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Brooke Army Medical Center
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PEDIATRIC NEWS

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Pediatric Speech Pathology Services

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Pediatric speech pathology is not just language and articulation anymore. I have been fortunate to work at BAMC for the past 4 ½ years. As part of the Exceptional Family Member Program I am able to see all types of children with various medical and educational needs that are referred to me for an evaluation of speech and language skills. However, my services do not stop there. I also evaluate children for possible learning disabilities (reading, writing, spelling, etc.), stuttering, voice disorders, central auditory processing and phonological processing disorders. I am part of a multidisciplinary team at BAMC that evaluates children from the San Antonio area as well as from Ft. Hood and Ft. Polk. Most of these children are to rule out/in Autism and/or Pervasive Developmental Disorders.

I am a supervisor for graduate students in speech pathology from Southwest Texas and Our Lady of the Lake University. I work closely with these universities in providing their graduate students with an opportunity to work in a major medical center with a diverse group of children. These students learn how to evaluate children with a variety of disorders, work within a multidisciplinary team, make appropriate referrals to different pediatric services within the hospital, and outside of the hospital. They learn to write SOAP notes, home programs, and are required to provide families with resources based on their child's specific needs.

My services do not stop with an evaluation. For parents with children under the age of three that need therapy, I phone the local early childhood intervention service and make the referral for the family. For children under five, a home program is provided to increase language skills and to address articulation needs. A child who is at least three years of age qualifies for services in the public schools and is referred to their local elementary school. The parents of school age children with language and learning difficulties are provided with resources addressing their child's specific needs and information on becoming an advocate for their child when requesting services, testing, etc. Those children who suffer more severe disabilities, e.g., Autism, Pervasive Developmental Disorders, Apraxia, I educate the families on the programs available through Foundation Health, i.e., Program for Person's with Disabilities. If a child has a specific problem I have numerous contacts in the community that are considered "experts" in their field and can provide families with additional information and/or therapy (Although Tri-Care does not pay for most speech therapy, unless you have a medical diagnosis).

I work closely with SAMPC, neurology, ENT, Audiology, and the CAPS program to ensure our children's needs are being met. I am more than willing to speak to doctors or families with questions or concerns regarding their child's educational needs, types of testing needed, and ways to deal with

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Trauma: Impact on Kids et.al

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We are faced with a challenge in explaining the recent terrorist attacks to children when in fact we as adults, parents, and providers, try to make sense of it ourselves. Despite our best efforts, our struggle to continue to some degree of normalcy, both as professionals as well as parent and role models is not a simple task. Assimilating the recent events into our daily lives both present and future is a difficult challenge.

Virtually every child in America will witness at least one disaster that involves death. According to Brooks and Siegel in The Scared Child, "Trauma by Proxy" is experienced by children who indirectly experience a devastating event. Children in today's era witness events via the media that other generations rarely did. Because of the lack of a geographically safe zone, disaster-related bereavement brings to the surface the anxiety of death or subjective feelings of being unsafe and vulnerable. This is clearly evident with today's most recent events. The Handbook of Clinical Child Psychology concludes the importance of working through the trauma effects of disasters first, before grief work can be addressed.

A quick assessment of your little patient with input from the parents will help determine if the child could benefit from short term behavioral health intervention due to various degrees of trauma: These include:

- * Regressive behavior such as biting, encopresis, enuresis
- * Fears and worries

- * Changes in sleep patterns
- * Apathetic behavior and lack of motivation
- * Changes in relationships with family/peers such as clinginess, dependence
- * Grades in school

As a provider, it is helpful to remind your parents that there will be a disruption of normal patterns of their lives and of the children's. Other signs and symptoms such as hostility and aggression towards others, positive findings using SIGECAPS during screens, nightmares/terrors, excessive fears/anxieties/dependencies may require further assessment and intervention. You may see somatic complaints such as headaches and abdominal pain, excessive hyperactivity during the visit, or psychosocial concerns.

