innominate artery. The aortic arch is then repaired, usually taking 20–30 minutes. Total body perfusion is then re-instituted, and the VSD is subsequently closed. Among 85 patients with CoA VSD who were operated upon using this
technique, there were 2 deaths (2.3%), similar to the results published by Sandhu et al. (5.3%) [4] and Gaynor et al. (4%) [5].

Using selective cerebral perfusion, we have performed 206 arch reconstructions without noticing clinically significant neurological events. Furthermore, we have performed 71 Norwood Sano operations with 19% mortality, which favorably compares with the results reported by the STS (24%), EACTS (36.2%), and with results reported from high volume leading North American institutions (17%) [11].

OUR SERVICE

Neonatal cardiac surgery has evolved and changed over the last two decades, many insights were acquired, and as experience and confidence were built the surgical procedures were stretched even further and closer to the limit. With time, our specialized neonatal service has evolved as well, and 1000 cases have taught us many lessons. Strategically, the quest to achieve complete and early physiologic repair, although technically more complex and demanding, is for the benefit of the patient. The evolution of new surgical routines and the use of selective cerebral perfusion further allowed us to improve our results and decrease morbidity and mortality.

Achieving surgical results that are on par with the highest international standards has been made possible through years of cumulative experience and the incorporation of improvements and innovations into our service. The success of a cardiovascular service is not only dependent on flawless, non-compromising surgical results but also on a sound and solid supporting infrastructure providing accurate diagnosis and making the correct preoperative decisions. Prenatal diagnosis allows better planning of birth place and immediate postnatal assessment and treatment. Intraoperative cardiology support is imperative for confirming the diagnosis and for providing perioperative online quality control. Smooth and experienced anesthesia decreases the morbidity associated with the treatment of the smaller babies. Postoperative proactive intensive care unit (ICU) treatment with tight cooperation between the surgeons, the intensivists and the cardiologists provide continuity of care, where the sick child is at all times treated by a senior physician well acquainted with his or her disease.

Finally, beyond technological advances and the availability of the various disciplines, we strongly believe that two additional elements are absolutely necessary (but not sufficient) for achieving the results like the ones we have attained: (i) concentration of the activity in order to gain expertise through experience, even at the expense of patient convenience, and (ii) a truly cohesive team that works together, putting the optimal outcome of the patient as its only goal and achieving a total that far exceeds its components.

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References

Occult Bacteremia: Should We Look for the Needle in the Haystack?

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ABSTRACT: Background: Once a well-recognized entity, occult bacteremia (OB) is no longer a significant serious bacterial infection. First following the introduction of the Haemophilus influenzae type B vaccine and now with the implementation of the conjugate pneumococcal vaccine (PCV), the number of cases has declined significantly. This has led to a change in many published guidelines to avoid taking blood cultures in fully vaccinated children presenting with fever. In Israel, the introduction of the PCV13 is now widespread.

Objectives: To assess the incidence and outcome of OB, specifically by Streptococcus pneumoniae, in a single large pediatric medical center.

Methods: We conducted a retrospective review of all cases of pneumococcal bacteremias in the years 2008–2013 and specifically those considered occult.

Results: Of 355 cases of bacteremia diagnosed during the study period, 164 were caused by S. pneumoniae and 20 (12.8%) were considered occult. None of the OB cases had any complications. OB was not found in children over the age of 36 months. There was a change in the serotypes involving pneumococcal OB.

Conclusions: OB is uncommon in the PCV-vaccinated population and the serotypes involved have changed.

KEY WORDS: bacteremia, Pneumococcus, fever, blood culture, conjugate vaccine

Patients and Methods

A retrospective cohort study was performed using the Shaare Zedek computerized database. All true bacteremias were identified and verified by the Infectious Disease Unit. The files of pneumococcal bacteremias were reviewed in order to identify those fitting the diagnosis of OB (a well-appearing child with fever without source, regardless of laboratory findings). Contaminants were determined based on an evaluation of such cases by an infectious disease specialist. At Shaare Zedek all cases of pneumococcal bacteremia are further assessed for specific serotyping.

The files included children aged 3 months–18 years who had blood cultures drawn in the PED. In the event of positive cultures and specifically Streptococcus pneumoniae, the files were reviewed by two of the researchers to determine the bacteremia as occult.

The pneumococcal bacteremias were divided into OB, bacteremias with a source, and bacteremias in ill-appearing children with fever and no obvious source. The investigators reviewed each case and agreed on the final allocation of each case. This study was approved by the hospital’s ethics committee. Statistical analysis was based on Microsoft Excel (Microsoft Inc.) and McCallum-Layton & Co. (UK).
RESULTS

BACTEREMIAS
During the years 2008–2013 a total of 43,650 blood cultures were taken from febrile children. Of these, 354 cases were determined to be true bacteremias, of which 163 were caused by S. pneumoniae (46%). Other common causes were S. aureus (14%), Haemophilus influenzae (all types) (7%), Escherichia coli (6%) and group A Streptococcus (5%). Compared to other bacteremias, pneumococcal bacteremias showed the greatest decline.

OCCULT BACTEREMIAS [Table 1]
Of 26 cases considered as occult, 20 were caused by S. pneumoniae (77.7%). The other causes were Salmonella spp. (2 cases), H. influenzae non-typable (2 cases), Neisseria meningitidis (1 case) and Brucella melitensis (1 case). The children with S. pneumoniae OB met the criteria originally set by Baraff [3] with white blood cell counts (WBC) above 15,000 cells and elevated absolute neutrophil counts. There were 12 males and 8 females with an average age of 22.2 months [SD ± 8.77, 95% confidence interval (95%CI) 13.4–30.9]. An interesting finding was associated febrile seizures (FS) in 7 cases (33%). All cases of OB were discharged from the Emergency Department (ED). The majority of children were discharged with oral antibiotics (19/20) with one child receiving no treatment and one who received two doses of ceftriaxone and was then continued on oral antibiotics. Amoxicillin was the most commonly prescribed antibiotic (14/18) and four others received oral cefuroxime due to a suspected penicillin allergy. Two cases required admission. One was a 15 month old male who in addition had signs of glomerulonephritis and a 5 year old female who on readmission was described as “still looking ill to the parents.” Only two cases were over the age of 36 months. One was later diagnosed with a lobar pneumonia and the second child, as mentioned previously, may not have met the standard of “well appearing.” None of the pneumococcal OB cases developed complications [Table 2].

PNEUMOCOCCAL BACTEREMIA SEROTYPES
The distribution of serotypes was different between the bacteremia and OB groups. The OB group showed only single cases caused by serotypes 5 and 1, which accounted for approximately half of identified serotype bacteremias [Figure 1]. This may represent a direct effect of the coverage achieved by the PCV.

DISCUSSION
This study shows the relative paucity of pneumococcal bacteremias in general and OB specifically. This may help in focusing the use of blood cultures and less as a sampling aid for febrile children. Although the number of cases of OB in this study is too small to draw statistical conclusions, it would seem that OB is rare in vaccinated febrile patients in the PED. By sampling all febrile children our results are more likely to avoid possible biases.

Our results show, as has been previously published, that introduction of the PCV led to a sharp decline in pneumococcal OB. This decline can be seen even though none of the patients with pneumococcal OB received PCV13, and only five were given at least one dose of PCV7. However, only partial information regarding vaccinations was available and in only 14 cases. In addition, cases of OB were managed orally with no significant

Table 1. Bacteremia and occult bacteremia in the Department of Pediatrics at Shaare Zedek

<table>
<thead>
<tr>
<th>Non-pneumococcal bacteremias</th>
<th>Pneumococcal bacteremias: OB/non-occult (%)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>6/29 (20%)</td>
<td>2008</td>
</tr>
<tr>
<td>28</td>
<td>9/39 (23%)</td>
<td>2009</td>
</tr>
<tr>
<td>46</td>
<td>1/24 (4%)</td>
<td>2010</td>
</tr>
<tr>
<td>30</td>
<td>3/33 (9%)</td>
<td>2011</td>
</tr>
<tr>
<td>29</td>
<td>1/17 (5%)</td>
<td>2012</td>
</tr>
<tr>
<td>27</td>
<td>0/13 (0%)</td>
<td>2013</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of occult bacteremia

<table>
<thead>
<tr>
<th>Occult pneumococcal bacteremia (n)</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>22.2 (SD ± 8.77, 95%CI 13.4–30.9)</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>8/12</td>
</tr>
<tr>
<td>Discharge/Admission</td>
<td>18/2</td>
</tr>
<tr>
<td>Antibiotics (IV/oral/none)</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Complications</td>
<td>0</td>
</tr>
</tbody>
</table>
complications. This was described recently by Vaillancourt et al. [5] who showed no immediate complications in children who returned to the ED with a final diagnosis of bacteremia or meningitis compared to children with the same diagnosis who were admitted on their first visit.

Since cases of OB are rare today, the use of additional markers beyond the traditional WBC, such as CRP or procalcitonin, may have a greater role than ever. Several studies have shown improved diagnosis incorporating additional biomarkers (e.g., CRP, procalcitonin, and interleukin-6) into the workup of FWS [6,7]. At Shaare Zedek these markers were not readily available and thus were under-utilized in the evaluation of febrile children.

In our study the distribution of pneumococcal serotypes in OB was different to that described in southern Israel [8]. The dominant serotypes in our center were 6A, 12F, 14 and 23F, compared to the results in southern Israel which consisted mostly of serotypes 19A, 1, 6B and 9V. The number of cases is relatively small so it may be hard to conclude the significance of this finding within the same country.

In this single-center retrospective study, the decline in OB by Pneumococcus is strongly reiterated. In Israel there has been a continued decline since the introduction of PCV7 followed by PCV13 [9]. The balance between the fear of missing bacteremia with severe complications compared to what seems a very high number needed to treat is a continuing challenge in the ED setting [10].

The presentation of a third of the cases of OB with a febrile seizure was unexpected. It has long been demonstrated that febrile seizures do not convey a higher risk for bacteremia than any other febrile child [11,12]. This was demonstrated even before PCV was fully implemented. Previous reviews, including in Israel, already showed that a febrile seizure was not associated with bacterial meningitis [13].

This study has several limitations. Its retrospective nature is an inherent limitation. In addition, we were unable to find the number of febrile children discharged with antibiotics and no growth in their cultures. Since treating empirically is common at our institute when OB is suspected, it may be assumed that the number far exceeds its need. Our total number of cultures is likely to include some of the repeated cultures.

CONCLUSIONS
The number of OB cases in the age of PCV13 continues to decline in our center, as has been described in other studies. This calls for more accurate consideration based both on the history (vaccination status) and laboratory results (CRP, procalcitonin, etc.). The serotypes involved in OB at our center are different than those described in other regions in Israel, yet still show a serotype shift from the pre-PCV period.

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References

“The opposite of love is not hate, it’s indifference. The opposite of art is not ugliness, it’s indifference. The opposite of faith is not heresy, it’s indifference. And the opposite of life is not death, it’s indifference”

Elie Wiesel (1928-2016), Romanian-born American Jewish writer, professor, political activist, Nobel Laureate and Holocaust survivor. He was the author of 57 books, written mostly in French and English, including Night, a work based on his experiences as a prisoner in the Auschwitz and Buchenwald concentration camps.
Exploring the Association between Legg-Calvé-Perthes Disease and Attention Deficit Hyperactivity Disorder in Children

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1Hebrew University-Hadassah Medical School, and Departments of 2Pediatric Neurology and 3Orthopedic Surgery, Shaare Zedek Medical Center affiliated with Hebrew University-Hadassah Medical School, Jerusalem, Israel

ABSTRACT: Background: Legg-Calvé-Perthes disease (LCPD) is an idiopathic hip osteonecrosis prevalent in children < age 15 years. The etiology remains incompletely understood, partly because of multiple potential environmental risk factors and partly because of lack of genetic markers. It has been hypothesized that hyperactivity may induce mechanical stress and/or vascular damage at a fragile joint.

Objectives: To assess children with LCPD for markers of attention deficit hyperactivity disorder (ADHD) relative to their unaffected comparably aged siblings to exclude the contribution of hyperactive behavior versus environmental and/or genetic factors in LCPD.

Methods: All children followed in the Pediatric Orthopedic Clinic, and their comparably aged siblings, were recruited. ADHD was assessed using the TOVA computerized test and DSM-IV criteria. Quality of life and sleep disorders as ancillary tests were assessed using the Child Health Questionnaire (Parent Form 50), Pediatric Outcomes Data Collection Instrument, and Pediatric Daytime Sleepiness Scale.

Results: Sixteen children with LCPD (age 9.1 ± 3.3, 75% males) were compared with their closest-aged siblings (age 9.3 ± 2.6, 30% males). Mean TOVA scores of children with LCPD (3.79 ± 2.6) and of their non-LCPD siblings (-3.6 ± 4.04) were lower relative to the general population (0 ± 1.8, P < 0.0001). Both group means were in the ADHD range (≤ -1.8) implying that 73% of this LCPD cohort and 53% of their non-LCPD siblings performed in the ADHD range, relative to 3.6% incidence expected in the general population (P < 0.0001). Other test results were similar in both groups.

Conclusions: Our findings in a small cohort of children with LCPD and their comparably aged siblings do not support an association between LCPD and ADHD. ADHD markers were equally high in the LCPD children and siblings.

KEY WORDS: attention deficit hyperactivity disorder (ADHD), Legg-Calvé-Perthes disease (LCPD), sibling study

Despite decades of experience with varying medical and surgical management approaches to Legg-Calvé-Perthes disease (LCPD), an idiopathic osteonecrosis of the hip in children, the etiology remains incompletely understood. Hence, identifying at-risk pediatric patients has been unsuccessful. The incidence of LCPD ranges from 0.4/100,000 to 29.0/100,000 (approximately 1 in 1200) among children under 15 years of age with peak presentation between the ages of 4 and 8 years. There is some heterogeneity based on racial groupings and socioeconomic status, and some abnormalities in growth parameters [1,2]. While LCPD is more frequent among boys, it is generally accepted that the prognosis is worse for girls, who often present with radiological evidence of a greater degree of damage [3].

There is little evidence implicating a purely genetic etiology, whereas rat models of mechanical stress at the hip joint successfully mimic the LCPD hip [4]. Other indices of a non-genetic nature of those at risk of developing LCPD include commonality of some conditions: many of these children are products of a breech delivery, many are constitutionally shorter than their siblings and parents, they are often third- or later-born, and generally many are from low-income families. These factors presumably render these specific children at greater risk of trauma [5].

The more classic hypotheses of the pathophysiology of LCPD, such as intermittent arterial occlusion and/or repeated trauma to vulnerable revascularizing bone [6], are being re-interpreted as also being reflective of mechanical stressors such as impeded or forestalled plasticity of the acetabulum by age 9 years [7] and retroversion of the acetabulum [8]. Interestingly, both of these theories consider possible initiation and/or exacerbation of bone damage by hyperactivity. Indeed in a recent study, a significant percentage (> 90%) of LCPD patients reported being active at a moderate or high level although half of them also reported moderate or severe bone pain [9].

The long-term consequences of this complex hip deformity are readily recognized in terms of impaired ambulation/functioning, chronic pain, and reduced quality of life even in adulthood and regardless of therapeutic correction in childhood [9]. Associations with other disorders that evince hyperactivity in
children have become of interest as a means towards understanding the pathology of LCPD [10,11]. Consequently, attention deficit hyperactivity disorder (ADHD) has been scrutinized as a confounding variable in the etiology of LCPD in children [9,10,12,13]. Those previous studies contained small cohorts and did not include evaluation of ADHD in control groups.

Meta-regression analyses have estimated the worldwide prevalence of ADHD to be between 5.3% and 7.1% in children and adolescents with an increased incidence among boys [14]. The hypothetical basis of the association of LCPD (which might yet have some unidentified genetic predilection) with ADHD is that LCPD could be induced by early and physiologically abnormal stress of a fragile bone because of hyperactivity.

The purpose of the present study was to assess (Israeli) children with LCPD for objective markers of ADHD relative to their unaffected and comparably aged siblings, to exclude the relative contribution of behavioral rather than environmental features of LCPD.

PATIENTS AND METHODS

All 16 children aged 4–15 years currently being followed for LCPD in the Pediatric Orthopedic Clinic were recruited. Healthy siblings of these patients who were aged 4–15 years, none of whom have LCPD or ADHD, were recruited as controls. Institutional Helsinki Committee approval was received for this study.

The diagnosis of LCPD was based on the child’s complaints and history, complete physical examination, and repeated radiological evidence, characteristic of LCPD. ADHD was assessed using the TOVA computerized test [15], where a score of 0 ± 1.8 points represents the norm. An in-depth interview was conducted with the child to evaluate the degree of meeting the criteria of the DSM-IV for ADHD by one of us (J.B.). In addition, the following tests were administered:

- Complete neurological physical examination
- The Child Health Questionnaire (Parent Form 50, CHQ-PF50) in Hebrew that queries 14 domains of physical, psychosocial, and familial conditions
- The Pediatric Outcomes Data Collection Instrument (PODCI), a standard form to assess changes in pediatric patients with musculoskeletal signs after orthopedic event/intervention. It is based on four functional assessment scores, a global function score, and a happiness score with each having a possible range from 0 to 100 [16]
- The Pediatric Daytime Sleepiness Scale (PDSS), since daytime sleepiness is related to reduced educational achievement, possibly due to inattention [17].

STATISTICAL ANALYSIS

The chi-square, Fisher’s exact, Student’s t-test and McNemar tests were applied as appropriate. For non-parametric comparisons, the Mann-Whitney-Wilcoxon U test or Kruskal-Wallis R test was used.

RESULTS

Among the siblings of the LCPD patients, 13 met the age criterion and were recruited as the control population; for 3 children with LCPD there were no siblings to match the age criteria. None of the LCPD children had a sibling of any age with LCPD.

Table 1 presents the demographic features and outcomes in pediatric LCPD patients and their comparably aged siblings.

<table>
<thead>
<tr>
<th>Diagnosis of ADHD as per TOVA</th>
<th>LCPD patients (n=16)</th>
<th>Siblings (n=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean TOVA score SD</td>
<td>-3.79 ± 2.67</td>
<td>3.6 ± 4.04</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis of ADHD as per TOVA</td>
<td>12 (75%)</td>
<td>7 (53.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean TOVA score SD</td>
<td>-3.79 ± 2.67</td>
<td>3.6 ± 4.04</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis of ADHD as per TOVA</td>
<td>12 (75%)</td>
<td>7 (53.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PDSS score</td>
<td>7.75</td>
<td>7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PODCI score</td>
<td>88.25</td>
<td>Not applicable</td>
<td></td>
</tr>
</tbody>
</table>

ADHD = attention deficit hyperactivity disorder, CHQ = Child Health Questionnaire, PDSS = Pediatric Daytime Sleepiness Scale, PODCI = Pediatric Outcomes Data Collection Instrument, NS = not significant

DISCUSSION

This study attempted to evaluate the incidence of ADHD among patients with LCPD. Earlier studies have postulated it to be higher than in the general population [9,10,12,18]. It was assumed that the comparably aged healthy siblings of children with LCPD would be representative of the general
A potential explanation for comparable Quality of Life scores between groups is that the parent is the one who completes the questionnaire for both of the children and may thus inadvertently bias the results. However, the comparable TOVA scores, based on testing that is individual to each child and unrelated to a parental assessment, represents an unexpected finding of comparable performance indicative of ADHD among both groups of children, none of whom had been suspected of being ADHD. The imputation of a genetic factor in ADHD was previously reported as an endophenotype of ADHD/inattention [20] and is independent of gender.

In summary, this study aimed to implicate a predisposition to hyperactivity as an underlying stressor for hip osteonecrosis in LCPD patients. We uncovered a high percentage of children suspected of having ADHD among both the LCPD children and their non-LCPD siblings based on TOVA scores. This study attempted to isolate hyperactive behavior patterns as an etiological factor in LCPD by employing a comparably aged sibling cohort to decrease the environmental and genetic confounders. Thus, the hypothesis that a predilection to ADHD predisposes to LCPD is not supported by our findings.

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References

“Don’t walk in front of me… I may not follow
Don’t walk behind me… I may not lead
Walk beside me… just be my friend”

Albert Camus (1913-1960), French philosopher, author, and journalist
Seasonality of Methylphenidate Administration among Children in Israel

Herman A. Cohen MD, Bella Savitsky MPH, Arie Ashkenasi MD and Moshe Hoshen PhD

Background: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattention, impulsivity and hyperactivity. Recently, increases in ADHD prevalence and methylphenidate use have been reported. There is evidence that children and adolescents use ADHD medication only during the school year.

Objectives: To investigate trends in methylphenidate dispensing over a period of 3 years (2010–2012) at the monthly level and to investigate whether there is any monthly variation, especially during the summer season.

Methods: The database of Clalit Health Services (the largest of the four health funds in Israel) was used to identify (i) patients aged 6–17 years with a diagnosis of ADHD, and (ii) methylphenidate dispensation during the period 2010–2012.

Results: Among children aged 6–17 years diagnosed with ADHD, 43% were treated with methylphenidate. For the period 2010 to 2012 there was an annual drop in methylphenidate dispensing, beginning in June and continuing through the 2 months of summer vacation, with a 2.5-fold reduction from July as compared to May. This decline was consistently followed by a rise in medications dispensed starting August. A similar small drop was observed during the Passover school vacation. The summer drop decreased over the years.

Conclusions: Our findings showed a decrease in the number of methylphenidate prescriptions dispensed during the summer months and Passover as compared to the rest of the year. However, this phenomenon appears to be decreasing. Given that ADHD is a chronic disease state that can effectively be managed with pharmacotherapy, discontinuation of treatment may be harmful for patients and should be considered only on a patient-by-patient basis.

Key Words: attention deficit hyperactive disorder (ADHD), children, adolescents, prescription, dispensing, seasonality

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder characterized by the symptoms of inattention, impulsivity and hyperactivity. It occurs in approximately 8% of children and youth [1]. ADHD is a disorder that affects children and adolescents in multiple ways and to varying extents, with the consequences of the condition greatly impacting patients, their families and those around them. Treatments and interventions for ADHD differ, with the focus mainly on psychological therapies and pharmacological treatment [1-3]. Over the last decade, increases in ADHD prevalence and use of ADHD prescription medications have been reported in many countries, including Israel [4,5]. In Israel, when drug treatment is considered appropriate for the patient, the central nervous system stimulant methylphenidate is recommended as the first-line therapy in children aged 6 years and older [4,5]. Consistent with the increasing trends in prevalence, a recent study showed that the consumption of ADHD drugs in Israel doubled between 2005 and 2012 [4].

The risks of untreated ADHD can include under-achievement at school, impaired relationships with family members, teachers and friends, increased rates of criminality and accidents, and the development of co-morbid psychiatric symptoms including oppositionality, anxiety, depression and substance abuse [6]. Most of the evidence suggests that the benefits of pharmacological treatments in managing ADHD outweigh the potential for adverse events or side effects from the medications, e.g., appetite suppression and growth delay [7]. However, there is considerable individual variation in physician management of these side effects, the most debated being the issue of “medication holidays” [8]. There is some evidence that many children and adolescents use ADHD medication only during the school year [9]. Cascade et al. [9] demonstrated a significant seasonality, with the total volume of monthly prescriptions falling between 22% and 29% from May to July, depending on the year [9]. Further research comparing adherence during the school year to adherence year-round found that adherence levels are higher during the school year than over the entire year [10], suggesting an effect of seasonality associated with ADHD medication use. The extent of methylphenidate discontinuation during summer school vacation in Israel is unknown. The aim of this study was to investigate the trends in monthly levels of methylphenidate dispensing over a 3-year period (2010–2012), including whether there are seasonal or monthly variations and whether these trends are changing.

In Israel, there are differences between cultural and socioeconomic groups in educational frameworks, as well as in awareness about behavioral disorders. This can affect the avail-
ability of adequate medical services for diagnosis and access to certain treatments. In the north of the country this gap was shown to result in differences in diagnosis and treatment rates of ADHD [11]. Increases in ADHD diagnosis and treatment with methylphenidate have been particularly notable among girls [5]. In this study different population groups such as Arab and ultra-Orthodox will be studied separately to provide additional knowledge on ADHD-related trends.

SUBJECTS AND METHODS

Clalit Health Services is Israel’s largest health fund which serves as an insurer and health care provider, covering 53% of Israel’s population and supplying most of the health care services within its system. In Clalit, children are predominantly treated at community primary care clinics by board-certified pediatricians, non-board-certified pediatricians, and general practitioners. Membership in one of four health funds is mandatory and, while transferring is simple, members rarely switch health funds in Israel (~1% per year), thus enabling long-term case histories. All of Clalit’s primary and secondary care physicians and pharmacies use an advanced electronic medical records system which feeds into the central database of the organization. This database contains over a decade of patient-level data including sociodemographic, clinical, health care utilization, and drug purchasing data.

STUDY DESIGN

We conducted a historical cohort study of Clalit children aged 6–17 years old during 2010–2012 (study period) with active diagnoses of ADHD. With the diagnosis – a legal pre-condition for methylphenidate prescriptions – methylphenidate dispensing patterns were analyzed among children diagnosed during the study period. Although there is no confirmation that medications were taken after prescription purchases, those for whom prescriptions were purchased were considered to be treated for the purposes of this study.

<table>
<thead>
<tr>
<th>Data Sources and Covariates</th>
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</table>
| Information on ADHD diagnosis was gathered from all Clalit primary care physicians through the Clalit chronic and permanent diagnosis databases (ICD-9 codes 314.00 and 314.01 were included). In the Israeli health care system, only methylphenidate is included in the pharmaceutical reimbursement list for ADHD treatment, hence methylphenidate is the drug of choice for treatment of ADHD. Information on the dispensing of methylphenidate prescriptions summed by month during the entire study period, and summed by week for the months June–September was gathered from the Clalit pharmacy database. The month and the week within a calendar year were taken as variables for the analysis of seasonality changes in methylphenidate dispensing. Other covariates included age (categorized into two groups: 6–11 years and 12–17 years, determined at the start of each calendar year), gender and population sector (a variable taken at the clinic level, indicating whether the clinic is serving predominantly General Jewish, ultra-Orthodox-Jewish or Arab populations). The study was approved by the Clalit community health institutional review board.

<table>
<thead>
<tr>
<th>Statistical Analysis</th>
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</table>
| The prevalence of ADHD in 2012 was calculated as the number of children with existent diagnoses of ADHD at the beginning of 2012 divided by the total number of children aged 6–17 years in the Clalit database at the same time, using either crude rates or split by age, gender and/or population sector groups. The annual rate of treatment with methylphenidate was calculated as the proportion of children filling at least one methylphenidate prescription during the year among the children diagnosed with ADHD by the beginning of the year. This rate was assessed according to age, gender and population group. The number of children treated by methylphenidate was also calculated on a monthly basis, with analysis comparing the 2 months of summer vacation (July and August) to the rest of the year. These rates were also based on the population at the beginning of the year. In addition, weekly trends were analyzed for the summer vacation period (from the end of June until the beginning of September) to determine the time point of change in the methylphenidate dispensing trend. The rate of stopping treatment was defined as the ratio of the number of children for whom medication was not purchased during July and August over the number of children for whom medication was purchased during May and June. The ratio was calculated separately for every population group and for each year of study. Comparisons were assessed by chi-square test and by ANOVA.

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of ADHD</td>
</tr>
</tbody>
</table>
| A total of 795,057 members aged 6–17 years old were identified in the Clalit database as of 1 January 2012 [Table 1]. Among them, 13.3% (105,806) were diagnosed as having ADHD. Boys comprised 69% of ADHD-diagnosed children, and 79.0% were...
SUMMER DISCONTINUATION OF METHYLPHENIDATE TREATMENT

From 2010 to 2012 there was a clear downward annual drop in the dispensing of methylphenidate during the 2 months of summer vacation (July and August), beginning in June and continuing into August. Medications were dispensed in July at a rate that was 2.5-fold lower than in May (range 2.4–2.6 during 2010–2012). A smaller but similar drop was observed in the spring seasons of March 2010 and April 2011 and 2012, corresponding to shorter holiday vacation breaks [Figure 1]. When examining the drop in medications dispensed during the summer at higher temporal resolution (by week), the drop begins annually during the two last weeks of June and continues during July and early August [Figure 2]. During the last 2 weeks of August, dispensing increases. In 2012, this elevation was sharpest (in this particular year the school year started 1 week earlier). Overall, a drop of 38% was observed in the last week of June (range 31%–44%), 57% in the third week of July (range 54–59%), and a drop of 64% (range 62–65%) in the second week of August, all relative to the first week of June. The same analysis was conducted separately for children aged 6–11 years and those 12–17 years old, and for boys and girls. Similar annual patterns were observed in these subgroup analyses, indicating a decrease in drug issuing during the summer vacation months.

We conducted a separate analysis to study the discontinuation of treatment during July and August among children who were treated during May and June [Table 2]. Overall, the percentage of children stopping treatment in July and August declined over the 3 year period: 37.0% in 2010, 30.0% in 2011 and 24.0% in 2012 (P value for trend < 0.0001). This downward trend in stopping treatment during the summer months was consistent and significant among all subgroups. A comparison of demographic characteristics of children who were untreated during the 2 months of summer vacation shows that the frequency of stopping treatment was slightly lower among boys (vs. girls), aged 6–11 (vs. aged 12–17) and among ultra-Orthodox Jews (vs. the Arab group and General Jewish groups), as depicted in Table 2.

Figure 1. Number of children aged 6–17 treated with methylphenidate by month and year

Figure 2. Number of children aged 6–17 treated with methylphenidate end of June–beginning of September, by week

Table 2. Percentage of children who were not treated with methylphenidate during summer vacation (July and August) among those treated in previous May and June, by gender, age and population group, by year

<table>
<thead>
<tr>
<th>Gender</th>
<th>2010</th>
<th>P value</th>
<th>2011</th>
<th>P value</th>
<th>2012</th>
<th>P value</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>36.1</td>
<td>0.0005</td>
<td>29.0</td>
<td>0.002</td>
<td>23.1</td>
<td>0.001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>40.2</td>
<td></td>
<td>33.4</td>
<td></td>
<td>27.0</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population group</th>
<th>2010</th>
<th>P value</th>
<th>2011</th>
<th>P value</th>
<th>2012</th>
<th>P value</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabs</td>
<td>38.0</td>
<td>&lt; 0.0001</td>
<td>36.2</td>
<td>&lt; 0.0001</td>
<td>27.5</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Ultra-Orthodox</td>
<td>22.3</td>
<td>&lt; 0.0001</td>
<td>16.3</td>
<td>&lt; 0.0001</td>
<td>14.5</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
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<td>&lt; 0.0001</td>
<td>30.4</td>
<td>&lt; 0.0001</td>
<td>24.6</td>
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<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

<table>
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<th>Age group</th>
<th>6–11</th>
<th>P value</th>
<th>2011</th>
<th>P value</th>
<th>2012</th>
<th>P value</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35.9</td>
<td>&lt; 0.0001</td>
<td>28.2</td>
<td>&lt; 0.0001</td>
<td>22.5</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>40.5</td>
<td></td>
<td>33.9</td>
<td></td>
<td>28.8</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

from the General Jewish population sector, while ultra-Orthodox patients comprised 4.9% and Arab patients 16.1% (these population groups comprise 56.4%, 5.6% and 38.0% respectively of the entire relevant age group). Hence the General Jewish population had increased risk of being diagnosed with ADHD [relative risk (RR) 1.53, 95% confidence interval (95%CI) 1.49–1.57] compared to the ultra-Orthodox Jewish population, and even more compared to the Arab population (RR 3.40, 95%CI 3.35–4.46). The highest percentage of diagnosed children treated with methylphenidate was observed in the General Jewish group (46.9%), followed by the ultra-Orthodox group (41.7%), and the lowest in the Arab group (24.2%). Thus, Arab children had both lower diagnosis (in the total population) and lower treatment rates (among diagnosed patients) (RR 1.93, 95%CI 1.87–1.98) compared to the Jewish children from the General and ultra-Orthodox groups.
DISCUSSION

The prevalence of ADHD in the Israeli pediatric population found in this study (13%) is similar to previously reported prevalence statistics among schoolchildren worldwide (2%–17%) [12], with a higher prevalence of the disorder among boys. The prevalence of medication prescribed to those diagnosed in this study (43%) matches rates of treatment in other developed countries (32–71%) [13,14].

Medication is frequently used in the clinical management of ADHD, and clinical trials have shown psychostimulants to be highly efficacious, with a ≥ 70% rate of clinical responders [15]. Despite this efficacy, there is evidence that seasonal patterns in ADHD medication usage are related to school year calendars for many children and adolescents [9,16]. The findings of the current study show similar results; in Israel there was a consistent reduction in the dispensing of methylphenidate during June, July and August – 26%, 60% and 43% respectively – as compared to May. A more moderate reduction was also observed during the 3 week Passover school vacation (March 2010, April 2011 and April 2012). With no rise in medication dispensing in June, compared to previous school-year months, over-purchasing of medications (stockpiling) before the summer vacation can be ruled out. This notable shift in treatment emphasizes the need for improved awareness among physicians, patients and their parents regarding the importance of continued treatment for those patients considered to need ongoing, uninterrupted medical treatment. Inconsistent or non-existent treatment of ADHD is quite problematic. When left untreated, the core symptoms of ADHD appear to increase the risk for substance abuse disorders and antisocial behavior. Substance abuse subsequently further negatively affects the core symptoms of ADHD, leading to more functional impairment [9]. A recent observational study reassessed a UK cohort of 126 school-aged children with ADHD 5 years later in adolescence. The research team found that about 70% of the sample met the full criteria for ADHD and that most of the sample exhibited high levels of antisocial and criminal behavior and substance abuse problems in adolescence [17]. Only 10% of the sample appeared to have functionally and symptomatically recovered, some of whom continued to be prescribed medication.

Beyond the public health concern that a high proportion of ADHD pediatric patients do not receive any treatment, many patients receive only intermittent dosing of ADHD medications. Intermittent dosing of ADHD medication can lead to problems from the frequent need to both redevelop initial medication tolerance and re-accommodate to adverse events. Unfortunately, patients’ and/or parents’ efforts to minimize time spent on ADHD medications require their starting and stopping ADHD medications repeatedly, which may actually have the paradoxical effect of increasing the overall side effect burden for patients. This repeated starting and stopping by patients or their parents in relation to the school year (and in many cases just for weekends [8]) may initiate stimulant discontinuation-related adverse events.

Barner et al. [18] and Marcus et al. [19] found poor persistence and adherence to ADHD medication over a 1 year period in the Texas Medicaid and California Medicaid systems respectively. Barner and co-authors reported 3.2 to 5.1 months persistence before a 30 day break, and Marcus et al. a 4.7 month period with extended-release methylphenidate and a 3.5 month period with immediate-release methylphenidate, indicating that children did not persist for half a year on therapy. Low adherence rates can be attributed to parents providing medications to their children only on school days, omitting weekends, holidays and summer months. This is supported by Faraone and colleagues [20] who reported that 30.5% of children in their study took “planned medication breaks.”

The strategy of weekend holidays during methylphenidate use is controversial. In the present study, the phenomenon of stopping treatment during summer vacation was slightly more frequent among girls. Prior research found that girls with ADHD may be less disruptive and less impulsive [21] than boys with ADHD, and it is possible that such behavioral differences permit a break in treatment during summer vacation. Additionally, the present study found a higher frequency of treatment breaks among adolescents aged 12–17 years. Prior research found a general alleviation of ADHD symptoms that occurs with age [22], and it is possible that this alleviation may contribute to treatment breaks. Among boys from the ultra-Orthodox group, the frequency of stopping treatment in the summertime was lower than among boys from other population groups, probably because of the shorter summer vacation in the ultra-Orthodox male education system, while the frequency of treatment breaks among ultra-Orthodox girls was similar among girls from other population groups, as the length of summer vacation for ultra-Orthodox girls is the same as in the other population sectors. This study shows that this tendency towards discontinuation of treatment during the summer vacation in Israel is in decline.

Continuation in treatment is generally desirable. There are significant life impairments found in individuals with ADHD. Among young people, difficulties with completion of homework, participation in extracurricular activities, the ability to pay attention while driving and to resist engaging in risky behaviors have been noted, and uninterrupted treatment may help to reduce such difficulties [23]. Furthermore, children and adolescents adhering to consistent medication management for their ADHD treatment may be better able to control their behavior and impulsivity, resulting in less criticism and better feedback from caregivers and peers. Such feedback is likely to bolster the children and adolescents’ self-esteem. During their late adolescent years, relationships, self-esteem, substance abuse, work, and other problems are
associated with having had ADHD as a child. Suspending the treatment that improves these conditions is not in a patient's best interests.

Current guidelines suggest that physicians treat ADHD as a chronic medical condition [1,24] and, certainly, consistent treatment of most chronic medical illnesses usually gives patients and those treating them better results than episodic medication management. While school-year-only dosing of ADHD medications may be acceptable for some, the vast majority of children and adolescents do better even in extra-school behavior when they take their ADHD medication regularly [19]. As Findling et al. discuss [25], there are myriad non-school-related activities in patients’ lives that may benefit from continued treatment. As such, compulsory medication breaks are not recommended; rather, the need to take such breaks should be considered on a case-by-case basis and should not be implemented as a general rule.

According to Van De Loo-Neus and team [15], there is limited and inconsistent evidence for long-term advantages of medication treatment beyond symptom control, such as improved social functioning, academic achievement, employment status and fewer adverse psychiatric outcomes. In terms of safety, long-term effects of medication on growth, blood pressure and heart rate are limited and the occurrence of suicidal, psychotic and manic symptoms is rare [15]. Therefore, this group recommends that clinical decisions about starting, continuing, and stopping ADHD medication be made on an individual basis and medication-free periods implemented at regular times to investigate the need for an ongoing benefit of medication [15]. It is worth considering Findling’s assertion that child psychiatrists and neurologists generally continue pharmacological treatment of their patients throughout the summer months, while pediatricians tend towards summer breaks in treatment [25]. Clearly, there is a discrepancy in the information dispensed to psychiatrists and neurologists versus that dispensed to pediatricians.

Use of a retrospective prescription database to examine ADHD adherence and persistence patterns has the advantage of examining large populations (such as the present cohort of 105,806 children with a previous or current diagnosis of ADHD, of whom 45,516 were treated with methylphenidate during the study period) and medication prescribing patterns over longer follow-up periods.

LIMITATIONS
This study, while analyzing a large cohort, carries some limitations. To begin with, diagnoses are registered by a physician during a parent-initiated visit to a clinic, in contrast to a survey with psychological evaluation. This may carry the risk of a few causes of bias, under-reporting due to parents’ and teachers’ lack of attention to the child’s behavioral condition or due to parents’ intention to avoid blemishing a child’s clinical file (two factors that may partially cause the gender and sector imbalance). In addition, some contacts may be initiated with the intent to receive methylphenidate prescriptions to “calm” disorderly but healthy children. While we have complete data on patient primary care physician visits and drug purchasing, we obviously do not know whether the drugs were consumed immediately or at all; we may, however, assume that most patients will not purchase more chronic medications when they have considerable supplies at home. Thus, incomplete adherence will tend to smooth out over time. On the other hand, the examination of potential early purchases of stocks before summer trips abroad did not suggest an increase in late June–early July before children travel with their parents, but rather indicated a decrease in such purchases. In addition, our database does not allow us to distinguish reliably between subtypes of ADHD which could potentially show different seasonal patterns. This study did not compare written prescriptions with filled prescriptions and thus we cannot differentiate whether low purchase rates are due to physicians’ instructions or to low patient compliance.

CONCLUSIONS
The present study determined that, indeed, there is a decrease in the number of methylphenidate prescriptions dispensed in Israel during the summer months and Passover break as compared to the rest of the year. However, it is worth noting that this phenomenon appears to be decreasing on an annual basis. It is possible that such a decrease is related to increased awareness among doctors, parents and patients of the potential harms associated with treatment breaks. Given that ADHD is a chronic disease state that can effectively be managed with pharmacotherapy, discontinuation of treatment may be harmful for patients and should be considered only on a patient-by-patient basis. Because treatment breaks can result in symptom deterioration, it is recommended that providers identify patients with poor adherence and determine the reasons for non-adherence (e.g., side effects, forgetfulness, parent or child opposition, etc.). After doing so, providers may be able to successfully intervene with strategies to address any barriers to medication adherence, which will likely improve patient outcome.

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References


Do You See It My Way? The Clinical Evaluation of ADHD by the Different Pediatric Subspecialties

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2Child Development Center, Clalit Health Care Services, Netanya, Israel
3Child and Adolescent Psychiatry, Beer Yaacov Psychiatric Hospital, Nes Tziona, Israel

ABSTRACT: Background: Three medical disciplines are responsible for assessment, diagnosis and treatment of people with attention deficit hyperactivity disorder (ADHD) in Israel: pediatricians/family doctors, adult and child neurologists, and adult and child psychiatrists.

Objectives: To investigate differences in ADHD diagnostic practices between three different pediatric subspecialties in the clinical setting in order to establish a common ground for a future unified approach.

Methods: An anonymous web-based questionnaire was administered to child psychiatrists, pediatric neurologists and general pediatricians who are actively involved in ADHD diagnosis (n=104).

Results: Neurologists and pediatricians rarely use the mental status examination, while psychiatrists rarely perform a neurological or physical examination (P < 0.0001). A general clinical impression of learning abilities and/or neurodevelopmental skills was implemented more often by pediatric neurologists (P < 0.04).

Conclusions: The significant differences found between the three medical specialties with regard to the clinical evaluation of ADHD could be attributed, at least in part, to the ambiguity of available guidelines concerning the clinical examination, and to the adherence of each specialty to its own “skills.” Larger surveys in other countries should be considered and an effort made to create a common, “inter-disciplinary” ground on this important part of ADHD evaluation, differential diagnosis, and research.

KEY WORDS: attention deficit hyperactivity disorder (ADHD), clinical evaluation, pediatric subspecialties

The diagnostic process required in attention deficit hyperactivity disorder (ADHD) is described by several consensus statements and guidelines in the medical literature worldwide [1-3]. Most guidelines describe in great detail how to gather information regarding the patient’s functioning and symptoms of ADHD by performing both an open interview and a structured interview in accordance with the DSM-5 and/or ICD-10 criteria, and by the use of rating scales answered by both parents and teachers or other caregivers familiar with the patient. As for the direct clinical impression and/or examination, guidelines tend to be less descriptive. The NICE [1] Guideline 2008 states that the diagnosis should be based on “a full clinical and psychosocial assessment of the person; this should include discussion about behavior and symptoms in the different domains and settings of the person’s everyday life, a full developmental and psychiatric history, and observer reports and assessment of the person’s mental state.” Tools to use in the assessment of younger school-age children are not specifically described.

In the American Association of Pediatrics (AAP) Clinical Practice Guidelines for the Diagnosis, Evaluation & Treatment of ADHD, from 2011 [2,3], aimed at primary care physicians, the clinician is asked (in Recommendation 2) to establish DSM criteria [4] by obtaining reports from those involved in the child’s care. With regard to the direct clinical evaluation of the child/adolescent, the Guidelines require a “clinical interview with the child” and an updated physical examination (including hearing and vision). Here, again, the nature and content of the “clinical interview” is not specifically described.

The American Academy of Child and Adolescent Psychiatry practice parameters from 2007 [3] (Recommendation 2) ask the clinician to first interview caregivers, and then to evaluate the child or adolescent. The guidelines mention that the primary purpose of the interview with the child or adolescent is not to confirm or refute the diagnosis of ADHD; rather it is meant to “to identify signs or symptoms inconsistent with ADHD or suggestive of other serious co-morbid disorders.” The authors explain that “Young children are often unaware of their symptoms of ADHD, and older children and adolescents may be aware of symptoms but will minimize their significance.” Therefore, it is recommended that the clinician perform a mental status examination, assessing appearance, sensorial, mood, affect, and thought processes. No other clinical tools, (e.g., neurodevelopmental assessment or a neurological examination), except for the mental status examination, are mentioned. ICD-10 [5] does not mention a physical exam at all in the context of ADHD or its differential diagnosis (World Health Organization, 1993). To date, The American Academy of Neurology (AAN)
and the Child Neurology Society (CNS) have not published guidelines or a consensus regarding the clinical tools for the diagnosis of ADHD.

In Israel, the official Ministry of Health Guidelines [6], published in 2010, describe in detail the tools that should be used in the diagnostic process of ADHD in both adults and children, including a detailed history, establishing symptoms in accordance with DSM criteria, the use of rating scales and questionnaires, and the necessity to evaluate co-morbidity and consider the differential diagnosis. When it comes to the clinical evaluation, the guidelines only ask for it to be a “thorough” examination, without further details. Psychiatric evaluation, cognitive or psycho-educational assessment, is defined as optional.

Doodley et al. [7] found that for the majority of children (including children with ADHD) the critical component of the pediatric neurology consultation is a detailed clinical history, but most clinicians agree that physical examination is at least necessary to rule out other conditions in the differential diagnosis of ADHD [1-10]. In most countries, several (pediatric) subspecialists – such as primary care pediatricians/family physicians, developmental-behavioral pediatricians, pediatric neurologists and child psychiatrists – are involved in the initial diagnosis and care of children with ADHD. The present Practice Guidelines, coming from both Pediatric/Family practice and from Psychiatry, as earlier mentioned, do not provide a common ground from which these various disciplines can derive a common understanding on how to clinically assess their pediatric patients. In light of this ambiguity, the aim of the present survey was to study the clinical tools used by different medical disciplines with regard to the examination of the child and/or adolescent suspected of having ADHD. We hypothesized that while all disciplines use similar tools to elicit DSM-5/ICD-10 criteria for the diagnosis, their ways of obtaining direct clinical impression of the patient are diverse.

**SUBJECTS AND METHODS**

An anonymous web-based questionnaire was administered to physicians who are actively involved in the diagnosis and treatment of children and adolescents with ADHD, in both the public and private sectors. In Israel, child psychiatrists and pediatric neurologists, as well as primary care pediatricians with Ministry of Health continuing medical education (CME) training in ADHD are involved in the diagnosis of the disorder, while the continuous management and treatment are usually managed by the primary care pediatrician. These physicians were personally approached at medical conferences and local seminars, and others were contacted by telephone, and urged by the study investigators to answer the web-based questionnaire. All were informed of the anonymous nature of the questionnaire.

The questionnaire included 30 questions, most with 4 possible answers (regularly, sometimes, rarely, never) or other choices relevant to the questions. Questions reviewed the demographic and professional characteristics of the physician and description of his/her work environment, and his/her ADHD diagnostic protocol, with a special emphasis on the direct clinical encounter with the patient. Other questions reviewed the physician’s preferences with regard to ADHD clinical guidelines and participation in continuous education activities and conferences. The questions relevant to the description of the clinical diagnostic process were translated to English [Table 1]. The study was approved by the Medical Center Ethics Committee no. TLV-0457-14.