Other helpful tidbits to use with families include:

1. Young children may show confusion, and are unable to tell if something has happened to them or to other people. They may be sensitive to the emotions of adults and may mimic anxieties and fears without understanding the precipitous of the feelings. Parents should supervise what children watch and what they are exposed to. Remind parents to limit what children are exposed to in the media, as younger children don't have the cognitive abilities to process as adults.

2. Elementary school children are more verbal and may want to have explanations of the event and may ask, "Why". Each child will have a different level of understanding, especially pertaining to media coverage of the event. Remind the parents that children process and cognitively master experiences through repetitiveness in telling of the event, and through play. Ask the

parents to have patience while this is done. Suggest to parents of this age range to encourage exploration of feelings by using art, letters, music and puppets or toys. Play is a great avenue to process feelings, while keeping vulnerability and emotional safety in check.

3. Adolescents tend to want information and detail. They often see the world as black and white with little gray and conceptualize such information as good vs bad. Remind the parents to engage them in conversation around the separation between evil of the event from the value of people. The surreal feelings vocalized by adults around the attacks may also be voiced by adolescents, especially in relation to or comparison with movies/video games etc.

In addition sense of normal routine is a critical factor in creating an environment that is predictable and one in which all children and adolescents feel some sense of control.

Family, friends and community will help the child demonstrate a physically safe and emotionally secure place in a world that is not always so. Encourage parents to get involved with their communities, places of worship, neighborhoods, as it truly does take a village to raise a child...and to support the parents!

In particular to the recent terrorist attacks, Dr Schwartz, Division of Child and Adolescent Psychiatry at the Evanston Hospital in Illinois suggests three key areas to help families work through feelings.

First, a balancing act is necessary to help children feel safe, while acknowledging the existence of violence. Dr Schwartz suggests discussing the event as much as the child wishes to. Don't offer extra

details, especially if the child can not comprehend them. Getting one's thoughts and feeling in check is the second suggestion: Although this is difficult, the parents should have some level of understanding of the event when helping work through their child's. Lastly, parents can show how much love, devotion and safety there is in their lives through the "review" of good times IE. birthdays, special holidays, etc. It is also important, keeping the developmental age of the child in mind, to remind children of different emotions and how to work through them such as anger, sadness, and loss.

Pediatrics encompasses many components when providing the best comprehensive care for your patients. During these challenging times, parents and children how they cope with the most recent events: This question targets ongoing issues and addresses prevention of future behavioral health complications. As the saying goes, if you don't ask, they mostly won't tell.

Our profession as members of the Air Force plays an important role in identifying and working thru families concerns about deployment, separation, and crisis all in the name of ensuring our little patients continue to thrive. For our children, our role is not always understood and accepted, especially in times of real world deployments. But that article can be put off until another time.

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Housestaff Puzzler

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CM is a 17-year old previously healthy female who presented to the adolescent clinic with a chief complaint of “frequent urination and thirst” for 1 month. She was urinating large volumes once an hour during the day, and awakening twice at night to urinate. She was “constantly drinking” due to thirst and would drink 3 glasses of juice and 2 glasses of water in one sitting. She lost 40 lbs in 5 months, although was trying to lose weight. For the past several months she had been intermittently taking an herbal weight loss supplement that contained a diuretic, but had not taken any in the past 2 weeks. She also complained of non-bloody diarrhea for the past week that seemed to be improving, and daily nosebleeds for the past 3-4 days after blowing her nose in the morning. She denied dysuria and had no history of urinary tract infections. Her last menstrual period was 2 weeks ago. She was not on any medications except for the herbal weight loss supplement that she stopped 2 weeks ago. Family history is positive for “adult onset” diabetes in her 2 grandmothers and a maternal aunt.