**STATISTICAL ANALYSIS**

All participants were grouped into three categories in accordance with their medical specialty. Descriptive statistics were used to analyze the demographic data such as age and years of experience using one-way ANOVA. In some of the questions we merged several answers into a joint category, e.g., place of medical school or residency were recategorized to “Israel” or “other.” The answers to elements of the clinical impression performed were grouped into two categories: “regularly” or “other” instead of “sometimes,” “rarely” or “never.” The total duration of examination was restructured as 15 minutes, up to one hour, or over an hour. The number of visits was regarded as one or more. Follow-up frequency was analyzed in three categories instead of six (> 3 per year, 1-2 per year, or as needed). Patients’ ages were divided into all ages vs. 6–18 years old. All questions were compared using χ² tests between-group rates; significant values were those for which the P value was < 0.05.

**Table 1. Description of the direct* clinical evaluation of the child/adolescent by the three medical disciplines**

<table>
<thead>
<tr>
<th>Question: Which of the following items are included in your diagnostic evaluation of ADHD?</th>
<th>Psychiatrists</th>
<th>Neurologists</th>
<th>Pediatrists</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>An open interview with parents or caregivers Regularly/Other</td>
<td>33/0 (100%)</td>
<td>29/0 (100%)</td>
<td>42/0 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>A structured interview in accordance with DSM criteria Regularly/Other</td>
<td>22/10 (68.8%/31.2%)</td>
<td>23/4 (85.2%/14.8%)</td>
<td>40/2 (95.2%/4.8%)</td>
<td>&lt; 0.008</td>
</tr>
<tr>
<td>A neurological examination Regularly/Other</td>
<td>1/31 (3.1%/96.9%)</td>
<td>29/0 (100%/0%)</td>
<td>32/11 (59.6%/40.4%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A physical examination Regularly/Other</td>
<td>1/29 (3.5%/96.7%)</td>
<td>25/3 (88.9%/10.7%)</td>
<td>36/7 (83.7%/16.3%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Clinical impression from learning abilities, and/or neurodevelopment Regularly/Other</td>
<td>23/10 (69.7%/30.3%)</td>
<td>26/3 (89.7%/10.3%)</td>
<td>27/16 (62.8%/37.2%)</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>Psychiatric evaluation (mental status) Regularly/Other</td>
<td>33/0 (100%/0%)</td>
<td>3/17 (15%/85%)</td>
<td>7/29 (19.4%/80.6%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Excluding use of rating scales, questionnaires, or computerized tests  
** Yes = usually, Other = occasionally, rarely, never
**RESULTS**

A total of 104 physicians completed the questionnaire, 42 pediatricians, 33 child psychiatrists, and 29 pediatric neurologists. No significant differences were found between the three medical specialties with regard to demographic characteristics (age, gender, and country of birth, country of medical studies, country of internship or years of experience); 69.9% graduated from medical schools in Israel, and 93.3% completed their residency in Israel. The mean time of active medical practice after residency was 16.03 years (SD 9.8), with no significant difference between the three medical specialties [Table 2]. Pediatricians gained their knowledge regarding ADHD in the CME courses, while psychiatrists and neurologists reported to have acquired their knowledge during their primary residency (P < 0.0001). Pediatricians usually evaluated ADHD patients within their primary care pediatric practice (mostly in the public sector), while pediatric neurologists and child psychiatrists divided their practices between the public sector and private consultations (P < 0.001). Pediatric neurologists were significantly more involved in the diagnosis and treatment of preschool children (younger than 6 years), while the other two specialties reported that they treated patients between the ages of 6 and 18 years (P < 0.0001). Question 12 in the questionnaire was devoted to the details of the clinical examination of children evaluated for ADHD [Table 1]. All groups reported that they conducted an open interview with the parents, with no significant difference between the three specialties. Pediatricians used a structured interview in accordance with the DSM-5 criteria significantly more than the other specialties (P < 0.008). A most striking difference was found with regard to the neurological examination: with 31/32 psychiatrists (96.6%) reporting that they do not regularly perform this examination and only three of them reporting they perform it sometimes, while 74% of pediatricians and 100% of pediatric neurologists report performing a neurological examination regularly during the initial evaluation of their patients (P < 0.0001). All the child psychiatrists reported regularly performing a mental status examination/interview as part of their clinical evaluation of the patient, but only 19% and 15% of pediatricians and pediatric neurologists, respectively, reported doing so regularly (P < 0.0001), while 7/29 pediatricians and 3/17 neurologists reported assessing it sometimes. Furthermore, 89% and 83% of neurologists and pediatricians, respectively, regularly perform a general physical examination, while 3% of psychiatrists report doing so (P < 0.0001). As for a general evaluation of learning abilities and/or neurodevelopment, e.g., reading, writing, mathematical, memory, grapho-motor abilities, expressive and receptive language, general knowledge, etc. (some or all of these), 89.7% of neurologists, 69.7% of psychiatrists and 62.8% of pediatricians reported regularly assessing these skills (P < 0.04).

All specialists reported using parental and teacher rating scales (93% and 95% respectively), such as the Vanderbilt or Conner, with no significant difference between the groups, but only 37.5% of the whole group reported using a co-morbidity rating scale, with no significant difference between the specialties. Pediatricians reported that they rarely or never ask for a psycho-educational evaluation as part of the initial ADHD diagnostic process, while psychiatrists and neurologists do so more often (14%–15% of the cases) (P < 0.0001). Of all physicians, 54% reported using a computerized performance test (CPT) as part of their initial diagnostic process, but psychiatrists tended to use these tests more often (P < 0.023). Regarding duration of testing, 59.2% of respondents reported that their evaluation takes more than 60 minutes, while the others reported a single diagnostic visit to be shorter than 60 minutes, with no significant difference between the groups. Psychiatrists need more than one visit to complete the diagnostic process, significantly more often than the other disciplines (P < 0.0001). Moreover, 52.4% of physicians reported regularly including another professional in their diagnostic process (a psychologist, social worker, nurse or student), with no significant difference between the specialties.

Blood tests and electroencephalogram (EEG) are recommended significantly more often by psychiatrists (P < 0.011). Vision and hearing tests are recommended as an integral part of the ADHD evaluation by only 34–35% of the physicians, with no significant differences between the specialties. Pediatricians and psychiatrists request more frequent follow-up visits (> 3 per year) than neurologists (P < 0.004).

As for Continuous Medical Education activities, most physicians (64%) reported attending at least one workshop or ADHD conference annually. Pediatricians and pediatric neurologists (48.8% and 51.7%) stated that they refer to the AAP guidelines regarding ADHD, while only 9.1% of psychiatrists reported using these guidelines (P < 0.0001); 72.7% of psychiatrists reported referring to the AACAP guidelines, compared to 23% and 10%

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**Table 2. Demographic data of the physicians who participated in the survey**

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Psychiatrists</th>
<th>Neurologists</th>
<th>Pediatricians</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Female/Male</td>
<td>23/10</td>
<td>16/13</td>
<td>21/21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(69.7%/30.3%)</td>
<td>(55.2%/44.8%)</td>
<td>(50%/50%)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs) Mean (SD)</td>
<td>51.4 (9.8)</td>
<td>51.8 (8.7)</td>
<td>53.6 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Israel/Other</td>
<td>16/17</td>
<td>10/10</td>
<td>16/27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(48.5%/51.5%)</td>
<td>(65.5%/34.5%)</td>
<td>(57.2%/42.8%)</td>
<td></td>
</tr>
<tr>
<td>Country of medical school</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Israel/Other</td>
<td>25/7</td>
<td>20/9</td>
<td>27/15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(78.1%/21.9%)</td>
<td>(69%/31%)</td>
<td>(84.3%/15.7%)</td>
<td></td>
</tr>
<tr>
<td>Country of internship</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Israel/Other</td>
<td>32/1</td>
<td>27/2</td>
<td>38/4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(97%/3%)</td>
<td>(93.1%/6.9%)</td>
<td>(90.5%/9.5%)</td>
<td></td>
</tr>
<tr>
<td>Professional experience (yrs)</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>15.45</td>
<td>13.93</td>
<td>18.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(11.2)</td>
<td>(10.9)</td>
<td>(7.5)</td>
<td></td>
</tr>
<tr>
<td>Patients’ age range</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6–18 yrs/6 yrs</td>
<td>19/14</td>
<td>6/23</td>
<td>32/11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(57.6%/42.4%)</td>
<td>(20.7%/79.3%)</td>
<td>(74.4%/25.6%)</td>
<td></td>
</tr>
<tr>
<td>ADHD knowledge acquisition</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Internship/CME</td>
<td>31/1</td>
<td>26/2</td>
<td>5/38</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(96.9%/3.1%)</td>
<td>(92.0%/7.1%)</td>
<td>(11.6%/88.4%)</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

Our survey showed that physicians from all three medical specialties involved in ADHD diagnosis apply similar protocols with regard to obtaining the DSM-5 or ICD-10 criteria from parent or caregiver interviews, and by using well-accepted rating scales. The direct clinical examination of children and adolescents, however, differs significantly between the specialties. Neurologists and general pediatricians rarely use the mental status examination as a routine tool, while psychiatrists rarely perform a neurological or physical examination. A general clinical impression of learning abilities and/or neurodevelopmental skills is reported to be included as part of ADHD evaluation significantly more often by pediatric neurologists than by the other two disciplines. Pediatricians rarely ask for a psychoeducational evaluation as part of their ADHD evaluation. Laboratory tests are significantly more often recommended by psychiatrists. Surprisingly, and despite present guidelines, only 35% of all physicians ask for a vision and hearing test as part of their initial evaluation. Practitioners from different medical specialties tend to use their “own” guidelines with regard to the diagnostic protocol. In a recent study [11] of the clinical practices used by developmental-behavioral pediatricians (DBPs) in the United States, using the DBPnet, the authors found that DBPs were highly likely to complete comprehensive assessments of ADHD that went beyond the requirements of primary care (AAP) practice guidelines. They typically identified coexisting developmental and learning conditions. In our survey, such practices were partly reported by pediatric neurologists, but not by the other medical specialties.

The weakness of this survey is its small size, reflecting local practices in our country, and the fact that surveys only show what the respondent chooses to report. While it has its limitations, we believe the very significant differences found between the medical disciplines reflect the present ambiguity of global consensus statements and clinical guidelines with regard to the specifics of the clinical evaluation of the child or adolescent. As we mentioned earlier, most of these guidelines are very descriptive and specific with regard to the tools used to elicit DSM-5/ICD-10 behavioral criteria, but are less descriptive and at times confusing with regard to the nature of the clinical examination.

It seems that the guidelines recommend using diagnostic tools that are familiar to each medical specialty, avoiding a more “holistic” approach to the examination.

CONCLUSIONS

While the contribution of the clinical impression of ADHD in the setting of the physician's office is known to be limited, as it does not reflect the child's natural environments, we feel the significant differences described here should at least prompt further and larger surveys in other countries. To the best of our knowledge no such surveys have been reported. If indeed similar differences are found in other countries, an effort should be made to reach a common interdisciplinary ground with regard to the actual clinical examination of the child or adolescent with ADHD. It is essential not only for the correct differential diagnosis but also for creating a uniform language with regard to ADHD science and research.

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References


“If you tell the truth, you don't have to remember anything”

Mark Twain (1835-1910), American writer, best known for his novels The Adventures of Tom Sawyer and its sequel, Adventures of Huckleberry Finn, the latter often called “The Great American Novel"
Angiographic Embolization in Pediatric Abdominal Trauma

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ABSTRACT: Background: Trauma is the leading cause of childhood morbidity and mortality. Abdominal bleeding is one of the common causes of mortality due to trauma. Angiography and embolization are well recognized as the primary treatments in certain cases of acute traumatic hemorrhage in adults; however, evidence is lacking in the pediatric population.

Objectives: To assess the safety and efficacy of transcatheter arterial embolization (TAE) for blunt and penetrating abdominal and pelvic trauma in the pediatric age group.

Methods: Three children with blunt abdominal trauma and one child with iatrogenic renal injury (age 4–13 years) were managed with TAE for lacerated liver (one patient), pelvic fractures (one patient) and renal injuries (two patients). The first two patients, victims of road accidents, had multisystem injuries and were treated by emergency embolization after fluid resuscitation in the Emergency Department (ED). The other two patients had renal injuries: a 4 year old boy with blunt abdominal trauma was diagnosed on initial computed tomography with an unexpected Wilms tumor and was treated with embolization 1 day after admission due to hemodynamic deterioration caused by active arterial tumor bleeding. The following day he underwent successful nephrectomy. The other patient, a 13 year old boy with nephrotic syndrome, who transiently responded to the initial fluid resuscitation. The other patient was 13 year old boy with nephrotic syndrome who underwent renal biopsy and developed hemodynamic instability. After fluid resuscitation, he underwent an initial negative angiography, but second-look angiography the following day revealed active bleeding from an aberrant renal artery, which was then successfully embolized.

Results: In all four patients, TAE was diagnostic as well as therapeutic, and no child required surgical intervention for control of bleeding.

Conclusions: We propose that emergency transcatheter angiography and arterial embolization be considered following resuscitation in the ED as initial treatment in children with ongoing bleeding after blunt abdominal trauma or iatrogenic renal injury. Implementation of this policy demands availability and cooperation of the interventional radiology services.

KEY WORDS: angiography, embolization, abdominal trauma, bleeding, resuscitation, Wilms tumor

For more than 40 years trauma has been considered the leading cause of childhood death (age < 18 years), with an annual mortality that is continuously increasing [1,2]. Ninety percent of childhood injuries are associated with blunt trauma, with head and limb injuries being the most common forms. Abdominal trauma in up to 8% of these severe cases includes primarily solid organs (ASO), liver, spleen and kidney involvement [3]. The spleen is the most commonly injured intraabdominal organ. Injuries to the liver, spleen and pancreas occur in two typical scenarios: isolated injury caused by a direct blow to the upper abdomen, or multisystem trauma caused by high energy mechanisms (e.g., motor vehicle or all-terrain vehicle crash, fall from a great height) [4].

In the adult population, liver, splenic, renal and pelvic arterial embolization (AE) was introduced to achieve organ preservation in injured patients who would traditionally have undergone organ dissection [5]. Pediatric experience with AE for blunt ASO injuries is limited [6,7]. Most children with solid organ injuries are managed in accordance with the NOM protocol; this includes observation and blood transfusion, which although uncommon, is the most frequent therapeutic intervention. Angiographic embolization and laparotomy are infrequently performed [8].

We present four pediatric trauma patients in which transcatheter arterial embolization (TAE) was performed to determine the efficacy and safety of this non-surgical management. TAE was performed in pediatric patients with blunt multiple trauma (three patients) and penetrating injury (one patient) who transiently responded to the initial fluid resuscitation.

PATIENT DESCRIPTIONS

Three children with blunt abdominal trauma and one child with iatrogenic renal injury (ages 4–13 years) were managed with TAE for lacerated liver (one patient), pelvic fracture (one patient) and renal injuries (two patients). The first two patients, victims of road accidents, were resuscitated in the ED. The other two patients had renal injuries: a 4 year old boy with blunt abdominal trauma was diagnosed on initial computed tomography (CT) with an unexpected Wilms tumor and was treated with embolization for an arterial tumor bleeding. The following day he underwent successful nephrectomy. The other patient, a 13 year old boy with
nephrotic syndrome, underwent renal biopsy and developed hemodynamic instability. He underwent an initial negative angiography, but second-look angiography the following day revealed active bleeding from an aberrant renal artery, which was then successfully embolized.

**PATIENT 1**

A 5 year old boy arrived at the ED after being hit by a car while crossing the road. His vital signs were: Glasgow Coma Scale (GCS) 15, heart rate 160–170/min, blood pressure 140/75 and 100% saturation. A scalp laceration and fracture of the left humerus were diagnosed. Chest X-ray demonstrated bilateral pneumothorax and bilateral lung contusions with a fracture of the right clavicle. On arrival he was treated with fluid resuscitation, placement of two chest tube drains and tracheal intubation. Focused abdominal sonography (FAST) examination showed fluid in the abdominal cavity. Head CT was normal without skull fracture or intracranial bleeding. Abdominal CT showed active liver bleeding with associated hematoma of the right hepatic lobe. Figure 1A demonstrates contrast blush on CT angiography in an actively bleeding branch of the right hepatic artery; Figure 1B shows the bleeding on conventional selective hepatic angiography.

After the successful angiography and embolization, his scalp laceration was sutured and the arm fracture was reduced. The boy was released home in good condition after 1 week of hospitalization.

**PATIENT 2**

A 4½ year old boy arrived at the emergency room after an abdominal injury as a result of a fall. His vital signs were pulse 130/min, saturation 98% and GCS 15. His physical examination demonstrated a slightly swollen abdomen. His left upper abdomen was sensitive to palpation, suspicious for splenic injury. However, abdominal CT demonstrated a neoplastic mass emerging from the left kidney. The mass was 15 cm in diameter and suspicious for Wilms tumor.

Pathological blood vessels were seen covering the tumor; in addition, some pelvic fluid was also detected. Subsequent to the abdominal tumor diagnosis, the child was admitted to our pediatric surgical department. On the following day he developed pallor and tachycardia. Intravenous fluid and blood transfusion were administered, and he was sent for repeat abdominal CT, including CT angiography. Using this approach, active tumor bleeding was identified. Figure 2 demonstrates the findings of the second abdominal CT. Figure 2A and 2B show the contrast blush in both transverse and coronal planes. Figure 2C demonstrates a selective left renal arteriogram that pinpointed the actively bleeding vessels. Following the diagnosis of active bleeding, percutaneous selective catheter insertion was used for arterial embolization. The following day the child was hemo-
dynamically stable and on the second post-embolization day he underwent left nephrectomy combined with placement of Port-A-Cath for chemotherapy treatment.

The child successfully completed the chemotherapy and radiotherapy protocol. On our last follow-up exam, 6 years after surgery, he was in good condition.

**PATIENT 3**

A 13 year old boy, who had previously been diagnosed with nephrotic syndrome, arrived at the emergency room complaining of abdominal pain. The child’s renal function progressively deteriorated and he began to suffer from anuria. He underwent a renal biopsy which was followed by hemodynamic and respiratory deterioration. In addition, his hemoglobin values were decreased. Abdominal ultrasound followed by abdominal CT demonstrated a large left retroperitoneal hematoma. No active bleeding had been recognized at this stage. After 48 hours of hospitalization the patient’s clinical condition further deteriorated including tachycardia and a decrease in hemoglobin levels. To determine the reason for this clinical picture it was decided to perform second-look angiography, which showed that the recognized retroperitoneal hematoma diameter had increased. In a selective angiogram of the third aberrant left renal artery, active bleeding was detected. Figure 3 demonstrates the retroperitoneal hematoma and the selective angiogram of the aberrant renal artery, showing contrast extravasation. The hemodynamic condition of the child was stabilized. Following the angiographic embolization, the diagnosed large abdominal hematoma gradually began to shrink.

**PATIENT 4**

An injured 10 year old girl arrived at the emergency room after being hit by a car while walking. Her vital signs were GCS 15, pulse 136/min, blood pressure 130/86, and 100% saturation. A hematoma of the left pelvis and vaginal bleeding had been noticed during physical examination. Her neck and chest X-ray were normal but pelvic X-ray confirmed pelvic fractures. Abdominal CT demonstrated several injuries: left kidney contusion, retroperitoneal hematoma, pelvic fractures, and bilateral ramus pubis and sacro-iliac joint fractures. In addition, active pelvic bleeding was diagnosed.

Initial emergency treatment included intravenous fluids and blood transfusion. Angiography of the left iliac artery showed active bleeding which was treated by embolization. In the selective angiogram of the left internal iliac artery [Figure 4] extravasation is seen; after embolization there was no extravasation.

After the angiographic embolization, the external pelvic fractures were stabilized. Her vaginal bleeding and tears in the vaginal wall were treated by packing. After hospitalization of 1 week she was discharged home in good condition.

**DISCUSSION**

Angiography is a common treatment specifically used in adults with blunt abdominal trauma and/or severe pelvic fractures. The usefulness of such treatment in the pediatric trauma care setting is unclear. Recently, the Committee on Trauma of the American College of Surgeons advocated that angiography be urgently available at pediatric trauma centers. Angiography and embolization techniques are well described in arresting severe active bleeding in adults. CT angiography followed by catheter angiography is beneficial: it saves time, and enables precise identification of the injury locus and dimensions. The quicker these parameters are recognized and categorized, the quicker the health care personnel can plan an effective method to stop the bleeding. Such prompt and accurate treatment might constitute a lifesaving method in cases of severe bleeding.

The knowledge regarding pediatric treatment applying angiography and embolization for blunt ASO injuries is comparatively limited [8,9]. Skattum et al. [10] demonstrated improvement of non-operative management with splenic preservation from 90% to 98% with use of splenic angio-embolization. Kiankhooy and team [6] successfully treated seven children...
with angio-embolization: three hepatic and four splenic. Interestingly, the average time from evaluation to embolization in this study was 11 hours. Vo et al. [9] demonstrated that hemorrhage due to pelvic fractures could successfully be managed with embolization.

Our purpose was to determine the efficacy and safety of angiography in the treatment of blunt abdominal trauma in injured children. This report described four cases of successful treatment for pediatric abdominal injuries using angiographic embolization. The age range of the described cases was 4.5–13 years old. In all four cases the use of angiography and embolization was found effective in three aspects: it is an improved diagnostic tool, an accurate treatment method, and an efficient treatment method. It was shown by us and others that the use of angiography embolization in the pediatric population leads to a favorable treatment outcome. In particular, it was shown that among patients who transiently respond to initial fluid resuscitation, transcatheter arterial embolization (TAE) was found valuable.

CONCLUSIONS
We have presented four cases showing various scenarios of pediatric trauma and demonstrated that angiographic embolization can have tremendous value in stabilization and definitive treatment of serious trauma. We strongly believe that pediatric trauma surgeons as well as invasive radiologists should be able to treat children applying these techniques. It should be mentioned that the described method requires highly skilled personnel and adequate equipment availability around the clock in any trauma medical center. In addition, the success of this modality is based on cooperation among the personnel of several departments and units, including pediatric surgery, interventional radiology, anesthesiology and pediatric intensive care.

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References
One-Stage Laparoscopic Orchiopexy for the Treatment of Intraabdominal Testis

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ABSTRACT: Background: Laparoscopy has gradually become the gold standard for the treatment of non-palpable testicles (NPT), with different success and complication rates. Objectives: To evaluate outcomes of the one-stage laparoscopic orchiopexy for NPT in our department. Methods: We retrospectively evaluated the medical files of patients who underwent laparoscopic orchiopexy with the identical technique. Only patients with at least one year follow-up were included. At follow-up we assessed the age (at surgery), follow-up time, laterality of testes, postoperative complications, testicular size and testicular localization. Results: Thirty-six consecutive patients, median age 16 months, underwent one-stage laparoscopic orchiopexy. Sixteen patients (44.4%) had peeping testis type, in 13 patients (36.1%) the testicle was located within 2 cm from the internal ring and in the remaining 7 patients (19.4%) it was detected > 2 cm from the internal ring. In six children (16.7%) dividing the spermatic vessels was performed in one stage with laparoscopic orchiopexy. In the remaining 30 patients (83.7%) a laparoscopic one-stage procedure was performed with preservation of the spermatic vessels. Testicular atrophy was observed in 2 cases (5.6%), and 6 patients (16%) had a relatively small testicle compared to the contralateral normal testicle at follow-up. Two patients (5.6%) presented with testicle positioning at the entrance area into the scrotum. None of the patients demonstrated hernia recurrence at follow-up. There was no difference in surgical outcome in children who had surgery with preservation of the spermatic vessels versus those who underwent orchiopexy with division of the spermatic vessels in one stage. Conclusions: Laparoscopic transection of the testicular vessels appeared to be safe in boys with high abdominal testes that did not reach the scrotum after laparoscopic high retroperitoneal dissection.

KEY WORDS: intraabdominal testis, one-stage laparoscopic orchiopexy

Laparoscopy has attained full acceptance, both diagnostically and therapeutically, in the realm of pediatric urology for the management of a non-palpable testis. Since the earliest reported cases over a quarter of a century ago, there are now several thousand cases in the literature documenting the impact of laparoscopy on the management of a non-palpable testis.

The advantages of laparoscopy over a conventional “open” surgical approach to a non-palpable testes include not only better exposure, lighting, and magnification but also accurate anatomic assessment of testicular position and viability and, when necessary, optimal accessibility to the crux of the surgical problem.

There is ongoing debate with regard to the type of laparoscopic orchiopexy that should be employed in patients with intraabdominal testes. Some authors advocate a two-stage procedure for patients who present with high intraabdominal testis with division of the testicular artery at the first stage and formal orchiopexy later on. Others stress the fact that division of the spermatic vessels at the first stage does not diminish the risk of testicular atrophy and propose the vessel division and orchiopexy at one stage, thereby avoiding a two-stage procedure. The present study assesses our results following one-stage laparoscopic orchiopexy for all cases of intraabdominal testis.

PATIENTS AND METHODS

We retrospectively evaluated the medical files of patients who underwent laparoscopic orchiopexy. Only patients with at least one year of follow-up were included. The follow-up assessed the age (at surgery), follow-up time, laterality of testes, postoperative complications, testicular size and testicular localization.

Our operative technique was identical in all patients. Following induction of general anesthesia the scrotal and inguinal regions were examined again, and once the absence of the testicle was confirmed the decision to proceed with laparoscopy was finally made.

The patient is positioned in the supine position and Folly’s catheter is introduced into the urinary bladder and removed at the end of surgery. Laparoscopy is performed utilizing three VersaStep™ trocars (Covidien Medtronic, USA) (one trocar of 5 mm and two trocars of 3 mm are inserted at the umbilical level laterally to the rectal muscle). Diagnostic laparoscopy is...
performed first, followed by assessment of the testes location, size, and proximity to the internal inguinal ring.

Following identification of testicular localization the testicular dissection is started from the gubernaculum detachment deep inside the inguinal channel in patients whose inguinal channel is open in order to avoid injury to the collateral vessels between the vas artery and spermatic vessels [Figure 1]. In patients with a closed process vaginalis the gubernaculum detachment is done as far away as possible from the testis. Special care is taken to handle the testis only, sparing the epididymis. Mobilization of the spermatic vessels and vas is performed on the wide peritoneal strip, after which a decision is made regarding the division of spermatic vessels [Figure 2]. In those patients where the testicle does not reach a contralateral inguinal rung the division of spermatic vessels is performed. A 12 mm VersaStep™ trocar is inserted through the scrotum, facilitating delivery of the testis to the scrotum without twisting the cord inside the inguinal channel and avoiding possible injury to the epigastric vessels. A dartos pouch orchiopexy is then performed [Figure 3]. All patients are discharged on the following day and followed at 6 months and 1 year after surgery. If the testis identified in the scrotum is of good size the next follow-up is suggested for age 13 years. If the testis is identified high in the scrotum or of smaller size than expected an annual follow-up is recommended.

For statistical analysis, commercially available software GraphPad Prism Version 6.07 for Windows (GraphPad software, San Diego, CA) was used. The Mann-Whitney and Fisher test were utilized, considering a $P$ value of $< 0.05$ as significant.

**RESULTS**

Thirty-six consecutive patients, with a median age of 16 months, underwent one-stage laparoscopic orchiopexy. Sixteen patients (44.4%) had peeping testis type, in 13 patients (36.1%) the testicle was located within 2 cm from the internal ring, and in the remaining 7 patients (19.4%) it was detected $> 2$ cm from the internal ring. In 6 children (16.7%) division of the spermatic vessels was performed in one stage with laparoscopic orchiopexy. In the remaining 30 patients (83.7%) a laparoscopic one-stage procedure was performed with preservation of the spermatic vessels. Testicular atrophy was observed in 2 cases (5.6%) (one from each group), and 6 patients (16%) (2 from the group without spermatic vessels division and 4 from the group where division of spermatic vessels was performed in one stage with orchiopexy) had a relatively small testicle compared to the contralateral normal testicle at follow-up. Two patients (5.6%) presented with testicle positioning at the entrance area into the scrotum. None of the patients demonstrated hernia recurrence at follow-up. There was no difference in surgical outcome in children who had surgery that preserved the spermatic vessels versus those who underwent orchiopexy with spermatic vessels division in one stage ($P = 0.121$).
**DISCUSSION**

Laparoscopic orchiopexy is now standard in the urologists' armamentarium of management for an intraabdominal testis [1-6]. A laparoscopic approach to an intraabdominal undescended testis has advantages over open orchiopexy performed through either an extended inguinal incision or a high inguinal incision. Laparoscopy accurately assesses the presence, absence, viability, and entire anatomy of an intraabdominal testis. Success in testicular mobilization may require complete and proximal dissection of the spermatic vessels and redirecting the line of "descent" via the shortest route to the scrotum.

Laparoscopic orchiopexy allows accessibility to the entire course of the spermatic vessels to their origin, usually the limiting factor in tension-free mobilization of an intraabdominal testis. Dissection close to the origin of the spermatic vessels is possible because the surgeon's range of motion with laparoscopic instrumentation extends across the entire abdominal cavity. Magnification of these delicate vessels aids in dissection and preservation of the main and collateral blood supply. Success rates of laparoscopic orchiopexy were comparable to the published results for laparoscopic orchiopexy and are based on postoperative testicular position and viability. There is still an ongoing debate in the literature regarding how to deal with spermatic vessels in cases where the spermatic vessels are too short and do not allow bringing the testis without tension to the scrotum. Some authors suggest applying the Fowler-Stephens (F-S) principle to these cases [5]. In 1959 Fowler and Stephens [6] described the vascular supply of the testis in children with intraabdominal testis and proposed ligation of the testicular vessels with the hope of preserving function by collateral circulation through the deferential artery, a branch of the inferior vesical artery and the cremasteric artery, a branch of the inferior epigastric artery. In their experience, orchiopexy was performed under the same anesthetic. Ransley et al. [7] introduced the practice of ligating the testicular vessels and waiting 6 to 12 months before performing an orchiopexy to allow the deferential artery to increase its flow. Bloom [8] was the first to describe a laparoscopic approach for the first stage, after which the laparoscopic Fowler-Stephens procedure was introduced, performing both stages laparoscopically, which has gained wide acceptance. Staging the procedure will enable delivery of the testis into the scrotum without tension and a decreased risk of atrophy. Since then many authors have compared their results using this approach in children with intraabdominal testis. Chang et al. [9] published their results in 80 children (101 impalpable testes) who underwent laparoscopic orchiopexy. Of these patients, standard laparoscopic orchiopexy was used in 72 testes, a one-stage F-S in 20 and a two-stage F-S in 9 (first stage in 2 patients, second stage in 7). The overall success rate for all F-S procedures was 85%. However, excluding patients who had previous testicular surgery or who required extensive dissection near the vas, 96% of the testes were successfully placed into the scrotum with no atrophy [9]. Another study by Baker and co-authors [10] reported a 97.2% success rate for “primary” laparoscopic orchiopexy, 74.1% for one-stage F-S orchiopexy and 87.9% for two-stage F-S orchiopexy, with an overall atrophy rate of 6.1%. Atrophy rates were found to be highest in the single-stage F-S orchiopexy, 22%, whereas atrophy occurred in only 2% of testes after a straightforward laparoscopic orchiopexy [10]. Recently, Ostlie et al. [11] reported on 27 of the 112 patients with intraabdominal testis who required division of spermatic vessels during laparoscopic orchiopexy. Fourteen had one-stage F-S and the remaining 13 had the two-stage procedure. The outcome was similar in both groups [11].

Our results support the previous observations. We did not find any difference in the outcome of one-stage laparoscopic orchiopexy in patients who required spermatic vessels division vs. those who did not require the F-S procedure. We attribute this to our careful handling of the blood supply. The careful dissection of the gubernaculum far from the testis allows the surgeon to preserve the collaterals from the deferential artery to the testicular vessels and reduce the possibility of ischemic injury following division of the spermatic vessels. We avoid any handling of the epididymis during surgery in order to avoid possible crush injury induced by the laparoscopic grasper. It is important to perform the dissection of the spermatic vessels and the vas with the deferential artery on the wide peritoneal strip in order to diminish possible vascular injury. Admittedly, it is difficult to judge the testicular size in a retrospective study since it is not always possible to find the exact testicular size in the surgery report. Another limitation of this study is that we do not conduct follow-up until after puberty, so we cannot report whether our patients have caught up their normal testicular size during adolescence. Finally, since this was not a randomized study it is difficult to report on the efficacy of one-stage laparoscopic orchiopexy with spermatic vessel division. However, our atrophy rate of 5.6% was even lower than reported in many previous studies. We also did not find any difference among patients who left with intact spermatic vessels vs. those who required vessel division during surgery. Finally, we found it useful and safe to deliver the testis to the scrotum after dissection by means of the VersaStep trocar introduced via the scrotal incision. Insertion of the VersaStep trocar allows gradual dilatation of the scrotal incision and safe insertion of the trocar into the abdominal cavity without incidental injury of epigastric vessels and testicular twisting during delivery.

**CONCLUSIONS**

Our data show that laparoscopic transection of the testicular vessels is safe in boys with high abdominal testes that do not reach the scrotum after laparoscopic high retroperitoneal dis-
section. The magnification and wide mobilization of laparoscopy likely allow better preservation of the collateral vascular supply. The one-stage procedure avoids repeat anesthesia and the extensive, sometimes tedious, dissection that is occasionally required during reoperation. There is no doubt that monitoring the child into adolescence will provide the answer with regard to the long-term effectiveness of this technique.

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References

Capsule
Plunging into a domain of silence
Female mammals have two X chromosomes. One must be silenced to “balance” gene dosage with male XY cells. The Xist long non-coding RNA coats the inactive X chromosome in female mammalian cells. Chen et al. show that the Xist RNA helps recruit the X chromosome to the internal rim of the cell nucleus, a region where gene expression is silenced. Xist is recruited to the domain through an interaction with the Lamin B receptor. This recruitment allows the Xist RNA to spread across the future inactive X chromosome, shutting down gene expression.

Science 2016; 354: 468
Eitan Israel

Capsule
Keeping white fat from expanding
Excess body fat caused by adipogenesis – the expansion of white adipose tissue – poses serious health risks. Wong et al. found that mice exposed to glucocorticoids or fed a high fat diet had decreased levels of the extracellular protein ADAMTS1 in white adipocytes, which was associated with increased adipogenesis. Increased caloric intake in human volunteers enhanced the expression of ADAMTS1 in adipose tissue. Mice that over-expressed Adamts1 had smaller white adipose deposits, suggesting that ADAMTS1 treatment could prevent diet- or glucocorticoid-induced obesity.

Sci Signal 2016; 9:ra103
Eitan Israeli

Capsule
Wreaking havoc while (growth-)arrested
Cells enter a state of senescence in response to certain stresses. Studying mouse models, Childs and team examined the role of senescent lipid-loaded macrophages (so-called foam cells) in the pathogenesis of atherosclerosis. At early stages of atherosclerosis, senescent foam cells promoted the expression of inflammatory cytokines. At later stages, they promoted the expression of matrix metalloproteases implicated in the rupture of atherosclerotic plaque, which can lead to blood clots. Experimental removal of the senescent cells had beneficial effects at both stages of the disease.

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Eitan Israeli
Laparoscopic Surgery of Urachal Anomalies: A Single-Center Experience

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ABSTRACT: Background: The traditional surgical approach to the excision of persistent urachal remnants is a lower midline laparotomy or semicircular infraumbilical incision.

Objectives: To report our experience with laparoscopic/open urachus excision as a minimally invasive diagnostic and surgical technique.

Methods: This was a retrospective study involving patients who were diagnosed with persistent urachus and underwent laparoscopic/open excision. The morbidity, recovery, and outcomes of surgery were reviewed.

Results: Eight patients (males:females 6:2) with an age range of 1 month to 17 years underwent laparoscopic or open excision (six and two patients respectively). All patients presented with discharge from the umbilicus. Although three patients had no sonographic evidence of a patent urachus, diagnostic laparoscopy detected a patent urachus that was excised laparoscopically. The operative time of laparoscopic surgery ranged from 19 to 71 minutes (the last case was combined with bilateral laparoscopic inguinal hernia repair), and the mean duration of hospital stay was 2.0 ± 0.36 days. Pathological examination confirmed a benign urachal remnant in all cases.

Conclusions: Laparoscopy is a useful alternative for the management of persistent or infected urachus, especially when its presence is clinically suspected despite the lack of sonographic evidence. The procedure is associated with low morbidity, although a small risk of bladder injury exists, particularly in cases of severe active inflammation.

KEY WORDS: urachus, remnant, cyst, laparoscopy, morbidity

Urachus is the embryonal duct connecting the dome of the urinary bladder to the umbilical ring. It is normally obliterated prior to birth as the urachus goes on to definitively form the median umbilical ligament [1]. Urachal remnants represent a failure in this obliteration at birth that connects the bladder to the umbilicus [2]. Patent urachus is a rare congenital anomaly. It occurs in 1.6% of children under 15 years of age and in 0.06% of adults [3]. There are four variants of urachal anomalies: urachal cysts, sinus, diverticulum, and patent urachus [4]. Non-closure of the entire tract leads to a patent urachus, which is the most common urachal anomaly, whereas closure of both ends but patency of the tract inbetween may trap fluid in an urachal cyst. Closure on the bladder side creates an umbilical sinus. A bladder diverticulum results when the distal tract involutes; it is the rarest urachal anomaly.

Persistence of the urachal lumen after birth manifests in a variety of clinical presentations, the most common of which is recurrent periumbilical discharge. A urachal cyst most commonly presents once it has become infected. An affected patient will present with infraumbilical swelling, abdominal pain and erythema. The symptoms may mimic appendicitis. A patent urachus drains urine and may predispose to cystitis or recurrent urinary tract infections.

Management of urachal remnants requires wide local excision of the urachus and adjacent extraperitoneal tissue. Patent urachus was traditionally performed via a lower midline laparotomy incision. Although effective, it shares the same associated morbidities of any laparotomy incision, such as inherent postoperative pain, risk of wound infection, bleeding, and slow return to normal activities. Since its first description in 1993 [5], laparoscopic surgery has been considered an alternative to conventional open resection of urachal remnants. The laparoscopic approach has the benefit of being able to confirm the presence of urachal remnant and enables magnified dissection along the extraperitoneal plane until the dome of the bladder in the space of Retzius, with minimal postoperative pain, rapid recovery and return to normal activities. The benefit of superior cosmesis compared to a lower midline incision is an added bonus. Studies on the laparoscopic management of urachal remnants and outcomes are scarce. There are only a few isolated case reports or small case series owing to the rarity of this pathology. In this retrospective review we present our center's experience with the laparoscopic management of symptomatic urachal remnants and their short-term outcomes.

PATIENTS AND METHODS

Eight children (mean age 8.9 ± 2.6 years, range 0.5–17) visited our institution with symptomatic urachal remnants between...
January 2014 and May 2016. The patients’ medical records were reviewed retrospectively. We reviewed the perioperative and postoperative records to assess perioperative data, operation time, blood loss, complications, pathological evaluation, and follow-up. The patients were interviewed by telephone to evaluate their long-term outcomes.

Presentation of urachal remnants included umbilical discharge, low abdominal infraumbilical mass, with or without fever, local pain, and signs of inflammation. Preoperative evaluations included ultrasonography, blood and urine tests. Computerized tomography (CT) was used for patients with unusual presentations. Initial treatment of infected urachal remnant consisted of antibiotics and drainage; bacterial cultures and sensitivity tests were performed. After the patients’ acute symptoms subsided, each patient underwent complete excision of the urachal remnant laparoscopically or by open approach.

During the laparoscopic procedure, a Foley catheter was inserted with the patient under general anesthesia in a supine position. The visualization port was accessed with a 5 mm trocar in the left upper abdomen and was insufflated by CO₂ with intraabdominal pressure maintained at 12–15 mmHg. Another two 5 mm working ports were inserted under direct vision on the right upper and left lower side of the abdomen. The patient was then placed in the Trendelenburg position. A 5 mm, 30° angled lens camera is typically used. First, any bowel or omental adhesions from prior surgeries or inflammatory reactions to the infected urachal remnant were lysed off with monopolar scissors, and the median and lateral umbilical ligaments were identified. The cephalic side of the urachus was dissected from the umbilicus, and the caudal stump of the median umbilical ligament was transected just above the bladder dome with ultrasonic scissors. The excised specimen was exteriorized with a laparoscopic retrieval bag via the left lower port and sent for histopathological examination.

### RESULTS

Patient demographic and perioperative data are shown in Table 1. The patients, six boys (75%) and two girls (25%), had a mean age of 8.9 ± 2.6 years (range 0.5–17). The most common presentation was umbilical discharge in all patients (100%). On examination two patients had abnormal appearance of the umbilicus. In two patients, infraumbilical mass was palpated. Three patients presented with findings suggestive of an infection and were treated with antibiotics following by complete excision of the urachal remnant laparoscopically or by open approach within 2 months. No patients presented with hematuria, urinary retention or urinary tract infection. One patient presented with severe local pain and was operated in another hospital for suspected incarcerated umbilical hernia. During the surgery no hernia was detected. The patient continued to suffer from umbilical discharge. Ultrasound examination demonstrated urachal cyst, and the patient underwent urachal remnant excision in our institution.

Although abdominal ultrasonography was done in all eight patients, only six (75%) had sonographic evidence of patent urachal remnants. Urachal cyst was found in four patients (4.5 x 2 cm, 1.5 x 0.7 cm, 1.2 x 0.9 cm, 1.1 x 0.7 cm), and patent urachus or urachal sinus in two.

Six patients underwent laparoscopic excision of urachal remnant, while two patients underwent open removal of urachus. The indication for open approach was a palpated infraumbilical mass (close to the umbilicus). At surgery, urachal cyst was found in both cases. Of the six patients who were operated by laparoscopic approach, all were found to have patent urachus without urachal cyst (despite preoperative ultrasonographic findings). This discrepancy between preoperative sonographic and intraoperative findings is reported in Table 2. There were two patients who presented acutely with umbilical omphalitis and overlying cellulitis. These patients were initially managed with parenteral antibiotics, and wide laparoscopic local excision was performed electively 8 weeks later after the inflammation had subsided.

Laparoscopic local excision was successfully completed in all cases without conversion to a lower midline incision [Table 3]. The mean operative time was 36 ± 6 minutes (range

### Table 1. Patient demographics and clinical presentations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>8</td>
</tr>
<tr>
<td>Age (yr), mean (standard error)</td>
<td>8.9 ± 2.6</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>6:2</td>
</tr>
<tr>
<td>Umbilical discharge</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Abnormal appearance of the umbilicus on examination</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Infraumbilical mass</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Findings suggestive of an infection (fever/erythema)</td>
<td>3 (37%)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Sonographic evidence of patent urachus</td>
<td>6 (75%)</td>
</tr>
</tbody>
</table>

### Table 2. Comparison between preoperative diagnosis and intraoperative findings

<table>
<thead>
<tr>
<th>Preoperative diagnosis (n)</th>
<th>Postoperative diagnosis (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urachal cyst (n=5)</td>
<td>Urachal cyst (n=2)</td>
</tr>
<tr>
<td>Patient urachus (n=3)</td>
<td>Patient urachus (n=6)</td>
</tr>
<tr>
<td>Urachal sinus (n=0)</td>
<td>Urachal sinus (n=0)</td>
</tr>
<tr>
<td>Urachal diverticulum (n=0)</td>
<td>Urachal diverticulum (n=0)</td>
</tr>
</tbody>
</table>

### Table 3. Surgical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time (min), mean (SE)</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>Postoperative hospital stay (days), mean (SE)</td>
<td>2 ± 0.3</td>
</tr>
<tr>
<td>Operation-related complications</td>
<td>0</td>
</tr>
<tr>
<td>Conversion to laparotomy</td>
<td>0</td>
</tr>
<tr>
<td>Return to normal activities (days)</td>
<td>6.3 ± 0.9</td>
</tr>
</tbody>
</table>
DISCUSSION

The urachus, a remnant of the allantois, serves to excrete urine from the bladder via the umbilicus during the intrauterine life of a fetus [1,2]. After birth, the urachal portion fails to grow; thus, its lumen is narrow and usually obliterated by fibrous proliferation, giving rise to the median umbilical ligament. Occasionally, the allantois may fail to involute and depending on the completeness of this involution, a patent urachus, urachal cyst, urachal sinus or vesico-urachal diverticulum may arise [3].

Persistent clear fluid leakage (likely urine) in an infant is highly suggestive of a patent urachus, while cloudy, serous or bloody fluid is more indicative of a urachal sinus or cyst. In our series, umbilical discharge was the most common presentation and was seen in all patients. Two patients had abnormal appearance of the umbilicus on examination. In two patients infraumbilical mass was palpated. Infection is the most common complication of urachal remnants. The route of infection may be lymphatic, hematogenous or vesical, and is cultured from infected urachal remnants. It is the usual mode of presentation in an otherwise asymptomatic condition. Staphylococcus aureus is the most common organism cultured, although a wide variety of gram-positive and gram-negative microorganisms have been reported [6]. In our series, three patients presented with findings suggestive of an infection and were treated with antibiotics following by complete excision of the urachal remnant within 2 months. Abdominal pain may be the only symptom of disease and can mimic an acute abdomen due to appendicitis or Meckel's diverticulum [7]. One of our patients presented with abdominal pain and was operated in another institution for suspected incarcerated umbilical hernia; no hernia was found during the surgery. Because of persistent pain and discharge from the umbilicus, this patient underwent laparoscopic urachal remnant excision. Abdominal pain and umbilical discharge disappeared after surgery.

Galati et al. [8] reported 23 children with urachal remnants, 10 of whom underwent excision due to symptomatic problems. They found that spontaneous resolution with non-operative management is likely with remnants in patients younger than 6 months.

Although many methods are available today for diagnosing pathology of urachal remnants, none of these is completely accurate. Because CT and ultrasonography display cross-sectional images and the urachus in the anterior abdominal wall is located away from interfering intestinal structures, these modalities are ideally suited for demonstrating urachal anomalies. Ultrasonography is by far the most popular as it is easily performed, is non-invasive, and there are no concerns about radiation exposure. Ultrasound can be helpful in diagnosis of urachal remnant but is not sufficient, as shown by our series. Our data suggest that ultrasound has high sensitivity but low specificity rates. In four patients, ultrasound demonstrated urachal cyst that did not correlate with the intraoperative findings. Interestingly, in our series, two patients (25%) had no demonstrable urachal remnants on ultrasonography despite the typical clinical presentation. Diagnostic accuracy of ultrasonography for urachal remnants has been reported to range from 61.1% to 91.3% [9]. Siow et al. [10] described 14 patients with patent urachus. Only 71.4% of these patients had sonographic evidence of patent urachal remnant. Ueno and colleagues [11] described 56 children with anomalies of the urachus remnant identified by ultrasound; 20 of these cases were symptomatic urachal remnants, whereas the urachus remnants were seen incidentally by ultrasound scanning in the other 36 patients. In nine cases, including two symptomatic cases, urachal remnants disappeared spontaneously during the follow-up period. No symptom had developed during follow-up in asymptomatic cases [11]. Widni et al. [12] demonstrated that ultrasonography had a positive predictive value of 83% but a sensitivity of only 79%. Lack of specificity of ultrasound in the differential diagnosis of solid urachal masses has been reported by Yu and colleagues [13].