Physical Exam

Ht 62.5 in Wt 184 lbs
 Pulse 115 BP 135/84
 Gen – overweight, pleasant AA female accompanied by her mother, in no distress, well hydrated
 HEENT – normal
 Neck – diffusely enlarged thyroid without nodules
 CV – tachycardic, no murmur
 Resp – normal
 Abd – normal

Skin – acanthosis nigricans over nape of neck and in both axilla

Laboratory Studies (fasting)

CBC: WBC 7.3, Hgb 11.8, Hct 35.4, Plt 312

Chemistries: Na 141, K 4.3, Cl 104, HCO₃ 25, BUN 9, creat 0.3, glucose 99

Ca 9.6, TP 7.4, alb 3.3, AP 242, AST 32, ALT 27, bili 0.4

UA: specific gravity 1.024, pH 6.0, no glucose, no ketones, no protein, no blood, no nitrites, no LE
 Glycohemoglobin: 4.6 (4.4-6.7)
 Insulin: 26.4 (0-30)

Lipid profile: cholesterol 165, TG 86, HDL 57, LDL 91

TSH 0.03 (0.3-6.6), FT4 7.5 (0.6-1.5)

Course

Pediatric endocrinology was contacted regarding CM’s abnormal thyroid function tests. The diagnosis of Graves’ disease was made and she was started on methimazole 1mg/kg divided bid. Follow-up was arranged with pediatric endocrinology for 2 days later. In retrospect, CM’s mother had noted that her “eyes were bulging out” for the past 3 months. She indeed had mild exophthalmos compared to her driver’s license photo, for which she is currently followed by ophthalmology. She denied heart palpitations, tremulousness, hair loss or changes, heat intolerance, sleep problems, mood changes, menstrual changes, or polyphagia. Thyroid stimulating immunoglobulins were elevated at 130 (0-129) and 224 most recently (approximately 1 year after the initial diagnosis). Once CM’s thyroid function tests normalized with treatment, her polyuria and polydipsia resolved.

Discussion

In an overweight female presenting with polyuria, polydipsia

and weight loss, with a positive family history of type 2 diabetes, and acanthosis nigricans on exam, diabetes seems to be the likely diagnosis. However, CM’s diabetes labs were completely normal. Her final diagnosis instead was Graves’ disease. Polyuria with polydipsia is an unusual presentation of Graves’ disease. There are however several aspects of the history and physical exam consistent with hyperthyroidism and Graves’ disease: weight loss, diarrhea, mother noting “eyes bulging out”, tachycardia, systolic hypertension, and diffuse thyroid enlargement.

Polyuria and polydipsia as a manifestation of Graves’ disease can be explained. Cardiac output is increased due to the hyperthyroid state. The resulting increase in renal blood flow and glomerular filtration rate manifests as polyuria. Polydipsia then occurs as a mechanism to maintain fluid balance.

Graves’ disease is an autoimmune hyperthyroidism secondary to TSH (thyrotropin) receptor-stimulating antibodies. These antibodies bind to the TSH receptors on the thyroid gland and cause uncontrolled production of thyroid hormone by mimicking TSH action. Exophthalmos clinically distinguishes Graves’ disease from other causes of hyperthyroidism. Graves’ disease most commonly presents at age 20-40 with a 7-10:1 female to male predominance. There is an increased frequency of other autoimmune disorders in people with Graves’ disease and their family members.

In this case, treatment was initiated with methimazole. Methimazole inhibits the production of thyroid hormone at the level of the thyroid gland, and has some immunosuppressive action. Propylthiouracil (PTU) is another commonly used antithyroid medication. Supplemental thyroid hormone

(Synthroid) is often necessary to counteract the hypothyroidism induced by antithyroid medication. This “block-and-replace” approach confers improved thyroid control while maintaining the immunosuppressive effects of the antithyroid medication. Other treatment options include thyroid ablative therapy with radioactive iodine (I^{131}) and surgery. For patients with significant tremulousness, palpitations, tachycardia, systolic hypertension, or sweating, a β -blocker such as propranolol is indicated until the symptoms improve.