CT is the most important imaging modality in the diagnostic workup. It reveals the type of urachal anomaly with a sufficient degree of accuracy. Adult patients with urachal anomalies should especially undergo an abdominal CT and/or magnetic resonance imaging (MRI) scan because of the high risk of malignancy (up to 25%) and the increased risk of a malignant cystic urachal mass with increasing age [14].

The principal treatment for a urachal remnant is the complete excision of the whole tract. This requires a long midline skin incision in the lower abdomen, which inevitably causes the cosmetic disadvantage of a conspicuous scar. To alleviate this drawback, laparoscopic excision of the urachal remnant was first demonstrated in 1993 by Trondsen et al. [5]. Since this report, several trials of laparoscopic surgery to correct the urachal anomaly have been reported [15-17]. However, the
techniques, including port placement arrangements and division and suture of the bladder, have not yet been standardized. A laparoscopic excision of the urachal remnant has been suggested to be technically feasible and minimally invasive. It has also been claimed that a laparoscopic procedure provides better cosmesis, thus contributing to the quality of life of young female patients in particular.

In our series, six of eight patients with urachal remnants underwent laparoscopic surgery and two underwent open traditional surgery. Wide local excision of urachal remnants down to the dome of the bladder along with adjacent inflammatory tissue was performed. Inadequate resection risks recurrence of periumbilical discharge as well as possible malignant transformation of the urachal remnant. The mean operative time was 36 minutes, lower than reported previously [15-17]. The mean postoperative duration of hospital stay was 2 days. One patient complained of persistent abdominal pain. No patient had umbilical discharge postoperatively. Ultrasonography showed no evidence of an umbilical collection or urachal remnants.

The primary limitation of this study was the small number of patients and the retrospective analysis. Another limitation was the lack of a control group and lack of comparison between those with and without urachal resection.

In conclusion, the history and physical examination of patients with urachal remnant are crucial for the correct diagnosis. Ultrasonography may be helpful in the diagnosis of urachal remnant, but not sufficient; it has high sensitivity but low specificity rates. While laparoscopic excision seems to be a safe and less invasive method for the treatment of urachal anomalies, a prospective, large, multi-institutional randomized study is needed to prove the advantages of the laparoscopic compared to the open approach.

**References**


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**Capsule**

**Group B Streptococcus** circumvents neutrophils and neutrophil extracellular traps during amniotic cavity invasion and preterm labor

Preterm birth is a leading cause of neonatal morbidity and mortality. Although microbial invasion of the amniotic cavity (MIC) is associated with most early preterm births, the temporal events that occur during MIC and preterm labor are not known. Group B streptococci (GBS) are β-hemolytic, Gram-positive bacteria, which commonly colonize the vagina but have been recovered from the amniotic fluid in preterm birth cases. To understand temporal events that occur during MIC, Boldenow et al. used a chronically catheterized non-human primate model that closely emulates human pregnancy. This model allows monitoring of uterine contractions, timing of MIC, and immune responses during pregnancy-associated infections. The authors show that adverse outcomes such as preterm labor, MIC, and fetal sepsis were observed more frequently during infection with hemolytic GBS when compared with non-hemolytic GBS. Although MIC was associated with systemic progression in chorioamnionitis beginning with chorionic vasculitis and progressing to neutrophilic infiltration, the ability of the GBS hemolytic pigment toxin to induce neutrophil cell death and subvert killing by neutrophil extracellular traps (NETs) in placental membranes in vivo facilitated MIC and fetal injury. Furthermore, compared with maternal neutrophils, fetal neutrophils exhibit decreased neutrophil elastase activity and impaired phagocytic functions to GBS. Collectively, these studies demonstrate how a bacterial hemolytic lipid toxin enables GBS to circumvent neutrophils and NETs in placental membranes to induce fetal injury and preterm labor.

Eitan Israeli
Point-of-Care Ultrasound in a Department of Pediatric and Adolescent Surgery

Efrat Avinadav MD, Anastasia Almog MD, Dragan Kravarusic MD, Emanuelle Seguier MD, Inbal Samuk MD, Adrianna Nika MD and Enrique Freud MD

Background: Point-of-care ultrasound (POCUS) is becoming a common tool for routine use in emergency medicine, anesthesiology and intensive care for diagnostic and interventional purposes. When a portable ultrasound device became available for the department of Pediatric and Adolescent Surgery at the Schneider’s Children Medical Center of Israel, we added POCUS assessments to the physician’s daily rounds. POCUS is performed by pediatric surgeons trained in basic ultrasonography skills. Starting September 2015 all POCUS examinations were documented.

Objectives: To describe the current use and the diagnostic and therapeutic impacts of POCUS in a department of pediatric and adolescent surgery.

Methods: We conducted an observational study of all the documented POCUS procedures performed during a half-year period. Data regarding patient condition and the POCUS procedures were collected, as well as data on the use of other diagnostic modalities, mainly formal ultrasound exams (by radiologists) and computed tomography scans and their correlation with the POCUS assessment.

Results: Fifty-one POCUS exams were performed during the study period, most of which served to define the presence and resolution of a collection – intraabdominal (34%) and subcutaneous (31%). Despite a high rate for formal diagnostic studies (65%), probably due to a relative lack of confidence of surgeons performing the POCUS exams during this initial period, most results (92%) were compatible.

Conclusions: The ability and availability to perform multiple POCUS exams by the attending physician proved to be a valuable aide to the classical physical and laboratory examinations of surgical patients, and we predict its increasing use in daily practice.

KEY WORDS: bedside ultrasound, point-of-care ultrasound (POCUS)

ABSTRACT: Background: Point-of-care ultrasound (POCUS) is becoming a common tool for routine use in emergency medicine, anesthesiology and intensive care for diagnostic and interventional purposes. When a portable ultrasound device became available for the department of Pediatric and Adolescent Surgery at the Schneider’s Children Medical Center of Israel, we added POCUS assessments to the physician’s daily rounds. POCUS is performed by pediatric surgeons trained in basic ultrasonography skills. Starting September 2015 all POCUS examinations were documented.

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Conclusions: The ability and availability to perform multiple POCUS exams by the attending physician proved to be a valuable aide to the classical physical and laboratory examinations of surgical patients, and we predict its increasing use in daily practice.

Patients and Methods

For the purpose of assessing the value of POCUS exams, we documented all POCUS exams performed by surgeons in the department. POCUS assessment was performed using a Mindray M7 (Mindray Inc. Shenzen, China) with a 6–14 MHz linear transducer and a 2–5 MHz curved transducer. The exam results were correlated with the clinical follow-up, and with the use and results of other, formal, accessory imaging studies performed in the radiology department.

RESULTS

During a 6 month period we documented 51 examinations. The average patient age was 8.9 years (range 4 months–16 years). Most of our POCUS exams were done for the identification of an abscess, either subcutaneous or intraabdominal, as well as FAST (focused assessment with sonography for trauma) exams for trauma patients and other etiologies [Figure 1].
Most examinations demonstrated good correlation with the observed clinical follow-up [Figure 2]. Observed utilization of other accessory imaging examination varied with the suspected diagnosis [Figure 3], but the consistency remained high, also when compared with accessory imaging studies (formal ultrasound and CT scan) [Figure 4].

Some specific cases in which POCUS assessment provided a unique insight to a clinical problem are briefly described:

- A 12 year old girl was admitted for a recurrent wound infection post-appendectomy performed in another hospital. POCUS on admission demonstrated an enterocutaneous fistula, confirmed by a CT scan performed the following morning. Pathological examination of the appendectomy specimen was consistent with the presence of inflammatory bowel disease.

- A 2 year old boy continued to suffer bouts of mild abdominal pain after hydrostatic enema reduction of intussusception. A true intussusception was not demonstrated on POCUS; nonetheless, wall edema and an intraluminal finding were imaged. These elements were found to be an intussuscepted appendix on surgery.

- A 2 year old boy with a known mesenteric cyst was admitted for elective laparoscopic surgery the night before his scheduled operation. The parents were concerned that the lesion may have disappeared, but POCUS confirmed the presence of the lesion and it was successfully removed the following morning.

**DISCUSSION**

While formal ultrasound training is not yet an established practice in every medical specialty and in every institution, it is becoming increasingly common and the advantages of its rapid and accessible utilization are apparent. We therefore began to use a portable ultrasound device even though we had only basic training. As we have learned from observing our use of POCUS examinations, they supplement but do not replace the formal radiological examination. The convenience it offers is appealing for our routine practice, i.e., when formal radiological examination is not readily available, for a closer and frequent follow-up of a known or previously observed occult lesion (e.g., intraabdominal abscess), and as a confirmatory examination when clinical findings rule out a surgical condition (such as cellulitis vs. abscess).

One major concern with the increasing use of POCUS is the medico-legal implications of its use. The performing surgeon is not expected to perform a complete thorough sonographic examination as a trained radiologist since POCUS is used for specific conditions and as an adjunct to physical examination. Therefore, concern about missed diagnosis might arise. Indeed, our own studies do not show a 100% correlation with the formal studies, although higher than 90% for most examinations is a very satisfactory result considering the little formal training our staff had.

The fact that legal issues have not yet been fully defined in Israel should not prevent physicians from using the best tools available for the benefit of their patients. As shown in this series, generous use of accessory studies was still employed despite the valuable information gained from POCUS examinations, partly...
to avoid any missed diagnosis. POCUS examination should take its place as a part of the full clinical assessment and we strongly advise against relying exclusively on it.

We believe that the practice we have initiated – using POCUS assessments to complement the physical examination, regardless of formal radiological examinations – is a proper and suitable way to take full advantage of this available technology. Pediatric surgeons should not be reluctant to add POCUS to their daily practice for any reason.

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References

Capsule
Keeping hearts and blood vessels young
Activation of the G protein-coupled receptor GPER is thought to confer cardiovascular benefits. Unexpectedly, Meyer et al. found that aged mice that were deficient in Gper did not develop as much cardiac fibrosis as aged mice in the control group and retained greater cardiovascular function. Gper deficiency was associated with reduced production of tissue-damaging superoxide in blood vessels and the myocardium.

A GPER-blocking drug reduced blood pressure and superoxide production in hypertensive mice, suggesting that GPER inhibitors could be used to treat cardiovascular diseases caused by excessive superoxide generation.

Sci Signal 2016; 9: ra105
Eitan Israeli

Capsule
A global genetic suppression network
The genetic background of an organism can influence the overall effects of new genetic variants. Some mutations can amplify a deleterious phenotype, whereas others can suppress it. Starting with a literature survey and expanding into a genome-wide assay, van Leeuwen et al. generated a large-scale suppression network in yeast. The data set reveals a set of general properties that can be used to predict suppression interactions. Furthermore, the study provides a template for extending suppression studies to other genes or to more complex organisms.

Science 2106; 354: 599
Eitan Israeli

Capsule
Fulminant myocarditis with combination immune checkpoint blockade
Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high grade, immune related adverse events can occur, particularly with combination immunotherapy. Johnson et al. report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T cell and macrophage infiltrates. Selective clonal T cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T cell-driven drug reaction.

Eitan Israeli
Medical Clowns and Cortisol levels in Children Undergoing Venipuncture in the Emergency Department: A Pilot Study

Ayelet Rimon MD1*, Shelly Shalom MD1*, Ido Wolyniez MD1, Alejandro Gruber3, Anita Schachter-Davidov MD2 and Miguel Glatstein MD1

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3The Dream Doctors Project, Philnor Foundation, Israel

ABSTRACT: Background: Medical clowns are increasingly used for diminishing pain and anxiety during painful procedures being performed on children in the hospital setting. Cortisol levels rise as a response to emotional distress. Objectives: To investigate whether medical clown-assisted interventions to reduce child's distress during venipuncture have an effect on cortisol levels. Methods: During a 1 year period, children requiring blood work or intravenous access in the pediatric emergency department were prospectively randomized to either the presence or absence of a medical clown during the procedure. The child's distress was evaluated using the Faces Pain Scale - revised (FPS-R) for the 4–7 year age group and the visual analog scales (VAS) for those aged 8–15 years. Serum cortisol levels were measured in blood samples obtained by venipuncture. Results: Fifty-three children aged 2–15 years were randomly assigned to the study group (with medical clown, n=29) or to the control group (without medical clown, n=24). Combined pain scores of the study group and control group were 2.2 and 7.5 respectively (P < 0.001). No difference in mean cortisol levels was found between the study group and the control group at all ages (16.4 µg/dl vs. 18.3 µg/dl, P = 0.65). Conclusions: In this pilot study, medical clowns reduced the distress from venipuncture in children. No effect on cortisol levels was observed.

KEY WORDS: cortisol, medical clown, pain, emergency department (ED), pediatrics

The relief of pain and suffering is one of the most common reasons for seeking care at an emergency department (ED) [1]. Painful procedures are commonly indicated in children attending the ED and can be very disturbing for children and their families, with real long-term negative emotional and psychological sequelae [2]. The anxiety, fear and behavioral distress caused by medical procedures, particularly those involving needles, exacerbate children's pain and may interfere with the procedure [3]. Cognitive psychological techniques, including distraction, can increase pain tolerance [4] and physicians should be aware of and utilize this modality [5]. Examples of distraction techniques used in children for venous blood sampling include: blowing bubbles, reading stories to children [6], using a hand-held kaleidoscope [7], watching television, using virtual reality by audiovisual eyeglasses, and listening to music [8]. In recent years there have been claims that humor and laughter possess unique characteristics that help coping with pain and stress [9], and medical clowns and humor have been shown to have a positive effect on patients [10,11]. In the last decade there has been a rapid growth in the presence of medical clowns in hospitals, particularly in pediatric settings [12].

Cortisol is secreted in response to stress and can be used to assess responses to stressful stimuli or to determine the effectiveness of a stress-reducing intervention [13]. Cortisol and ACTH are released episodically in pulses every 30–120 minutes throughout the day, but plasma concentrations of ACTH and cortisol tend to peak at 8 a.m. and to be low in the evening. Diurnal rhythms of ACTH and cortisol secretion begin to be established at 6–12 months. Levels also vary according to individual patterns, activity, sleeping, eating, and certain medications and illnesses. Although physical stress such as major injury or severe trauma can increase the secretion of ACTH and cortisol, minor surgery or minor illness have been shown to have little effect on ACTH and cortisol secretion [14].

The aim of the present study was to investigate the association between medical clown-assisted distractions for reducing children's pain and distress during standard blood collection as well as serum cortisol levels (as a proxy for physiological stress response).
PATIENTS AND METHODS
This pilot study employed a prospective, randomized design. Children aged 2–15 years whose treatment plan included blood tests or intravenous (IV) cannulation in the pediatric ED were enrolled consecutively during a 1 year period ending September 2015. Children were enrolled in the study only if they were accompanied by at least one of their parents. Children were excluded if they needed urgent IV cannulation, had developmental disabilities, were critically ill or needed IV cannulation for the treatment of a severe bacterial infection, or if they had received glucocorticoids during the preceding 6 weeks. Following parental consent, study participants were randomly assigned to a control group or a study group by a patient allocation scheme implementing a stratified block design. Block size varied randomly from four to eight. Patient group assignment was determined at the time of patient enrollment by accessing consecutive sealed envelopes maintained in a dedicated location in the ED. Recruitment only occurred during the days when the medical clown was present in the ED. Prior to this study, the medical clown had not been part of routine care in the ED. Our control group consisted of children undergoing the same procedure with the regular distraction and comfort techniques that parents provide. The group randomized to the medical clown spent 15 minutes with the medical clown before the procedure, followed by blood collection in the presence of the medical clown. A single medical clown was involved in the study in order to reduce variation in technique. To minimize the effect of other behavioral factors, parents were not given any instructions regarding how to aid their child, nor did ED nurses utilize any guided imagery or distraction techniques, even though many were knowledgeable about distraction techniques. For the same reason, topical anesthetic was not used, although it is a well-established treatment in reducing pain. The cognitive behavioral techniques used by the medical clown for this project included:

- Distraction via humor before and during the procedure: this included various methods for entertaining the child (e.g., magic tricks, using puppets and telling jokes)
- Imagery: a technique to encourage the child to cope with the pain and distress of the procedure by asking them to imagine a pleasant object.

The primary outcome measurement was the child’s rating of pain, using an age-appropriate scale, immediately (1 minute) after the procedure. Children 4 to 7 years old used the Faces Pain Scale - revised (FPS-R) [15] which utilizes a picture scale with faces in different levels of pain-distress. The FPS-R is a simplified six-face adaption of Bieri’s validated faces pain scale. Patients indicate the level of their pain by identifying the face picture of the pain they experienced. It does not contain smiling faces or tears, thus avoiding the confounding of affect and pain intensity. A clinically significant change in pain in children is represented by a decrease in one face score, although a change of two faces indicates a more significant reduction [16]. For children 7 years and older, a visual analog scale (VAS) 100 mm in length, anchored by the terms “no pain” to “worst possible pain” was used. The children were asked to mark the point on the line that they felt represented their pain during the procedure. The minimum clinically significant change in measured patient pain severity is considered to be 13 mm [17,18].

Serum cortisol plasma levels were determined in blood samples collected during the IV cannulation to study the hypothalamic-pituitary-adrenal changes induced by this procedure, in an attempt to objectively measure stress response. The blood was collected at limited hours during the day (i.e., evening shift) to minimize the diurnal rhythm variation of cortisol secretion. Samples were centrifuged and plasma samples were stored at 4°C. Total plasma cortisol levels were determined with a commercially available chemiluminescent immunoassay kit within 2 hours of removal from storage. Information obtained from the medical record included the child’s age and gender, history of previous immunizations or other painful procedures, and any use of medications.

Details of the procedure, including overall success, number of attempts and procedure duration were documented. The calculation of the duration of the procedure did not include the time spent with the medical clown before the procedure since it did not consume any time or effort of the ED personnel.

Statistical analysis was performed by SAS for Windows, version 9.4. The t-test was used for continuous variables with normal distribution and the Wilcoxon test for non-normally distributed data as appropriate. Categorical data were analyzed using Fisher’s exact test. A P value of 0.05 was considered significant. The study was approved by the Institutional Ethics Committee.

RESULTS
A total of 55 children were enrolled in the study. Eleven patients were 2–3 years old, 7 patients were 3–4 years old, 16 were 4–7 years old, and 21 were older than 8 years of age. Twenty-six patients were randomly assigned to receive standard care (control) and 29 were assigned to have a medical clown present during the procedure [Figure 1]. Two participants who were randomized to the control group were removed from analysis because eventually the blood test was performed outside of the defined hours of the day (not during the evening shift).

Fifty-three children (24 in the control and 29 in the study group) were included in the analyses. There were no significant differences in demographics or previous clinical experience of patients assigned to either group [Table 1]. Most children had a previous painful experience in the form of immunization, but only two had undergone IV cannulation prior to the cur-
they showed that the presence of a therapeutic dog reduced pain and distress in children during venipuncture, but that although blood cortisol levels were reduced the difference was not statistically significant. Due to the small number of children in the different age groups, we combined the results of two pain assessments (VAS and FPS-R). This is based on the good agreement found between the VAS and the faces scale in a previous pain evaluation study in an intensive care unit [19].

It is possible that the measurement and timing of the cortisol sampling could not reflect changes that may in fact have occurred, or that the medical clown’s effect may have been nullified by the fact that drawing blood in younger children is often difficult and prolonged. A larger sample may also have revealed different results. The effect of the presence of a medical clown, employing humor in addition to traditional distraction techniques, during urgent medical procedures in children has only rarely been studied.

Hansen and colleagues [20] studied the effect of the presence of a hospital clown on 60 children treated with botulinum toxin in an outpatient setting, and Tener et al. [21] looked at the effect that medical clowns had on anxiety expressed by children undergoing evaluations after allegations of sexual abuse. The present study is a first pilot study to compare pain scores with cortisol levels, representing an objective measure of physiological stress. We attempted to assess the medical clown’s influence on cortisol levels during a stressful situation in a relatively homogeneous group of patients, and it seems that venipuncture, similar to minor surgery or minor illness, has little effect on the secretion of cortisol.

**LIMITATIONS**

There are several limitations to our study. Being a pilot study, our sample size was small and included children younger than 4 years of age, which only gave data of cortisol levels and no pain scoring. Secondly, we were unable to blind the subjects and parents to the intervention, due to the nature of the intervention which may have introduced significant bias into the results. Thirdly, the medical indication for the procedure was not controlled for in the design. In order to minimize this factor on the levels of cortisol we excluded patients with a severe illness (reflected by urgent blood tests or a diagnosis of a severe bacterial infection). Fourthly, our data are limited to IV cannulation attempts and may not be generalizable to other painful procedures performed in the ED. Finally, the pain scores we employed may not measure aspects of pain perception that are relevant to patients, and they may miss other valuable information.

**DISCUSSION**

We found that pain scores were significantly lower in children who were accompanied by a medical clown during IV cannulation, but that the serum levels of cortisol were not changed by this intervention. This indicates that although the presence of a medical clown was able to reduce the subjective appreciation of pain and distress, it did not reduce an objective measure of stress. Vagnoli et al. [4] obtained results similar to ours when
child laugh than an adult [7]. The use of medical clowns has already been well implemented on pediatric wards [22,23] and we believe they should be part of routine care for children in the ED.

Medical clowns have special training in acting and clowning and, combined with medical knowledge and an understanding of patient behavior, have become a very useful addition to ED personnel. This study demonstrated no difference in physiological stress response between the two groups, as represented by serum cortisol levels, but rather showed that a medical clown was able to reduce pain and distress subjectively in children undergoing a painful procedure in the ED. Research on the reproducibility of the instruments used in our study, and testing on larger numbers of children, would further elucidate the actual effect of the medical clown in the pediatric ED. We also suggest that future studies attempt to compare the medical clown intervention to proven pharmacological pain-reducing alternatives.

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References

Capsule
Assessing smoke damage in cancer genomes

We have known for over 50 years that smoking tobacco is one of the most avoidable risk factors for cancer. Yet the detailed mechanisms by which tobacco smoke damages the genome and creates the mutations that ultimately cause cancer are still not fully understood. Alexandrov and fellow-workers examined mutational signatures and DNA methylation changes in over 5000 genome sequences from 17 different cancer types linked to smoking. They found a complex pattern of mutational signatures. Only cancers originating in tissues directly exposed to smoke showed a signature characteristic of the known tobacco carcinogen benzo[a]pyrene. One mysterious signature was shared by all smoking-associated cancers but is of unknown origin. Smoking had only a modest effect on DNA methylation.

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Eitan Israeli
Infant Feeding: Swinging the Pendulum from Late to Early Introduction of Food

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KEY WORDS: food allergy, tolerance, peanut, cow's milk, hen's egg

Medical guidelines are constantly changing and some are even being reversed, as illustrated by a shift in focus from cholesterol numbers to a heart-healthy lifestyle, and cardiopulmonary resuscitation moving from a fixation on maintaining airway and breathing to sustaining circulation. There is no greater example of changing medical advice than what is currently emerging in the allergy field – a shift from avoiding exposure to furry pets (e.g., cats and dogs) to now emphasizing that early-life exposure to pets can be protective against the development of allergy. We review here the changing attitude towards the introduction of highly allergenic foods into the infant diet.

It is reasonable to assume that the anatomic, physiologic and metabolic requirements of human infants have not changed significantly during the last century, yet we, the medical community and authorities, are generating and issuing new infant feeding guidelines almost annually. Instructions that were the most updated medical information just years ago are now considered obsolete and possibly harmful. Fortunately, mothers have either ignored most medical advice or infants have survived despite it. However, in some cases, we may be paying for the mistakes.