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Contiguous Gene Syndromes

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Contiguous is an adjective that only an English teacher or an engineer could truly love. Try this multiple guess problem: “Pick the word or phrase

that most exactly reflects the meaning of *contiguous*.”

- a) Unbroken
- b) Bent but not broken
- c) Broken but don’t know it
- d) Just like the girl next door
- e) Adjacent

Of course, you have picked e), adjacent, touching edges, immediately proximate, and I am grateful that Mrs. Riley, who taught sophomore composition, drilled it in.

Schmickel coined the term “contiguous gene syndrome” (CGS) fifteen years ago to describe the distinctive phenotypic effects caused by an alteration of several neighboring genes. Most often the alteration is a deletion of a few neighboring genes, frequently termed a “microdeletion” or “submicroscopic deletion” because the defect is usually inapparent on routine chromosome analysis. However, on occasion the problem is a micro-duplication of a portion of the genome.

These alterations, by definition encompassing multiple genes, usually have complex effects – multiple major birth defects, developmental delays – often with a characteristic pattern, recognizable by the observant clinician. In fact, these dysmorphic syndromes were well documented years before their etiology was understood. For instance, Angelo DiGeorge and Robert Shphrintzen published their first papers on what would later come to be known as Chromosome 22q11 Deletion Syndrome (a.k.a. DiGeorge Syndrome, Velo-cardio-facial syndrome, Conotruncal Anomaly Face, Shphrintzen Syndrome, and CATCH 22) in 1968 and 1981, respectively. The microdeletion at this locus was only discovered in 1991, and not until 1997 did researchers have a reasonably detailed understanding of the molecular

anatomy of the 1.5 Mb DNA deletion within 22q11.21-q11.23.

How did this particular genomic regions come to be “discovered” as the site of a microdeletion? One of the relatively unknown but interesting facts about contiguous gene syndromes is the role of individual patients in fostering scientific breakthrough. Because nearly all affected individuals have genomic alterations that are below the threshold of recognition via standard (550 band) chromosome analysis, we usually did not suspect a particular region until a patient was encountered with a gross translocation or other rearrangement that transects a critical region. Once this is recognized, then other patients with seemingly normal chromosomes are re-analyzed, with careful determination of the presence or absence of molecular probes and markers flanking the area that was transected. In this way, specific phenotypes can be linked to aberrations of tightly clustered arrays of contiguous genes.

How can you “look” for a contiguous gene deletion? From a molecular perspective, several options are available, including PCR, Southern blot analysis, and pulsed-field gel electrophoresis. More powerful, however, is the use of *in situ* hybridization, usually incorporating a fluorescent label, to determine whether a specific DNA sequence is present on a particular chromosome. FISH, which stands for Fluorescent In Situ Hybridization, involves the synthesis or isolation of a well-defined segment of DNA, ranging in size from a few dozen nucleotides to an entire chromosome, and is considered a probe, ready to search for an DNA segment identical to itself. Selection of just the right segment, usually within the boundaries of a “critical region”, is of prime importance in searching for a contiguous gene deletion. This

DNA is then conjugated with a fluorochrome, such as fluorescein isothiocyanate or rhodamine. Next, chromosomes are prepared for analysis on a microscope slide, spread out in metaphase, much like a standard chromosome preparation, and the double stranded DNA is induced to denature, to become single-stranded. At this point the probe is applied, like a wash of watercolor over an unfinished painting, and the DNA is allowed to re-hybridize, to anneal. If the probe is able to successfully hybridize with chromosomal DNA, then it will remain in place when the slide goes through, essentially, a “rinse cycle.” Finally, the entire chromosome spread is viewed under a microscope fitted with specially designed light filters that enhance the appearance of the fluorochrome.