OPINION-BASED INFANT FEEDING GUIDELINES

It is notable that formal infant feeding guidelines issued by medical societies have only been in existence for the past five decades; before that, mothers and infants managed without formal guidelines [1]. The first reports of the American Academy Committee on Nutrition were educational and only in the mid-1960s did the Committee gain nutritional prominence through its assistance to the Food and Drug Administration (FDA) in defining nutritional requirements for infant formulas and setting policy for nutritional practices relating to infants, children and adolescents. The aims of the first guidelines were to address the metabolic and nutritional needs of newborns and infants.

In 1985, the FDA published the minimum concentrations of 29 nutrients and maximum concentrations of 9 of these nutrients [2]. In 1998, an Expert Panel made recommendations for revision of the Code of Federal Regulations (CFR) as it applied to the nutrient content of infant formulas [3].

In the second half of the twentieth century in parallel to the emergence of the allergy epidemic, starting with respiratory and skin allergies [4], there was a focus on preventing allergic diseases through dietary manipulations. Cow's milk protein (CMP) was the "immediate suspect" for respiratory, skin and food allergies. Various approaches such as delaying introduction of CMP and/or introduction of modified CMP – extensively or partially hydrolyzed CMP – were investigated. While a detailed description and discussion of these studies is beyond the scope of this review, it is now well established that partially hydrolyzed CMP [5-8] is not protective against eczema [9,10], and a recent large scale meta-analysis concluded that there is no consistent evidence to support the use of hydrolyzed formula for the prevention of allergic or autoimmune disease [11]. The rationale for avoiding CMP in infancy in an attempt to change the course of asthma or eczema remains unclear.

The emergence of the food allergy epidemic, especially the increasing prevalence and associated morbidity and mortality of peanut allergy in the United States, Britain and Australia, fueled efforts to reverse this trend. In 1998, the British Committee on Toxicity of Chemicals (COT) in Foods published detailed dietary recommendations, including the following [12]:

Pregnant women who are atopic, or for whom the father or any sibling of the unborn child has an atopic disease, may wish to avoid eating peanuts and peanut products during pregnancy. Breast-feeding mothers who are atopic, or those for whom the father or any sibling of the baby has an atopic disease, may wish to avoid eating peanuts and peanut products during lactation. During weaning of these infants, and until they are at least three years of age, peanuts and peanut products should be avoided.

In 2000, the American Academy of Pediatrics (AAP) adopted these recommendations [13]. In 2005, the Australian
Society of Clinical Immunology and Allergy published a position statement about allergy prevention in children [14], recommending avoidance of potentially allergenic foods such as egg and milk until 12 months of age, and peanuts, nuts and shellfish until after 2–4 years of age. While admitting the lack of evidence for these recommendations they justified this policy in the following statement: “there is no evidence that avoiding peanuts, nuts and shellfish during early life is harmful for high risk children.”

All these recommendations were based on an “opinion” rather than on solid evidence-based research. The experts in the various panels postulated that the infant immature immune system is “not ready” to successfully handle potentially allergenic proteins [14]. It did not take long before the medical community began to examine the outcome of these recommendations. In a sequential cohort from the same geographic location in the UK, peanut allergy increased from 0.5% in a cohort of 3–4 year old children born in 1989 to 1.4% in a cohort of similar aged children born between 1994 and 1996 [15]. Similarly, a twofold increase in the prevalence of peanut allergy among children in the USA (0.4% vs. 0.8%) was observed over a 5 year period (1997–2002) using random-digit telephone surveys [16].

The HealthNuts study, a population-based study conducted in Australia provided additional evidence for the rising prevalence of food allergy. More than 10% of infants born between 2006 and 2010 were diagnosed as having food challenge-proven immunoglobulin E (IgE)-mediated food allergy to egg (8.9%), peanut (3%) and sesame (0.8%). Moreover, 5.6% and 0.8% of the infants were sensitized to milk and shellfish, respectively [17]. Thus, evidence was emerging that the twentieth century Feeding Guidelines were clearly not successful in preventing food allergy.

**OBSERVATIONAL STUDIES**

In a widely cited study published in 2008, there was a tenfold higher prevalence of peanut allergy found among 5171 Jewish schoolchildren in the UK (1.85%) compared with 5615 schoolchildren in Israel (0.17%) [18]. Early exposure of Israeli infants to peanut, via the peanut-based snack Bamba™, was hypothesized to contribute to the low prevalence of peanut allergy in Israel.

This study started a new era in the research of the relation between infant feeding and development of food allergy. At least four additional observational studies from different geographic regions supported the concept that early introduction of potentially allergenic food was associated with lower prevalence of food allergy. First, in a prospective population-based study of a large cohort, over 13,000 newborns were followed from birth until they consumed CMP regularly. Of over 6500 infants who were never breastfed or only partially breastfed (thus started on CMP during the first 14 days of life), only 3 developed milk allergy, compared with 63 who developed IgE-mediated cow’s milk allergy (CMA) [19] from an equal-sized cohort exposed to cow’s milk starting after 14 days of life. The finding that early introduction of CMP was associated with lower incidence of IgE-mediated CMA was confirmed in a retrospective study from Japan [20]. Analysis of the HealthNuts study (in Australia) showed that early introduction of egg was associated with a lower incidence of egg allergy [21]. A recent Canadian multicenter study found a lower rate of sensitization to milk, peanut and egg among children who consume these foods earlier [22]. Thus, several observational studies suggested that early exposure to potentially allergenic foods such as milk, peanut and egg was associated with protection against allergy to the introduced food.

**RANDOMIZED CONTROL STUDIES**

In order to substantiate the link between the age at which potentially allergenic food is introduced and the incidence of allergy, several interventional, randomized controlled trials (RCT) have been undertaken. Early introduction of peanut to 4–11 month old infants who were considered at high risk to develop peanut allergy, suffering from severe atopic dermatitis and/or egg allergy, was shown to be very effective [23]. The prevalence of peanut allergy at age 60 months was several-fold higher among infants who avoided peanut protein compared with infants who consumed peanut regularly. The protective effect of regular consumption of peanut was higher among those infants at the age of 60 months who were not sensitized (see below) at the randomization: 0.4% and 1.9% peanut allergy (per protocol and intention to treat, respectively, consumption group) vs. 13.9% and 34% (per protocol and intention to treat, respectively, avoidance group). Furthermore, the effect persisted even after a year of peanut avoidance in the consumption group [24].

The STAR (Solids Timing for Allergy Research) study (Australia) included high risk infants (e.g., those with eczema) with a high proportion (~35%) who were sensitized and clinically reactive to hen’s egg [25]. Among those who completed the study, there was a trend for a lower, but not significant, proportion of infants in the egg group who were subsequently given a diagnosis of IgE-mediated egg allergy compared with the control group. The HEAP study (Hen’s Egg Allergy Research) in Germany examined non-sensitized infants, aged 4–6 months with egg-specific IgE < 0.35 kU/L, who were assigned to two treatment groups. At the age of 12 months, a higher proportion of the verum (pasteurized egg white powder) group were sensitized (5.6%) and egg allergic (2.1%) compared to the placebo group (2.6% and 0.6% respectively). The differences between the groups did not reach significance in either case, $P = 0.24$ and 0.35 for sensitization and allergy.
respectively [26]. In the STEP study (Starting Time of Egg Protein) (Australia), infants aged 4–6 months (actually 4.5–6.5) with hereditary risk of allergy (atopic mother) but without eczema were randomized to consume hen’s egg or to avoid egg up to 10 months of age. At age 12 months, 7% of the egg group and 10.3% of the control group had IgE-mediated egg allergy. The difference did reach statistical significance [27]. In Japan the PETIT study (Prevention of Egg Allergy with Tiny Amount InTake) randomly assigned 5–7 month old infants with atopic dermatitis to receive cooked egg powder or placebo at age 6 to 12 months. The prevalence of hen’s egg allergy was 37.7% in the placebo group and 8.3% in the intervention group (P = 0.0013) [28]. Finally, in the BEAT study (Beating Egg Allergy Trial), infants with at least one first-degree relative with allergic disease and skin prick test (SPT) < 2 mm to hen’s egg white were randomized at age 4 months to receive whole-egg powder or placebo. At the age of 12 months, 20% of the placebo group and 11% of the infants in the egg group showed sensitization to egg white (P = 0.03). However, 8.5% of the “egg group” infants (n=14) reacted to egg within 1 week of its re-introduction [29].

The EAT study (Enquiring About Tolerance) yielded mixed and somewhat disappointing results. The study population comprised 1303 exclusively breastfed infants (for 3 months) who were randomly assigned to receive early introduction of six allergenic foods (peanut, cooked egg, cow’s milk, sesame, whitefish, wheat) [30]. The primary outcome was food allergy to one or more of the six foods between age 1 and 3 years. Significant benefit was demonstrated for egg (1.4% vs. 5.5%) and peanut (0 vs. 2.5%). The rate of non-compliance was high: “only 42.8% of the participants in the early-introduction group …adhered to the protocol” (pp 1738) and the low number of participants probably contributed to the negative outcome with other foods.

**How Early Is Early Introduction of Potentially Allergenic Food?**

Several lines of evidence, with three different foods – milk, peanuts and hen’s egg – indicate that the age of 4 months or above may not be suitable for the term “early supplementation of potentially allergenic foods” in order to prevent or reduce the rate of development of food allergy. Firstly, in the observational study by Katz et al. [19], only 0.05% (3/6500) of the infants who started to regularly consume a milk-based formula during the first 14 days of life developed CMA, compared with a tenfold higher prevalence of CMA in the entire study group (> 13,000 newborns). Secondly, in the LEAP study [23,24], older age at food introduction was associated with less effective prevention. It is notable that ~12% (76/640) of infants aged 4–11 months were excluded from the intervention (consuming peanut) and control (avoiding peanut) groups because of significant sensitization to peanut: SPT > 4 mm. Another 51 (8%) were sensitized to a lesser extent, e.g., had positive SPT but the wheal size was less than 4 mm. These infants were included in the study unless they had clinical allergy, but had a less favorable outcome compared with the non-sensitized [23]. Furthermore, it was noted that older age at screening was associated with a higher rate of sensitization (1–4 mm SPT) or exclusion because of “significant sensitization” (SPT > 4 mm). At age 4 months, 91.4% of the candidates (infants with severe atopic dermatitis) had negative SPT to peanuts and 8.6% had mildly positive SPT (up to 4 mm), but none had SPT > 4 mm. At the age of 10 months 15.4%, and an additional 16.2% had SPT > 4 mm, or up to 4 mm, respectively, and only 68.2% had negative SPT (G. Lack, Oral presentation AAAAI Meeting, San Antonio, TX, USA, February 2015) [31]. Thirdly, in three prospective interventional studies on “early” introduction of egg where infants aged 4–6 months were exposed to egg (e.g., the HEAP [25], STEP [27] and BEAT [29] studies), 4–10% were already sensitized and about 4% exhibited allergy upon initial exposure. In two of these studies, infants with some degree of “high risk” were chosen: infants of atopic mothers (STEP) or infants with first-degree atopic relatives (BEAT). In the third study (HEAP), 23 infants (5.7%) were excluded on the basis of positive SPT (wheal ≥ 2 mm). Taken together, we raise the point that 4–6 month old infants are likely “too old” for “early” intervention to prevent allergy.

**Current Status and Expectations**

As an immediate consequence of the LEAP study [23], 10 international medical societies (American Academy of Allergy Asthma and Immunology, American Academy of Pediatrics, American College of Allergy Asthma and Immunology, Australian Society of Clinical Immunology and Allergy, Canadian Society of Allergy and Clinical Immunology, European Academy of Allergy and Clinical Immunology, Israel Association of Allergy and Clinical Immunology, Japanese Society of Allergology and Clinical Immunology, Society for Pediatric Dermatology, and World Allergy Organization) issued a consensus communication calling for early peanut introduction and the prevention of peanut allergy in high risk infants, rendering earlier guidelines obsolete [12-14]. This consensus communication was co-published in the relevant journals of these organizations [32] and was considered as a limited interim report until wider recommendations are to be published by the forthcoming Expert Panel meeting sponsored by the National Institute of Allergy and Infectious Diseases [31] of the U.S. National Institutes of Health.

The Israeli infant feeding guidelines have omitted the recommendation to remove potentially allergic foods from pregnant and lactating mothers.

What about other foods? A recent Cochrane library review considered the evidence for the benefits of adding allergenic...
food at the age of 4–6 months and did not find a reason to change the current recommendation [33]. In an even more recent review and meta-analysis Lerodiakonou et al. [34] concluded that there is evidence in favor of “early” introduction of CMS, peanuts and egg proteins. One of the above cited studies [27] was not included, probably because it was published too late. However, this study would support the conclusion of the meta-analysis.

While the World Health Organization (WHO) recommends exclusive breastfeeding for at least 6 months, this recommendation is based mainly on increased infant mortality from respiratory and gastrointestinal infection in infants on other forms of feeding [35]. These reports were from low-income and middle-income countries. However, while two of the three reports showed increased mortality in the non-exclusive breastfed group, there was no difference between exclusively breastfed and predominantly breastfed infants [36], or only a borderline difference [37,38].

Furthermore, the risk of severe allergic reaction in the first weeks or months of life are very small. Without being bound by theory, it is stipulated that there is not even a single case of food allergy-related death in the first months of life even though this is the age at which allergenic food is introduced to the diet. Food allergy-related deaths occur usually in the second decade of life or later, and the earliest age “real danger” is the second half of the first decade of life [39]. Furthermore, in the LEAP study, even infants with sensitization (up to 4 mm) who had a positive oral food challenge (OFC) only experienced mild cutaneous reactions; in contrast, there were much more severe allergic responses (24.5% had respiratory symptoms and 16% required treatment with epinephrine) in the 5 year old children who had an OFC at the end of the trial (G. Lack, Oral presentation AAAAI Meeting, February 2015).

Many physicians share the wonder of Dr. Bobrow from New York, who pondered: “When my daughters visited I could not feed my grandchildren bananas at 6 weeks of age, even though their mothers enjoyed them in their infancy. An entire generation attests to the safety and the benefits of early introduction…” [40].

Thus, as the pendulum has started to change direction as the body of evidence is moving toward early introduction of potentially allergenic foods to prevent food allergies, the authors of this article hope that reading this will help hold up the pendulum in the direction of adding allergenic food in the infant diet.

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References


Benefits and risks of antiretroviral therapy for perinatal HIV prevention

Randomized trial data on the risks and benefits of antiretroviral therapy (ART) as compared with zidovudine and single-dose nevirapine to prevent transmission of the human immunodeficiency virus (HIV) in HIV-infected pregnant women with high CD4 counts are lacking. Fowler et al. found that the median CD4 count was 530 cells per mm3 among 3490 primarily black African HIV-infected women enrolled at a median of 26 weeks of gestation (interquartile range 21-30). The rate of transmission was significantly lower with ART than with zidovudine alone (0.5% in the combined ART groups vs. 1.8%, difference -1.3 percentage points, repeated confidence interval -2.1 to -0.4). However, the rate of maternal grade 2 to 4 adverse events was significantly higher with zidovudine-based ART than with zidovudine alone (21.1% vs. 17.3%, P = 0.008), and the rate of grade 2 to 4 abnormal blood chemical values was higher with tenofovir-based ART than with zidovudine alone (2.9% vs. 0.8%, P = 0.03). Adverse events did not differ significantly between the ART groups (P > 0.99). A birth weight of less than 2500 g was more frequent with zidovudine-based ART than with zidovudine alone (23.0% vs. 12.0%, P > 0.001) and was more frequent with tenofovir-based ART than with zidovudine alone (16.9% vs. 8.9%, P = 0.004); preterm delivery before 37 weeks was more frequent with zidovudine-based ART than with zidovudine alone (20.5% vs. 13.1%, P > 0.001). Tenofovir-based ART was associated with higher rates than zidovudine-based ART of very preterm delivery before 34 weeks (6.0% vs. 2.6%, P = 0.04) and early infant death (4.4% vs. 0.6%, P = 0.001), but there were no significant differences between tenofovir-based ART and zidovudine alone (P = 0.10 and P = 0.43). The rate of HIV-free survival was highest among infants whose mothers received zidovudine-based ART.


Eitan Israeli

**Capsule**

**Ebola virus glycoprotein with increased infectivity dominated the 2013–2016 epidemic**

The magnitude of the 2013–2016 Ebola virus disease (EVD) epidemic enabled an unprecedented number of viral mutations to occur over successive human-to-human transmission events, increasing the probability that adaptation to the human host occurred during the outbreak. Diehl et al. investigated one non-synonymous mutation, Ebola virus (EBOV) glycoprotein (GP) mutant A82V, for its effect on viral infectivity. This mutation, located at the NPC1-binding site on EBOV GP, occurred early in the 2013–2016 outbreak and rose to high frequency. The authors found that GP-A82V had heightened ability to infect primate cells, including human dendritic cells. The increased infectivity was restricted to cells that have primate-specific NPC1 sequences at the EBOV interface, suggesting that this mutation was indeed an adaptation to the human host. GP-A82V was associated with increased mortality, consistent with the hypothesis that the heightened intrinsic infectivity of GP-A82V contributed to disease severity during the EVD epidemic.

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Eitan Israeli
Emergency Department Pain Management of Acute Abdominal Pain and Acute Appendicitis in Children

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**Key Words:** emergency, abdominal pain, appendicitis

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Acute pain is a common presenting symptom in the pediatric emergency department (ED). This adverse stimulus occurs as a result of injury and illness. If a child’s pain is not treated quickly and effectively, it can have long-term physical and psychological sequelae [1–3]. These long-term consequences may include anticipatory anxiety during future procedures, a lowering of the pain threshold and sensitization to future pain, reduced effectiveness of analgesics, and increased analgesic requirements [1–3].

**Pain Assessment**

Pain assessment is an important part of pain management, and ongoing assessment of the child’s pain in the ED is essential. Because pain is a subjective experience, individual self-reporting is the preferred method for assessing pain. However, in non-verbal children, observational and behavioral assessment tools are acceptable alternatives when a valid self-report is not available [3]. Five instruments are commonly used to assess pain in the 0–18 year old age group:

- The Alder Hey Triage Pain scale (AHTPS) [Table 1] and the Face, Legs, Activity, Cry, Consolability scale (FLACC) [Table 2] are observational scoring tools designed for use in children aged 0–2 years.
- The Faces Pain Rating scale (FPFR) [Figure 1] and the Visual Analog Scale (VAS) [Figure 2] are self-report scoring scales designed for use in children aged 3–7 years and 8–15 years, respectively.
- Similar to adults, the self-report verbal numeric rating scale is used in children aged 16–18 years [3,4].

Despite the frequency of pain in the ED, children’s pain assessment and documentation is often scarce, with poor correlation between pain perceived by children, parents and medical practitioners. The treatment of pain in infants and children has

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**Table 1. The Alder Hay Triage Pain Scale (AHTPS)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry or voice</td>
<td>No complaints</td>
<td>Consolable</td>
<td>Inconsolable Complaining of pain</td>
</tr>
<tr>
<td>Face expression</td>
<td>Normal conversation</td>
<td>Short grimace (&lt; 50% of the time)</td>
<td>Long grimace (&gt; 50% of the time)</td>
</tr>
<tr>
<td>Posture</td>
<td>Normal</td>
<td>Touching/Rubbing/Sparing</td>
<td>Defensive/Tense</td>
</tr>
<tr>
<td>Movement</td>
<td>Normal</td>
<td>Reduced or restless</td>
<td>Immobile or thrashing</td>
</tr>
<tr>
<td>Color</td>
<td>Normal</td>
<td>Pale</td>
<td>Very pale</td>
</tr>
</tbody>
</table>

**Table 2. The Face, Legs, Activity, Cry, Consolability (FLACC) Scale**

<table>
<thead>
<tr>
<th>Category</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>No particular expression or smile</td>
<td>Occasional grimace or frown, withdrawn, disinterested</td>
<td>Frequent to constant quivering chin, clenched jaw</td>
</tr>
<tr>
<td>Legs</td>
<td>Normal position or relaxed</td>
<td>Ueasy, restless, tense</td>
<td>Kicking, or legs drawn up</td>
</tr>
<tr>
<td>Activity</td>
<td>Lying quietly, normal position, moves easily</td>
<td>Squirming, shifting back and forth, tense</td>
<td>Arched, rigid or jittering</td>
</tr>
<tr>
<td>Cry</td>
<td>No cry (awake or asleep)</td>
<td>Moans or whimpers, occasional complaint</td>
<td>Crying steadily, screams or sobs, frequent complaints</td>
</tr>
<tr>
<td>Consolability</td>
<td>Content, relaxed</td>
<td>Reassured by occasional touching, hugging or being talked to, distractable</td>
<td>Difficulty to console or comfort</td>
</tr>
</tbody>
</table>
Table 3. List of analgesic medications available in Israel

<table>
<thead>
<tr>
<th>Pain level</th>
<th>Medication</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Paracetamol (oral)</td>
<td>Acetaminophen (500 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild / moderate</td>
<td>Ibuprofen (oral)</td>
<td>Nurofen syrup (60 mg, 125 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tiptipot Ibuta syrup</td>
</tr>
<tr>
<td>Mild / moderate</td>
<td>Dipyrone (oral)</td>
<td>Optalgin drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V-Dalgin drops</td>
</tr>
<tr>
<td>Moderate / Severe</td>
<td>Tramadol (oral)</td>
<td>Tramadex drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tramadex flashtab (50 mg)</td>
</tr>
<tr>
<td>Moderate / Severe</td>
<td>Tramadol/Paracetamol (oral)</td>
<td>Zaldiad tablets (325 mg/57.5 mg)</td>
</tr>
<tr>
<td>Moderate / Severe</td>
<td>Tramadol (intravenous)</td>
<td>Tramal IV ampules / Trama</td>
</tr>
<tr>
<td>Moderate / Severe</td>
<td>Oxycodone (oral)</td>
<td>Oxycode syrup (2 mg/ml)</td>
</tr>
<tr>
<td>Severe</td>
<td>Morphine (intravenous)</td>
<td>Morphine IV ampules</td>
</tr>
<tr>
<td>Severe</td>
<td>Morphine (oral)</td>
<td>Oramorph oral drops (20 mg/ml)</td>
</tr>
<tr>
<td>Severe</td>
<td>Fentanyl (intravenous, intranasal)</td>
<td>Beatryl IV ampules</td>
</tr>
</tbody>
</table>

children with acute abdominal pain are undertreated for pain in the ED [17–19]. There may be several reasons for the low rate of ED analgesia administration in children with abdominal pain, including inadequate pain assessment, belief that opioids can obscure a surgical condition, and fear of adverse events [17–20]. A delay in provision of analgesia may occur if analgesia is not being delivered until the surgeon has evaluated the patient [18]. Consequently, the 2012 report on pain by the American Academy of Pediatrics emphasized the importance of not withholding analgesia in children with abdominal pain in the ED [2].

OPIOIDS IN ACUTE ABDOMINAL PAIN IN CHILDREN

Four parallel-group randomized controlled studies have demonstrated the safety of opioids in acute abdominal pain in children [21–24]. A recent systematic review screened 1497 papers that investigated opioid management of acute abdominal pain in children. The findings of this comprehensive analysis suggest that, compared to placebo, opioid administration is associated with no difference in manageable side effects and it has no serious adverse events [20].

APPENDICITIS-RELATED PAIN IN THE ED

Recent reports from the United States and Canada demonstrate that in acute appendicitis the rate of any type of analgesia and the rate of opioids analgesia is low, especially when compared to adult patients [25-27]. One study reported that in the USA, general emergency physicians were more likely to provide analgesia to children diagnosed with appendicitis than were pediatric emergency physicians [28]. A large cross-sectional multicenter study of 0.94 million ED admissions in the USA demonstrated that the ED analgesia rate for children with appendicitis was approximately 60%, with an opioid analgesia rate of only 40% [25].

Despite its frequency, the diagnosis of acute appendicitis may be challenging and may take several hours during which the patients may suffer from pain if not treated. The American Academy of Pediatrics recommends the use of early analgesics in these patients to make the physical examination and diagnostic testing (such as sonography) more comfortable [2]. The findings of a recent systematic review concluded that with regard to acute appendicitis, opioids are not associated with an increased risk for perforation or abscess and can be provided safely [20].

CURRENT STATUS IN PEDIATRIC EDS ISRAEL

Acute pain is now recognized as the fifth vital sign, along with blood pressure, pulse, respiratory rate and temperature. In 2010, a report published by the Israel Medical Association emphasized the importance of using proper ED analgesia to treat children with acute abdominal pain [3]. To date, no Israeli study has investigated the rate of ED analgesia in these children. Research on a national level is needed to clarify the current
status of ED pain management of acute abdominal pain and acute appendicitis in Israeli children.

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References

Capsule

Quantifying the alarm from antibiotic resistance

Antibiotic resistance is a major global fear, but how fearful should we be? Multidrug resistance (MDR) is high among vulnerable to purveyors of substandard drugs and where over-the-counter sales are not controlled. Lim et al. collected mortality data on bacteremia from 10 public hospitals in northeast Thailand between 2004 and 2010. During this period, the incidence of bacteremia increased, and high case fatality rates were observed for MDR strains, especially hospital-acquired Acinetobacter spp. Extrapolating to the whole of Thailand for 2010 indicates that among patients with hospital-acquired MDR bacterial infection, 43% of deaths represented excess mortality caused by MDR – which is high compared with similar estimates for the United States or Europe.

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Etan Israeli

“It's no use going back to yesterday, because I was a different person then”

Lewis Carroll (1832-1898), English writer, mathematician, logician, Anglican deacon, and photographer. His most famous writings are Alice's Adventures in Wonderland and its sequel Through the Looking-Glass. He is noted for his facility at word play, logic and fantasy
Heparinization of Long Indwelling Lines in Neonates: Systematic Review and Practical Recommendations

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ABSTRACT: Prolonged vascular access is an essential element in the care of most critically ill and premature neonates. However, the role of prophylactic heparinization in achieving this remains controversial. The aim of this paper is to provide practical recommendations based on a systematic review of the literature on prophylactic heparinization by continuous infusion in indwelling long lines in preterm neonates. All randomized controlled trials, and non-randomized case-control studies, looking at heparin vs. no heparin in neonates were included. We concluded that the literature supports heparinization to prolong longevity of long lines. We then compared dosing vs. efficacy to determine optimal dosage recommendations, which we suggest to be 10–50 IU/kg/day. Finally, we devised a practical clinical aid which calculates the heparin exposure at various birth weights, infusion rates and heparin dosages in order to facilitate easy bedside determination as to which combination best meets the recommendations.

KEY WORDS: neonate, heparin, umbilical artery catheters (UAC), peripherally inserted central catheter (PICC)

Prolonged vascular access is an essential element in the care of most critically ill and premature neonates. However, indwelling long lines often become occluded and need to be removed. Furthermore, the incidence of catheter-related thrombosis in neonates is probably much higher than generally considered. In a review of central line thromboses Revel-Vilk and Ergaz [1] reported that umbilical artery catheters (UAC) thrombosis was found on autopsy in 59% of infants, whereas ultrasound demonstrated UAC thrombosis in only ~25% of neonates; UVC thrombosis was found on autopsy studies in up to 65% of infants, whereas ultrasound screening for thrombosis showed a rate of 22–43%. A retrospective large cohort of 882 infants with 1540 PICCs reported occurrence of clinical thrombosis (cord, phlebitis, extremity edema, extremity perfusion, and inability to draw or flush the catheter) in 14% of infants [2], while the rate of symptomatic peripherally inserted central catheter (PICC)-related thrombosis confirmed by ultrasound was reported at a significantly lower frequency (< 1.5%).

Studies have shown that heparinization of these lines can prolong their longevity [3]. However, heparinization of indwelling long lines in newborn infants has become the subject of intensive reevaluation in recent years. Clinically, we struggle with the most basic of issues –issues such as whether heparinization of indwelling lines is justified or even imperative? If so, for which type of lines and at what dose? And finally, what are the side effects and potential toxicities of heparinization, particularly in the extremely low birth weight population? Some of the controversy lies in the paucity of data and in the different endpoints sought in the existing studies. Some of the studies have looked at the efficacy of heparin in terms of line longevity; others have studied thromboses and/or sepsis prevention. In this paper we present a practical approach to the use of continuous heparinization of indwelling long lines which is based on a systematic review of these controversial issues. The criteria used for considering studies for this review were:

- **Types of studies**: All trials using random or quasi-random or retrospective patient allocation
- **Types of participant**: Premature infants who received continuous heparin infusion for the maintenance of PICC lines or umbilical lines
- **Types of interventions**: The use of continuous heparin infusion vs. placebo for the maintenance of central lines
- **Types of outcome measures**: The primary outcome of interest was the longevity of central lines. Secondary outcomes included rates of hemorrhagic complications, intraventricular hemorrhage and sepsis.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

We searched the following databases: Medline, OVID, Google Scholar, and The Cochrane Library. The key words for the search were: heparin, guidelines, umbilical catheter, PICC, and percutaneous central venous catheter (PCVC). The search applied to publications from 1980 to 2015. We limited the search to neonates and to continuous heparin infusions. Levels of evidence and grades were defined according to the classification of the Oxford Centre for Evidence based Medicine and are recorded in the appropriate tables. The authors assessed the risk of bias of individual studies.
UMBILICAL ARTERY CATHETERS

In a systematic Cochrane review, Barrington [3] documented that heparin infusion effectively decreased the incidence of UAC occlusion although it did not affect the frequency of aortic thromboses. There were no statistically significant adverse outcomes noted. He searched for randomized and quasi-randomized clinical studies of line heparinization in either term or preterm infants and identified and analyzed six randomized controlled trials of which we chose to include four (n=253) [Table 1] [4-7]. We excluded two trials: one study [8] because it did not include line longevity data, they dealt with intermittent flushes rather than continuous infusions, or they compared different catheter types or insertion sites. In addition, we searched references cited in relevant articles. We limited the search to neonates and to continuous heparin infusions (i.e., to the exclusion of lines treated with heparin flushes, studies dealing with routine peripheral intravenous infusions, and studies of therapeutic heparinization in the treatment of thrombi). Based on our review, we concluded that the current state of the art supports heparinization of long lines in neonates. We then developed a new clinical approach to the administration of heparin in long lines in the Neonatal Intensive Care Unit.

PICC LINES/UMBILICAL VENOUS CATHETERS

Previous studies have differentiated between peripherally inserted central venous catheter (PICC) lines and umbilical catheters. Randolph et al. [9] found that heparin (administered intermittently or as a continuous infusion) was effective in the prevention of peripheral arterial catheter complications but not for venous catheter complications. It can be hypothetically argued that data derived from umbilical artery catheters cannot be directly extrapolated to PICC lines, as the size of the catheters (internal diameter) used for umbilical arterial access is larger than that used for PICC placement. In addition, the more rapid flow patterns in the aorta, where umbilical arterial catheters are usually placed, differ from the relatively sluggish circulatory states of the venous system in which PICC lines are placed, thus potentially rendering PICC lines at even higher risk for occlusion.

As such, a series of studies looking specifically at heparinization of PICC lines has been published and analyzed in a Cochrane review [10]. This review identified four relevant randomized trials. Three of these trials [11-13] were determined to be of adequate methodology to meet the eligibility criteria. We identified and included four additional studies published after the Cochrane review [14-17] [Table 2].

The Betremieux study was excluded from the Cochrane review [10] because of methodological flaws. In this study, the infants were randomized to heparin or control at the time of insertion of umbilical catheters. If they later needed a PICC line, they were kept in the original treatment group without further randomization. Four infants had multiple catheter insertions and separate data were not available for the first catheter. Given the theoretical difficulties with the Betremieux study described above, we excluded it from our analysis as well. Heparin significantly reduced the risk of catheter occlusion (P < 0.0001). Despite the overall reduced risk of catheter occlusion, there was no statistically significant difference in the duration of catheter patency. This could be due to a higher incidence of elective catheter removals in neonates with completion of therapy in the heparin group (63% vs. 42%, P = 0.002). There were no statistically significant differences in the risk of thromboses [RR 0.93, 95% confidence interval (95%CI)

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Table 1. Summary of studies of heparinization of umbilical artery catheters

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Heparin dose</th>
<th>Grade of evidence</th>
<th>Catheter occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankola [4] 1993</td>
<td>30 infants, not blinded</td>
<td>0.25 IU/ml</td>
<td>1b</td>
<td>2/15 (H) vs. 11/15 (C) RR 0.18 (0.05, 0.68)</td>
</tr>
<tr>
<td>David [5] 1981</td>
<td>50 infants, randomized</td>
<td>1.0 IU/ml</td>
<td>1b</td>
<td>3/23 (H) vs. 15/25 (C) RR 0.23 (0.07, 0.68)</td>
</tr>
<tr>
<td>Rajani [6] 1979</td>
<td>62 Infants, randomized</td>
<td>1.0 IU/ml</td>
<td>1b</td>
<td>4/02 (H) vs. 19/30 (C) RR 0.20 (0.08, 0.51)</td>
</tr>
<tr>
<td>Horgan [7] 1987</td>
<td>111 infants, quasi-randomized</td>
<td>0.46-3.4 IU/kg/hr</td>
<td>3a</td>
<td>2/59 (H) vs. 10/52 (C) RR 0.18 (0.04, 0.77)</td>
</tr>
</tbody>
</table>

H = heparin, C = control, RR = relative risk.
Table 2. Summary of PICC line heparinization studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Heparin dose</th>
<th>Grade of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah [11] 2007</td>
<td>Multicenter (4 NICUs)</td>
<td>H: 0.5 IU/kg/hr C: 0.5 IU/kg/hr</td>
<td>1b</td>
<td>Catheter occlusion: 6 vs. 31% (P = 0.001) Elective catheter removal after therapy completed: 63 (H) vs. 42% (C) (P = 0.002) Increased duration of catheter usability in the heparin group (P &lt; 0.005)</td>
</tr>
<tr>
<td>Birch [12] 2010</td>
<td>H: n=118 C: n=125</td>
<td>0.5 IU/ml</td>
<td>1b</td>
<td>Catheter occlusion: 5/118 (H) vs. 3/125 (C) RR 1.76 (0.46–6.56) (P = 0.42) Reduction in incidence of catheter-related sepsis</td>
</tr>
<tr>
<td>Kamala [13] 2002</td>
<td>H: n=36 C: n=32</td>
<td>1.0 IU/ml</td>
<td>1b</td>
<td>Trend to decreased catheter occlusions (14% vs. 23%, P = 0.4) and increased elective catheter removal after completion of therapy (63% vs. 48%, P = 0.3) in heparin-exposed infants</td>
</tr>
<tr>
<td>Klenner [14] 2003</td>
<td>H: n = 145 C: n = 151</td>
<td>0.5 IU/ml</td>
<td>1b</td>
<td>Duration of catheter patency longer in heparin group (33.8 vs. 26.4 hr) (P = 0.001)</td>
</tr>
<tr>
<td>Uslu [15] 2010</td>
<td>H: n=118 C: n=121</td>
<td>0.5 IU/kg/hr</td>
<td>1b</td>
<td>Duration of catheter patency 12.4 ± 4.5 (H) vs. 9.7 ± 4.0 (C) days (P &lt; 0.0001) Less catheter occlusions with heparin: 23 (19.5%) vs. 55 (45.5%) RR 0.44, 95%CI 1.52–6.44 (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Isseman [16] 2012</td>
<td>H: n=189 C: n=188</td>
<td>0.25 IU/ml (if &gt; 100 ml/kg/day) or 0.5 IU/ml (if &lt; 100 ml/kg/day)</td>
<td>3a</td>
<td>Retrospective Heparin minimized occlusion and other complications although median catheter duration and complication rates did not differ</td>
</tr>
<tr>
<td>Tang [17] 2011</td>
<td>H: n=83 C: n=40</td>
<td>0.5 IU/ml</td>
<td>3a</td>
<td>Retrospective Catheter obstruction (5% vs. 20%), catheter-tip colonization (2% vs. 18%), and CLABSI were significantly lower in the heparin (H) group than in the control group (C) (P &lt; 0.05)</td>
</tr>
</tbody>
</table>

PICC = peripherally inserted central venous catheter; H = heparin, C = control, RR = relative risk, 95%CI = 95% confidence interval, CLABSI = central line-associated bloodstream infection

Sepsis

Studies have shown an association between catheter-related sepsis and thromboses [19]. Thus, it is theoretically possible that heparinization may also reduce the incidence of catheter-related sepsis. This has been reviewed in several studies. Birch and co-authors [12] reported, in a double-blinded study that included 210 infants, a significant reduction in culture-positive catheter-related sepsis in those infants with heparinized lines compared to those without heparin (P = 0.04, RR 0.57, 95%CI 0.32–0.98). In contrast, other smaller line heparinization studies that reported sepsis as a secondary outcome [11,13] found no difference in the incidence of sepsis with or without heparin. When we combined the data from these three studies, there was a trend towards less sepsis in the heparin-exposed infants which did not reach statistical significance (RR 0.70, 95%CI 0.4–1.1, P = 0.13).

Potential adverse effects

There is a theoretical concern regarding a potential increase in the incidence of intraventricular hemorrhage (IVH) secondary to heparin administration [20-23]. In actuality, however, no increase in the appearance of new IVH between the heparin and no-heparin group (RR 0.5, 95%CI 0.19–1.28) was reported by Kamala et al. in 2002 [13] or by Birch et al. in 2010 [12]; Shah and team in 2007 [11] reported no new or extension of hemorrhage in any of their patients. Chang et al. [20] studied the effect of heparin on bleeding tendencies and IVH and also found no effect on the incidence of IVH or on severe IVH (grades 3–4).

Heparin dose

While some of the literature reports heparin dosing as a concentration (IU/ml), others report a total daily dose as IU/kg/day. In order to develop a unified practical approach, existing data must first be transformed into a consistent format. For this purpose, we chose to view the data based on the total daily heparin dose per kilogram.

In five of eight studies reporting the total heparin dose/kg/day, the total daily dose ranged between ~100 and 200 IU/kg/day [Table 3]. In most studies in which the total heparin dose was not reported, heparin was administered at a rate of 1 IU/ml. Assuming that the infants received between 100 and 150 ml/kg/day, we surmise that the total heparin dose in most of these studies was also within the range of 100–150 IU/kg/day.

As can be seen in Table 3, there were four studies that reported a lower mean total daily heparin dose of 12–50 IU/kg/day. Even at these lower doses, heparin was found to prolong catheter patency without significant adverse outcomes. Studies of both PICC lines and umbilical catheters were involved in the high as well as the low dosing regimens.

0.58–1.51], catheter-related sepsis (RR 0.82, 95%CI 0.43–1.57), or extension of intraventricular hemorrhage (RR 0.50, 95%CI 0.19–1.28) between the two groups. Studies evaluating the heparinization of PICC lines are summarized in Table 2.

We identified one study that looked at heparinization of umbilical venous catheters. Unal et al. [18] in a prospective study of term neonates infused heparin (n=19) (0.5 IU/ml) or placebo (n=27) at a rate of 1 ml/hr and found no difference in the incidence of thrombosis 1, 3 or 5 days after catheter insertion.
Perhaps the only study that looked specifically at different levels of prophylactic heparin dosing in the neonatal population was that of Moclair and Bates [24]. Heparin at 0.1, 0.25, 0.5 and 1 IU/ml was added to total parenteral nutrition (TPN) infusions delivered through peripheral veins, and the survival time of the infusions was determined. For infusion sites receiving heparinized fluids, the relative risk of failure decreased and the median survival time increased as the heparin concentration increased, with a maximal effect at a heparin concentration of 0.5 IU/ml (P < 0.001). No incremental advantage was observed with heparin at doses above 0.5 IU/ml.

Both Cochrane reviews concluded that the prophylactic use of heparin for PICC lines and for umbilical artery catheters allows a greater number of infants to complete their intended use (complete therapy) by reducing occlusion. Although several of the PICC line studies that we reviewed used heparin doses that were similar to those used in the umbilical artery studies and demonstrated similar efficacy, the 9th American College of Chest Physicians consensus conference on antithrombotic therapy for neonates with central venous access devices (PICC lines) recommended maintenance of catheter patency through the use of unfractionated heparin at a continuous infusion rate of 0.5 IU/kg/hr, which would provide a total daily dose of 12 IU/kg/day. For neonates with umbilical artery catheters, they suggested prophylaxis with a heparin concentration of 0.25–1 IU/ml, which they suggest should yield a total daily heparin dose of 25–200 IU/kg/day to maintain patency [25]. Given the theoretical arguments that PICC lines may be at increased risk, it seems somewhat counterintuitive to recommend a lower dose for these lines. Thus, given a reasonable level of consensus derived from other PICC line studies, we feel that developing a separate set of recommendations for different types of lines is not supported by the literature and would be clinically confusing and therapeutically unnecessary.

After reviewing the literature, we sought to develop a unified, practical approach towards prophylactic heparin dosing that would take into account the above data, minimize risk and optimize efficacy. As seen in Table 3, the neonatal studies naturally divide into two groups, which we can define as high (~80–200 IU/kg/day) and low dose regimens (< 50 IU/kg/day). Both doses have shown efficacy and neither has been associated with significant adverse effects. In an effort to optimize efficacy while minimizing risk, we conclude that the lower total daily dose of between 10 and 50 IU/kg/day (0.5–2 IU/kg/hr) would best meet these needs. Of note, the American College of Chest Physicians recommended a daily dose of 12 IU/kg/day for PICC line prophylaxis and a daily heparin dose range of 25–200 units/kg per day for umbilical artery prophylaxis. Both of these recommendations are consistent with our recommendation of 10 to 50 IU/kg/day, although they overlap at different ends of the spectrum.

We then devised a practical clinical aid which calculates the heparin exposure infant weights from 500 to 4000 g, at infusion flow rates ranging from 0.5 to 4 ml/hr with continuous heparin infused at three different dosing regimens: 0.5 IU/ml, 0.25 IU/ml, and 0.5 IU/kg/hr in order to facilitate easy bedside determination as to what combination best meets the recommendations. [These recommendations have been consolidated in a table which is available on request from the corresponding author.]

### METHODODOLOGICAL LIMITATIONS

Of note, all of these studies are characterized by heterogeneity in both methodology and endpoints, thus precluding definitive meta-analyses of the effect of heparin on the longevity of long indwelling lines. Most studies confined themselves to the first catheter, while others used the same initial randomization for several catheters.

Study endpoints can be confusing as well. Line longevity has been studied and defined either as the presence or absence of line occlusion or the ability to infuse through the line for the prescribed duration for which it was intended. While sometimes overlapping, these endpoints can at times be quite different, for example when a line is electively removed for completion of therapy.

Furthermore, only one study compared different dosages, and no studies compared different types of lines. Thus, any unified recommendations must cull and combine data derived from different studies.

### SUMMARY OF EVIDENCE AND CONCLUSIONS

Although many aspects of long line heparinization in neonates remain controversial, we believe that this review resolves several important issues and brings them to a new, unified and practical clinical application. Most importantly, there are quite definitive data indicating that heparinization decreases catheter occlusions without increasing intraventricular hemorrhage or other adverse effects based mostly on high quality randomized controlled trials. However, there is no decrease...
in thrombi formation and the data on sepsis remain inconclusive. Additional studies are needed to further clarify and define these issues.

Whether or not prolonging catheter usability justifies adopting a therapy with minimal toxicity is subject to judgment/opinion. However, assuming that one does accept this premise, clinicians need a practical therapeutic approach while awaiting supplementary data. As such, we next suggested an optimal dosing schedule based on our review. We recommend that heparinization of long lines be based on the total daily dose of heparin; we suggest that a dose of between 10 and 50 IU/kg/day would provide therapeutic efficacy while minimizing toxicity. Finally, given that we found no significant differences in the therapeutic responsiveness of PICC lines vs. umbilical lines, we suggest that a universal recommendation for all types of long line prophylaxis in neonates would facilitate greater ease of use and increase acceptance. In summary, we have reviewed existing data and “re-packaged” it to provide a new, practical and unified clinical approach.

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References

“The truth isn’t always beauty, but the hunger for it is”
Nadine Gordimer (1923-2014), South African writer, political activist and recipient of the 1991 Nobel Prize in Literature. Gordimer’s writing dealt with moral and racial issues, particularly apartheid in South Africa. She was active in the anti-apartheid movement, joining the African National Congress during the days when the organization was banned. She was also active in HIV/AIDS causes

“You never really understand a person until you consider things from his point of view... Until you climb inside of his skin and walk around in it”
Harper Lee (1926-2016), American novelist widely known for her novel To Kill a Mockingbird, which won the 1961 Pulitzer Prize and has become a classic of modern American literature
Timing of Orchioptomy for Undescended Testis in Israel: A Quality of Care Study

Guy Hidas MD,1 Jacob Ben Chaim MD,1 Refael Udassin MD,2 Mary Graeb MD,1 Ofer N. Gofrit MD,2 Rachel Yaffa Zisk-Rony PhD,4 Dov Pode MD,2 Mordechai Duvdevani MD,2 Vladimir Yutkin MD,2 Amos Neheman MD,1 Amos Fruman MD,3 Dan Arbel MD,3 Vadim Kopuler MD,3 Yaron Armon MD,3 and Ezekiel H. Landau MD1

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ABSTRACT: Background: Strong evidence suggests that in order to prevent irreversible testicular damage surgical correction (orchiopexy) for undescended testis (UDT) should be performed before the age of 1 year.

Objectives: To evaluate whether orchiopexy is delayed in our medical system, and if so, to explore the pattern of referral for orchiopexy as a possible contributing factor in such delays.

Methods: We conducted a retrospective chart review of all children who underwent orchiopexy for UDT between 2003 and 2013 in our institution. We collected data on the age at surgery and the child's health insurance plan. We also surveyed pediatricians from around the country regarding their pattern of UDT patient referral to a pediatric urologist or surgeon for surgical correction.

Results: A total of 813 children underwent orchiopexy in our institute during the study period. The median age at surgery was 1.49 years (range 0.5–13). Only 11% of the children underwent surgery under the age of 1 year, and 53% between the ages of 1 and 2 years. These findings were consistent throughout the years, with no difference between the four health insurance plans. Sixty-three pediatricians who participated in the survey reported that they referred children to surgery at a median age of 1 year (range 0.5–3 years).

Conclusions: Our results demonstrate delayed orchiopexy in our medical system. There is a need to improve awareness for early specialist consultation in order to facilitate earlier surgery and better care.

KEY WORDS: orchiopexy, undescended testis (UDT), quality of care study, cryptorchidism, pediatrics

Undescended testes (UDT) are common, found in 3.4–5.8% of term boys and up to 30% of premature male infants. In most of these cases the testes descend spontaneously within the first few months of life and rarely after 6 months of age. By the age of 1 year 1% of male children have UDT [1]. UDT are associated with a higher risk of testicular malignancy [2] and torsion [3], reduced fertility and endocrine function [1]. In addition, in most cases there is a patent processus vaginalis, which if not treated may, albeit rarely, turn into a clinical indirect inguinal hernia [4]. Lastly, UDT is an esthetic problem with psychological consequences of an ipsilateral empty scrotum especially in puberty and adulthood [5].