In the case of X-linked contiguous gene syndromes, such as X-linked ichthyosis, absence of any fluorescent signal signifies nullisomy, for boys. Autosomal CGS will be detected when only one signal is present, implying halploinsufficiency for those genes. The sensitivity of FISH for microdeletion and microduplication syndromes varies, ranging from 100% to less than 10%. Consequently, it is good to keep in mind that for many of these genetic syndromes diagnosis remains clinical, with FISH studies a useful but variably definitive tool.

How do these DNA rearrangements occur? There seem to be several mechanisms for microdeletion and microduplication, often involving “mistakes” during the recombination of homologous DNA segments during meiosis. An illustrative story is that of Charcot-Marie-Tooth Disease Type 1 A (CMT1A) and Hereditary Neuropathy with liability to Pressure Palsy (HNPP).

Each of these disorders involves abnormalities of peripheral nerve myelin and is transmitted in an autosomal dominant fashion. CMT1A is a slowly progressive demyelinating neuropathy of both sensory and motor nerves with onset between 5 and 25 years of age, manifest as distal muscle weakness with foot drop, pes cavus, and slow nerve conduction velocity. CMT1A results from a tandem duplication of a 1.5-Mb region of DNA on chromosome 17p12. HNPP is caused by a deletion of the same region and presents as repeated pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop. The gene for peripheral myelin protein 22 (PMP-22) at this locus is flanked by two identical stretches of DNA. These flanking sections, termed CMT1A-REP, seem to have arisen during recent evolution – humans and chimpanzees have them, but gorillas do not! In any case, they seem to confuse certain gametes.

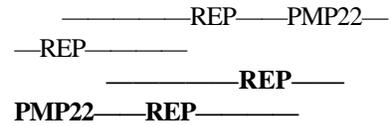
During meiosis, homologous chromosomes (i.e., the chromosome 17 inherited from mom and the chromosome 17 inherited from dad) pair up, in preparation for going their separate ways to make an egg or a sperm. While they are paired up, crossing over occurs, homologous chromosomes break and rejoin, trading entire segments wholesale – twice on average for every pair of homologs. If they are aligned precisely, the crossing over is equal. In the case of CMT1A and HNPP, however, there is misalignment and, if crossing over occurs exactly at the point of misalignment, the wholesale trade is unequal. One homolog is left without a segment of DNA, and the other homolog gets extra.

Normal Alignment:



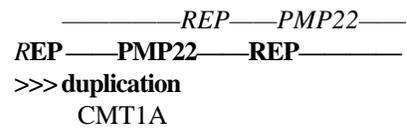
_____REP_____

Abnormal Alignment

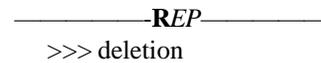


h

If crossing over occurshere, then the products of meiosis are



and



HNPP

Similar molecular mechanisms are either suspected or confirmed for the several dozen known microduplication and microdeletion contiguous gene syndromes. Table 1 summarizes some of the better-known CGS for which FISH testing is readily available.

The availability of a test, however, does not always guarantee appropriate usage. Some clinicians appropriately worry about the high cost of high technology. FISH for most CGS will be billed, fee-for-service, in a moderate range, on the order of one to several hundred dollars. Also, chromosome analysis/karyotyping is usually ordered at the same time, to exclude other rearrangements that could have an impact on genetic counseling or alter the clinical diagnosis. Consequently, the financial downside to testing for a brilliant (but tentative) diagnosis can run close to a thousand dollars, and this prospect can scare off even

the most careful clinician who has a good hunch. The humanitarian and clinical upside, though, is enticing. The benefits of accurate diagnosis are considerable – supportive counseling, accurate recurrence risks, honest prognostic guidelines, timely intervention to avert future complications, as well as the satisfaction of knowing truth.



Childhood acute lymphocytic leukemia

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(This is Part 2 of Childhood Acute Lymphocytic Leukemia . Part 1 can be found in the August 2001 issue of Pediatric News.)

Treatment

There is no standard ALL treatment as different protocols exist for the treatment of low and high-risk precursor B cell, B cell, T cell and infant leukemia. This risk-adjusted treatment is of critical importance as tailored chemotherapy can now overcome many of the poor prognostic features described in the past. The specific chemotherapy used and duration of therapy will vary depending on the age and sex of the patient and the biologic subtype of ALL they have, but all protocols approach treatment in a similar fashion.

I will discuss the treatment of precursor B cell ALL in details as this accounts for the vast majority of

patients we treat. Initially, patients are placed in standard risk (SR) and high risk (HR) treatment groups based on National Cancer Institute (NCI) risk group criteria. Standard risk patients are between 1 and 9.99 years and have WBC of less than 50,000. All other patients are high risk. The first month of therapy is called induction and the goal is to reduce tumor burden by >99% with the bone marrow having less than 5% blasts after 1 month of chemotherapy. SR patients receive 3 drugs, Vincristine, Prednisone and L-Asparaginase (VPL) and Intrathecal chemotherapy with Methotrexate. HR patients receive the same drugs with the addition of an anthracycline. Greater than 95% of patients are in remission at the end of induction. Patients who fail to go into remission after 1 month of therapy have a very poor prognosis. Maintaining remission and preventing disease in sanctuary sites is the purpose of consolidation therapy for the next two months. Intrathecal chemotherapy and chemotherapy that crosses the blood-brain barrier are given to reduce the risk of CNS recurrence. Consolidation is followed by interim maintenance and delayed intensification. During this period, rotations of chemotherapy agents with different mechanisms of action and non-overlapping toxicities are given to prevent the emergence of resistant leukemic clones and lower the risk of relapse. Delayed intensification has been shown to reduce the risk of relapse and improve relapse free survival. This is followed by maintenance, which consists of pulses of antimetabolites, such as methotrexate, vincristine and bursts of prednisone, in conjunction with daily mercaptopurine to form the backbone of maintenance therapy. Girls receive 2 years of maintenance and boys receive 3 years of maintenance. With individualized therapy for the sexes, there is no difference in the outcome between girls and boys. To further

complicate matters, we are now dividing patients in 4 groups:

1. Low risk
2. Standard Risk (SR)
3. High Risk (HR)
4. Very High Risk

The majority of patients continue to be SR or HR patients. Low risk patients are otherwise SR patients who must have the presence of favorable cytogenetic markers, such as Trisomies 4 & 10. They receive less intensive therapy than SR patients and have an excellent prognosis (>92% relapse free survival). On the other end of the spectrum, very high risk patients are SR or HR patients whose cytogenetics have one of the high risk chromosomal translocation, such as the Philadelphia chromosome, the t(9.22) translocation. These patients receive very intensive therapy, which often includes Bone Marrow Transplant (BMT).

High-risk patients are more likely to relapse during treatment than standard-risk patients, who have a 90% chance of three-year disease-free survival. Children who are younger than 1 year or older than 10 at the time of diagnosis have a poorer prognosis. Patients older than 10 have benefited from more intensive treatment with improved survival, with current patients have long term survival rates of 75% with aggressive treatment. Those younger than 1 have not benefited as much as other children from the therapeutic progress in childhood ALL, most do not achieve long-term survival.

Patients with T cell ALL receive a similar treatment schema as precursor B cell patients. Traditionally, these treatment has been more intense and of a shorter duration. It was also felt that T cell subtype was associated with a worse outcome. Recent studies have suggested that when corrected for age and WBC count at diagnosis, there is no difference in outcome between T cell

and precursor B cell patients. New studies are underway to answer this question. Mature B cell ALL (Burkitt's Leukemia) requires very intense treatment but of a short duration (6 months of treatment). Morbidity and mortality from the chemotherapy are very high but those who successful complete therapy have a good prognosis.