Strong evidence [6-9] suggests that in order to prevent irreversible testicular damage surgical correction (orchiopexy) should be performed before the age of 1 year. Those studies showed that any delay in orchiopexy will increase the risk of testicular growth failure, histological changes such as fibrosis, as well as low sperm count. In 1996 the American Academy of Pediatrics (AAP) published clinical guidelines stating that orchiopexy for UDT should be performed before the age of 1 year. Recently, a large database study [10] using the PHIS (Pediatric Hospital Information System) database that included over 28,000 patients from 41 children's hospitals in the United States showed that despite the AAP guidelines, only 16% of children with UDT underwent orchiopexy before 1 year of age and 43% before the age of 2 years. In addition, a recent study from Germany [11] found that only 18.7% underwent orchiopexy before 1 year of age, 24.3% at 1–2 years, and 57% after age 2 years. In reality, some of the cases, even today, are operated at a later age.

Those results were the basis of this study which aimed to determine the age of patients with UDT at the time of the surgical correction (phase I); and if there was a delay, to explore the pattern of referral for orchiopexy as a possible contributing factor to such delays (phase II).

PATIENTS AND METHODS

This study received Institutional Review Board approval. Phase I was a chart review. Participation in phase II was voluntary and anonymous.

PHASE I: PATIENT POPULATION

We used our institutional electronic medical records to collect data on all patients who underwent orchiopexy between 2003 and 2013. Inclusion criteria included orchiopexy due to UDT between 0 and 18 years. We collected data on each child's
co-morbidity and health insurance plan (one of four in Israel). We excluded cases of orchiopexy due to testicular torsion and iatrogenic UDT post-inguinal surgery. To avoid dual counting of two-stage orchidopexies, bilateral orchiopexy or redo procedures, only the first surgical procedure for any individual patient was included in the final data set. In order to examine trends in practice during the study period, the year of procedure was also documented.

Our primary outcome of interest was patient age at the time of orchiopexy (1 year, 2 years, etc.)

**PHASE 2: PEDIATRICIANS SURVEY**

We conducted a short survey of active pediatricians in the community. The survey was distributed to community-based pediatricians during a continuous medical education lecture gathering. All were asked three questions:

- In your everyday practice, what is the age for referral of a patient with UDT to a specialist (pediatric urologist or surgeon)?
- What health insurance plan do you belong to?
- How many years have you been in practice?

**RESULTS**

**PHASE 1**

We identified 947 surgeries for orchiopexy in our institution between 2003 and 2013. After exclusion of 144 patients who had orchiopexy for a reason other than UDT, 803 children remained in the study group. The median age at surgery was 1.49 years. Eleven percent of the patients underwent surgery at age less than 1 year, 53% were operated on at age 1–2 years, and 36% underwent orchiopexy after age 2 years [Figure 1]. We found that these findings were stable throughout the years of the study period (range 1.17–1.67 years). We did not observe any difference in the timing of orchiopexy between the four health insurance plans. Seventy-nine patients (9.7%) had other major background diseases, mostly other congenital anomalies. In that group of patients the median age at surgery was 2 years.

**Table 1. Pediatrician survey: age of child referred for orchiopexy**

<table>
<thead>
<tr>
<th>Child’s age (yr) at pediatrician’s referral</th>
<th>No. of pediatricians</th>
<th>Percentage of pediatricians</th>
<th>Cumulative percentage of pediatricians</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>20</td>
<td>31.3%</td>
<td>31.3%</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>62.5%</td>
<td>93.8%</td>
</tr>
<tr>
<td>1.5</td>
<td>2</td>
<td>31%</td>
<td>96.9%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.6%</td>
<td>98.4%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1.6%</td>
<td>100%</td>
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**Figure 1. Frequency of orchiopexy according to age**

**DISCUSSION**

The primary aim of this study was to determine the age at which orchiopexy is performed in our institution and to examine factors associated with delay in surgery. Contrary to our expectations, many orchidopexies were performed after the age of 2 years. In addition, this figure remained constant during the study period, despite the presence of robust literature and guidelines recommending early surgery.

Given that the evidence for early repair of congenital cryptorchidism is extremely strong, delays in surgery are worrisome. Kollin et al. [6] showed in a randomized controlled study that catch-up growth of the cryptorchid testis occurred after orchiopexy at 9 months, but not when surgery was delayed until age 3 years. Biopsy at the time of orchiopexy has shown that testicular histology tends to worsen with age. Moreover, interstitial fibrosis and poor tubular characteristics are more common in UDT repaired after 2 years [7]. Hadziselimovic and co-authors [8] found that in the case of intraabdominal testes, germ-cell counts may be normal in the newborn period, but if left untreated beyond 2 years of age there is a 30–40% chance of complete spermatogenic failure. Similarly, Canavese et al. [9] noted that both sperm counts and motility are higher in young men who underwent orchiopexy before the age of 1 year.

These robust literature data of the past few decades reveal that the recommended age for orchiopexy has been consistently lowered. In 1975, the American Academy of Pediatrics (AAP) still recommended surgery at age 4–6 years for undescended testis [12]. Once it became clear that the histological changes in testicular tissue associated with this condition are not congenital but in fact develop from the age of 6 months onward, the AAP and other international pediatric associations [13-15] devised
guidelines recommending orchiopexy at age 1 year. The rare reported cases of spontaneous testicular descent after the age of 6 months should not be cited to support a general policy of watchful waiting. Such observations are likely due to a missed distinction between retractile and undescended testis [16].

In 2014 the American Urological Association (AUA) published its guidelines on cryptorchidism. Statement 11 clarifies: “In the absence of spontaneous testicular descent by six months (corrected for gestational age), specialists should perform surgery within the next year (Standard; Evidence Strength: Grade B)” [17]. The current European Urological Association (EAU) guidelines confirmed that orchiopexy should be performed by age 12 months, or 18 months at the latest [18]. In the present study we have shown that for 50% of our patients these new more flexible guidelines were followed.

Physicians should be aware that the potential rare complications of orchiopexy – such as anesthesia-related incidents, hemorrhage, wound infection, recurrent undescended testis, testicular atrophy and injury to the vas deferens – are not more common when the procedure is undertaken in the child’s first year compared to later, as long as it is performed by an experienced and well-trained pediatric urologist or surgeon [19].

In this study we showed that despite the conclusive guidelines the surgery is still performed much later than the recommended time. We also showed that pediatricians tend to refer patients at a median age of 1 year. The fact that 50% of the pediatricians initiate the process after the recommended age of surgery may be one of the major causes of delay in surgery. Another possible cause of delay might be that surgeons do not operate at the recommended age.

Another potential delay in surgery may be that despite AAP well-child guidelines [20,21], which explicitly state that a physical exam should be performed at every visit and includes examination for testicular descent, studies in the USA have shown that only a minority of practicing pediatricians regularly follow such guidelines [22]. So, delay in referral may well be due to delay in diagnosis.

The results of this study emphasize the importance of early diagnosis and referral of children with UDT by primary care physicians and pediatricians. We recommend referral at age 6 months since the chance of spontaneous descent is very low and anesthesia is safe at this age, and because in many public institutions in Israel the time from referral to surgery might take several months. We believe that educating pediatricians and parents about the importance of early surgery should be the next step in improving management of these patients.

Our findings should be interpreted in light of their limitations, mainly the retrospective nature of the study. Data are limited to tertiary care, and as such, the patient population may not be generalizable to other academic or community hospitals in Israel. In phase II of the study, when a questionnaire was distributed to pediatricians, a regional bias might have occurred as we sampled pediatricians from a specific region of the country.

Ascending testes (testicles that are in the scrotum at birth and ascend later in life) may have been a confounder in our results. Although delayed diagnosis or treatment of cryptorchidism beyond the neonatal period is well documented, the relative proportion of cases of true testicular ascent vs. congenital cases that were not identified or referred early for care remains unclear. Given the potential for change in testicular position throughout childhood, careful evaluation of the scrotum should be performed at every scheduled well-child examination [17].

Other than ascending testes we are not aware of any specific important confounders not included in the model; however, given the observational nature of this investigation, there may be unmeasured confounding influences on our results.

In conclusion, in our institute, half of the children with UDT underwent orchiopexy before age 1.5 years and most of them before age 2. These results are better than those of the USA and Germany but are not optimal. A major factor contributing to the delay in surgery is that pediatricians tend to refer the patient to surgery too late. Improving awareness regarding the best orchiopexy timing among primary care pediatricians and surgeons is mandatory.

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References


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### Capsule

#### Risk factors for Middle East Respiratory syndrome coronavirus infection among health care personnel

Health care settings can amplify transmission of Middle East respiratory syndrome coronavirus (MERS-CoV), but knowledge gaps about the epidemiology of transmission remain. Alraddai et al. conducted a retrospective cohort study among health care personnel in hospital units that treated MERS-CoV patients. Participants were interviewed about exposures to MERS-CoV patients, use of personal protective equipment, and signs and symptoms of illness after exposure. Infection status was determined by the presence of antibodies against MERS-CoV.

To assess risk factors, the authors compared infected and uninfected participants. Health care personnel caring for MERS-CoV patients were at high risk for infection, but infection most often resulted in a relatively mild illness that might be unrecognized. In the health care personnel cohort reported here, infections occurred exclusively among those who had close contact with MERS-CoV patients.


Eitan Israeli

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### Capsule

#### Personalized medicine by another name

A vision of the Human Genome Project was that molecular profiling would enable identification of the molecular underpinnings of disease on an individual basis; “personalized medicine” became a watchword. However, a rebranding has been occurring since roughly 2012 in which the concept has been transmogrified into “precision medicine.” Juengst and colleagues describe conclusions from interviews and case studies conducted since 2011 with 143 supporters of personalized genomic medicine. The terminology change may minimize unrealistic expectations. However, a shift from “personal” could mean a reversal of the trend toward patient autonomy in decision making. The need for population-level sequencing to identify groups with particular molecular profiles carries its own risks in terms of pressures to participate and the possibility of stigmatization.

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Eitan Israeli

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### Capsule

#### Worms remodel immune responsiveness

Rural populations in less developed countries commonly show poor immunogenicity in vaccination programs. Helminth infestations remain common in some rural areas, and cellular immune hypo responsiveness is a hallmark of chronic helminth infections. Community deworming programs are in general believed to be a good thing to reverse the morbidity that a large worm burden can impose on children. Wammes et al. set up a 2 year clinical trial to systematically test the immunological consequences of deworming in > 1000 villagers in Indonesia. After treatment, subjects showed significant immune remodeling, with reduced expression of CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) and elevated pro-inflammatory cytokine responses to malaria parasite antigens. The challenge in the longer term could be that restored immune responsiveness might increase the prevalence of inflammatory diseases.

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Eitan Israeli
Facial nerve schwannomas (FNS) are uncommon benign tumors that can arise from all segments of the facial nerve. Intratemporal schwannoma is a rare tumor in pediatric patients. Clinical manifestations may vary from none to facial paralysis, deafness, tinnitus, vertigo and an ear mass. We present the case of a child with an intratemporal FNS, and provide a detailed description of the diagnostic characteristics and the treatment dilemmas.

**PATIENT DESCRIPTION**

A 5 year old girl with a history of slowly progressive peripheral facial nerve palsy lasting for more than 2 years was referred for evaluation. The parents reported worsening of the paralysis in the months prior to presentation. Her medical and surgical history was otherwise unremarkable.

Physical examination revealed left peripheral facial nerve palsy, House-Brackmann (HB) grade 5. The rest of the physical examination was normal. An audiogram recorded normal hearing. Magnetic resonance imaging (MRI) and computed tomography (CT) scans demonstrated an enlarged fallopian canal with a gadolinium-avid lesion extending from the mid-tympanic segment to the stylomastoid foramen compatible with a schwannoma [Figure 1]. No stigmata of neurofibromatosis were present.

During surgery the tumor was found to extend from proximal to the cochlleariform process to the neck just distal to the stylomastoid foramen. In its mastoid segment the tumor breached the fallopian canal towards the jugular bulb, and in its tympanic region reached the incus and pushed the stapes downwards towards the promontorium; the bulk of the tumor in this area prohibited preserving the posterior external auditory canal, necessitating creating a canal wall down cavity. The tumor was completely excised and nerve continuity reestablished with a sural nerve cable graft, supported by vascularized rotated temporalis muscle flaps. Frozen section microscopic studies established the health of the facial nerve edges. Hearing was reconstructed with a cartilage type 3 tympanoplasty. Facial nerve function returned to HB 4 but later deteriorated to HB 5. Therefore, at months 27 and 35 following surgery, she underwent a two-staged facial reanimation consisting of a cross-face nerve graft using a sural nerve followed by implantation of a gracillis muscle free flap.

Four years after surgery there is no evidence of a residual tumor. Although some asymmetry is noted in the resting state, dynamic facial nerve function is HB 2, and on audiometry a left conductive hearing loss with speech reception threshold is 35dB. Hearing on the right side is normal. Aeration of the residual middle ear and mastoid created a pseudo-posterior canal wall allowing exposure to water.

**Figure 1.** Images of an MRI scan of the temporal bones demonstrating the characteristics and extension of tumor. [A] T1-weighted gadolinium-enhanced axial section depicting a gadolinium-avid tumor in the fallopian canal. [B] T1-weighted gadolinium-enhanced coronal section. Tumor extended through the stylomastoid foramen to the neck. [C] T2-weighted axial cut, demonstrating the relationship of the tumor (arrow) at the second genu to the cochlea (arrowhead) and posterior semicircular canal.
COMMENT

Although rare, FNS are part of the differential diagnosis of progressive peripheral nerve weakness in a child. The majority of FNS cases involve an intratemporal segment such as the geniculate ganglion, labyrinthine and internal acoustic canal [1]. However, tumor involving the intratemporal nerve in a pediatric patient is extremely rare. The impact of facial nerve palsy and hearing loss on social development and academic and language-related skills must be accounted for in the management of pediatric patients.

Diagnosis is based on history, physical examination and imaging. Application of facial nerve function tests in young children is difficult as they can be uncomfortable or painful. Most commonly the degree of facial nerve dysfunction will be established based solely on physical examination. The appearance of FNS in imaging is heterogeneous [1]. On CT, intratemporal FNS are seen by sharply defined bony enlargement of the fallopian canal, and in the middle ear and mastoid they may be seen as a multi-lobulated mass. On MRI, intratemporal FNS appear as a well-circumscribed fusiform, homogeneously enhancing mass along the course of the intratumoral facial nerve. Most are isointense or hyperintense on T2-weighted images of the intratemporal facial nerve. A trans-labyrinthine approach may be used and possibly aided by a mastoid approach for bony decompression of the facial nerve. A trans-labyrinthine approach may be used for patients with a tumor of the internal acoustic canal without functional hearing for better exposure during surgery [3]. The exact proximal reach of the tumor should be defined by imaging. Extracranial tumors can be managed with tympanomastoidectomy, most commonly canal wall up procedures.

A few reports support the possibility of preserving the facial nerve intact during extirpation with better postoperative results compared to facial nerve reconstruction [4]. In the case presented, during microsurgery and pathological study the tumor completely replaced the facial nerve, requiring complete transection and cable grafting.

Primary anastomosis of the cut nerve provides the best chance for good postoperative function. In the vast majority of cases the cut ends of nerves cannot be approximated without an intervening graft. The most commonly used grafts are the greater auricular nerve and the sural nerve. The graft is best supported by vascularized local flaps [5]. These flaps may compromise the mechanism of conduction of hearing. Harvesting a lengthy graft that can circumnavigate the middle ear and ossicles may prevent postoperative conductive hearing loss.

CONCLUSIONS

Intratemporal facial nerve schwannomas are rare in childhood but should be sought in a patient with progressive facial nerve palsy. Management requires consideration of the significant impact of hearing and facial nerve functions on social, academic and language development. Surgery should be timed according to the facial nerve function and potential damage to adjacent structures. Proper design and placement of a nerve graft for reanimation can reduce the risk of postoperative conductive hearing loss.

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“Pursue some path, however narrow and crooked, in which you can walk with love and reverence”
Henry David Thoreau (1817-1862), American essayist, poet, philosopher, abolitionist, naturalist, and historian
Paroxysmal Tonic Upward Gaze at Adolescence: A Girl with Prader-Willi Syndrome

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KEY WORDS: Prader-Willi syndrome (PWS), ophthalmology, paroxysmal tonic upward gaze (PTUG), ataxia, imprinting disorders

Paroxysmal tonic upward gaze (PTUG) is a childhood oculomotor syndrome characterized by episodes of conjugate upward deviation of the eyes. Its pathogenesis is unknown and the etiology is heterogeneous. PTUG has been reported only in children younger than 9 years. Prader-Willi syndrome (PWS) is a complex neurogenetic, multisystem disorder caused by the absence of paternal expression of imprinted genes on 15q11-q13. Ophthalmologic phenomena are common in the syndrome, including myopia, strabismus and amblyopia, but PTUG has not been described in PWS. We describe a 13 year old girl with PWS who had recurrent episodes of PTUG.

PATIENT DESCRIPTION

A 13 year old adolescent female with PWS due to a paternal deletion on 15q11-q13 was treated from early age with an early-intervention holistic program and had received growth hormone treatment from the age of 6 months. Developmentally, she achieved most milestones as expected; she attended special educational frameworks due to mild mental retardation, learning disabilities and autistic spectrum disorder. She manifested obsessive-compulsive behavior, behavioral problems and attention deficit hyperactivity disorder pharmacologically treated with fluvoxamine, risperidone and methylphenidate, respectively. Food-related issues were under control. The girl had strabismus since birth which was corrected surgically at age 6 years.

At the age of 13, two episodes of sustained conjugate upward deviation of the eyes occurred, with neck flexion and down-beating saccades with no ataxia; during these episodes consciousness was maintained (Figure 1). These episodes lasted 12 hours and resolved spontaneously. On examination, several days after the second episode, her weight was 39.6 kg (37th percentile), body mass index 21.2 (82nd percentile), and physical examination, aside from central hypotonicity, was normal. Neither PTUG movements nor ataxia was observed. Ophthalmologic examination revealed: right eye – hypertropia that was comitant in left, right, up, and down gaze; and left eye – myopia and amblyopia. There was no stereo vision.

Electroencephalogram (EEG) was normal, and no epileptic activity was recorded. Brain magnetic resonance imaging (MRI) was normal. Genetic testing for mutations on the CACNA1A gene on chromosome 19 revealed no pathology.

COMMENT

PWS is a complex neurogenetic, multisystem disorder with a prevalence of 1/15,000 to 1/30,000, caused by a lack of expression of genes on the paternally inherited chromosome 15q11.2-q13. Ophthalmologic morbidity is common, and includes myopia, strabismus, esotopia, exotropia as well as reduced visual acuity, iris hypopigmentation, amblyopia, refractive errors and astigmatism [1]. Despite the variable ocular abnormalities PTUG has not been reported in individuals with Prader-Willi syndrome.

Paroxysmal tonic upward gaze in childhood is characterized by episodes of sustained conjugate upward deviation of the eyes with neck flexion, down-beating saccades in attempted downward gaze, and normal horizontal eye movements. Ataxia, in some cases, accompanies PTUG. Consciousness is maintained during these episodes and neurological exam is usually intact. PTUG appears usually before age 1 year or during early childhood. The oldest child described is a 9 year old boy [2,3]. The duration and frequency are variable: episodes usually last seconds, but in rare cases they can continue for more than 24 hours. The frequency ranges from daily episodes to once in several months. Exacerbations are common during febrile illnesses or after

Figure 1. Episode of upward deviation of the eyes and neck flexion
vaccinations [2]. The episodes are relieved by sleep and disappear spontaneously. Ataxia, ocular disability, language problems, mild cognitive or even (rarely) severe cognitive disorder may remain [2].

There is controversy in the literature regarding the efficacy and need of drug treatment for PTUG. Drugs that have been tested are L-DOPA, ACTH, acetazolamide, and antiepileptic drugs such as valproic acid, carbamazepine and benzodiazepines [2,3].

Although the etiology of PTUG is obscure in most cases [2], a genetic basis of PTUG was identified in some instances. There are a few familial cases with autosomal recessive and autosomal dominant inheritance [4]. A mutation in the CACNA1A gene, on chromosome 19, causing calcium channelopathy was reported in five cases. CACNA1A is linked to other paroxysmal disorders, such as benign paroxysmal torticollis of infancy, episodic ataxia, hemiplegic migraine and paroxysmal vertigo [4].

In addition to our patient, PTUG has been reported in two other children with chromosome 15 abnormalities. The first was a 3 month old infant with partial tetrasomy of chromosome 15, and the second, a 2 year old girl with Angelman syndrome caused by a maternal deletion of 15q11-13 [5]. PTUG was described in two other imprinting disorders: one was a case of a 2 week old boy with Beckwith Wiedemann syndrome [3] and the other was the above-mentioned girl with Angelman syndrome [5]. Although the vast majority of cases with PTUG show no brain abnormalities on imaging [2,4], there are rare case reports of demyelinating pathology [4], upper brain stem lesions, periventricular leukomalacia, hydrocephalus and a vein of Galen malformation [3]. EEG and metabolic findings are generally normal, but association with epileptic disorders has been reported [2,4]. Due to the early onset of PTUG some researchers hypothesized that it may be caused by either immaturity of eye movement control or secondary to a channelopathy, or due to neurotransmitter depletion [2,3]. Fukumura et al. [5] speculated that the dopaminergic abnormalities present in Angelman syndrome may cause PTUG [5].

In our case, the cause of PTUG is unclear: there was no clinical or laboratory evidence of epilepsy, structural brain anomalies, CACNA1A gene abnormalities, or maturational abnormalities in eye movement control. The girl was treated for years with fluvoxamine, risperidine and methylphenidate (MPH) before the PTUG onset. Fluvoxamine can cause, in rare cases, ophthalmologic adverse effects such as amblyopia, and risperidone is known to cause blurred vision, conjunctivitis and reduced visual acuity. MPH works through dopaminergic pathways, which were hypothesized to explain the pathophysiological basis of PTUG; nonetheless, our patient was treated with MPH for years at the same dosage. Neither of these drugs was reported to cause PTUG.

In summary, we describe a 13 year old adolescent with PWS who had PTUG, the oldest case reported. Genetic causes may elucidate the etiology of PTUG in some cases. Imprinting genetic disorders and abnormalities on chromosome 15 should be suspected in cases with PTUG and developmental disorders. Further genetic and epigenetic studies may shed light on the precise etiology of PTUG.

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**References**


**Capsule**

**Bidirectional intragraft alloreactivity drives the repopulation of human intestinal allografts and correlates with clinical outcome**

One paradigm in transplantation is that graft-infiltrating T cells are largely non-alloreactive “bystander” cells. However, the origin and specificity of allograft T cells over time have not been investigated in detail in animals or humans. Zuber and co-researchers used polychromatic flow cytometry and high-throughput T cell receptor sequencing of serial biopsies to show that gut-resident T cell turnover kinetics in human intestinal allografts are correlated with the balance between intragraft host-versus-graft (HvG) and graft-versus-host (GvH) reactivities and with clinical outcomes. In the absence of rejection, donor T cells were enriched for GvH-reactive clones that persisted in the long term in the graft. Early expansion of GvH clones in the graft correlated with the rapid replacement of donor antigen-presenting cells by the recipient. Rejection was associated with transient infiltration by blood-like recipient D28+ NKG2D+ CD8+ αβ T cells, marked predominance of HvG clones, and accelerated T cell turnover in the graft. Ultimately, these recipient T cells acquired a steady-state tissue-resident phenotype but regained CD28 expression during rejections. Increased ratios of GvH to HvG clones were seen in non-rejectors, potentially mitigating the constant threat of rejection posed by HvG clones persisting within the tissue-resident graft T cell population.


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