In summary, SR patients will have an 88-90% chance of long-term disease free survival (DFS). Patients with T cell ALL, B cell ALL and precursor B cell ALL with HR features can expect long term DFS of 70-75% with aggressive treatment. However, infants with ALL still have a very poor prognosis with DFS of 30-40%.

Relapse

Although 95% of patients with ALL achieve remission, the long-term survival rate for the disease is still only about 75%. Even with its relatively low mortality rate, ALL accounts for more deaths than all other childhood tumors combined. The primary site of treatment failure is the bone marrow. Reinduction of remission is possible in up to 80% of patients who relapse, but the probability of cure drops dramatically and continues to plummet with each subsequent relapse. Chances are better if the relapse occurs when the child is off therapy, is in maintenance phase, or has been in initial remission for at least 18 months. This is probably because disease that relapses on therapy has developed resistance to chemotherapeutic agents. Bone marrow relapse often follows relapses in sanctuary sites, the CNS or testes. Consequently, painless testicular swelling is a red flag in any boy with ALL. Localized relapses require intensified systemic therapy, as well as craniospinal or bilateral testicular irradiation.

Allogeneic bone marrow transplants (BMT) may be important in management of some patients with ALL. The transplant may be from a human leukocyte antigen-matched related donor, matched-unrelated donor, or mismatched donor; it can also be peripheral blood stem cells from related or unrelated sources or umbilical cord blood. Regardless of its form, significant morbidity and mortality, including graft-versus-host disease, organ damage from chemotherapy, and infection, accompany transplant. Nevertheless, it has a distinct role in ALL: for certain very high-risk groups in first remission, such as patients with Philadelphia-chromosome positive disease, and in second remission when a relapse occurs on therapy. Cure after BMT ranges from 30% to 60%; relapse after BMT portends a dismal outlook, however.

Supportive Care

Improvements in supportive care, especially infectious complications, have greatly decreased mortality during treatment. Fever in a child with ALL is defined as a temperature of 38.5° C on one occasion or 38° C or higher on two occasions. Even if he appears well, the child with these readings requires rapid evaluation and may need empiric broad-spectrum antibiotics pending the results of appropriate cultures. An indwelling central venous catheter places the child at additional risk of rapid overwhelming sepsis. Children with these devices will need antibiotic prophylaxis for invasive or dental procedures.

Patients who develop fevers when their WBC counts are low are hospitalized until they have become afebrile for at least 24 to 48 hours and their cultures are negative. Antibiotics are continued, either at home or in the hospital, until the

neutrophil count is rising. The febrile child with ALL should be considered to be a potential medical emergency. Consequently, the child's pediatrician and doctors at the community hospital emergency department need to be prepared to administer antibiotics rapidly if the tertiary care center is more than an hour away. It is desirable to obtain culture results before beginning antibiotics, but the child must be treated with antibiotics even when this is not possible. Phone consultation with the pediatric hematology/oncology service is always available. Even low-grade temperatures should be addressed promptly.

Infections that are problematic for patients with ALL include varicella, pneumonia, bacterial sepsis, and fungal infections. Most patients develop some infections, but these should not be life threatening with early recognition and therapy.

Fifteen years ago, varicella and *Pneumocystis carinii* pneumonia (PCP) were the two most common causes of remission death in ALL, because of impaired lymphocyte function related to treatment. Varicella claimed the lives of 7% of ALL patients from visceral complications-pneumonia, encephalitis, and hepatitis. Varicella and PCP now are usually preventable and can be treated when they occur. ALL patients at risk of developing varicella, those who not had the disease or been vaccinated, should receive VZIG within 72 hours of exposure and IV acyclovir started if varicella develops.

Incidence of PCP infection has been drastically reduced with use of trimethoprim-sulfamethoxazole prophylaxis. The agent is given to all patients with ALL three days a week at a dose of 5-10 mg/kg/day divided in two doses. Some patients have hematologic side effects: decreased

WBC or platelet counts. A monthly IV or aerosolized pentamidine can prevent the infection in patients unable to tolerate trimethoprim-sulfamethoxazole. Clinical signs and symptoms of *P carinii* pneumonia are often subtle. Tachypnea and cyanosis may be present with few or no lung findings; rales, rhonchi, and wheezing are rarely heard. Take a pulse oximetry reading if you suspect pneumonia-mild hypoxia may be the first clinical manifestation of infection. The chest X-ray may be normal or show bilateral infiltrates. Treatment with trimethoprim-sulfamethoxazole needs to be instituted promptly at a dose of 20 mg/kg/d divided for administration every six hours.

Immunizations for siblings

In general, there is no reason to avoid use of live viral vaccines-with the exception of polio-in siblings of patients with ALL. Healthy siblings of patients with ALL who have not had varicella should be vaccinated. No particular precautions are necessary, but if the vaccinated sibling develops a rash, he should avoid contact with the child with ALL until the rash is gone. Inactivated poliovirus vaccine should be used in all members of the family. Since the influenza vaccine is inactivated, I recommend yearly immunization for the family of the patient with ALL. Children with ALL are not routinely immunized for influenza because many of them don't make antibody.

Late effects of treatment

As more has been learned about the long-term sequelae of cancer treatment, the more-is-better approach to therapy favored through the 1970s and 1980s has given way to treatment governed by risk-benefit analysis.

The best-studied effects are on

cognition and neuropsychologic function. Many studies have shown that cranial irradiation for preventing CNS leukemia causes learning disabilities and impairs IQ, especially in children younger than 5 and when given in conjunction with intrathecal therapy. Recognition of the problem has led both to reduced cranial radiation doses and to earlier neuropsychologic testing.

Effects on growth are also pronounced in young children treated for ALL. Though most will catch up, additive effects of high-dose steroid therapy can cause muscle wasting and avascular necrosis of bone. Neuroendocrine effects also occur and may result in obesity and gonadal dysfunction. Alkylating agents such as cyclophosphamide may affect puberty and gonadal function if given in high doses, especially during puberty and in girls. Anthracyclines such as doxorubicin and daunomycin may cause cardiotoxicity. Even children who have received low total doses of these agents at very young ages have developed cardiomyopathy. For unknown reasons, the incidence is higher in girls than in boys. Because of this risk, children treated with anthracyclines are cautioned not to consume alcohol as adults, as this may increase the likelihood of cardiotoxicity. Such advice is better received by younger children than by adolescents and needs to be reinforced during high school and college. Similarly, the dangers of cigarette smoking are even greater for children who have been treated for ALL than for other youngsters. Pediatricians should discuss these issues often in their ongoing care of patients treated for ALL.

Some of the therapies used to treat malignancy may themselves be oncogenic. For example, irradiation to the brain may be followed 10 to 20 years later by a malignant glioma, though the chance is small. Second

leukemias, virtually always acute myeloid leukemia (AML), may develop in patients who have been treated with alkylating agents and epipodophyllotoxins, such as etoposide. The epipodophyllotoxins work by inhibiting DNA repair, and alkylators cause DNA damage. The risk of secondary AML begins early-two to 10 years after chemotherapy-and then appears to decrease markedly. Treatment protocols have been redesigned to lessen patients' exposure to these agents.

Fortunately, most of the drugs used to treat ALL are not associated with second malignancies.

Other late effects worth monitoring include infertility, caused by alkylator therapy; hemorrhagic cystitis or bladder dysfunction following cyclophosphamide; delayed recovery of normal immune function, which occasionally requires readministration of primary vaccinations; and psychosocial effects of chronic illness on survivors and their families. Recent studies have demonstrated that the offspring of patients treated for leukemia do not appear to have an increased risk of cancer or of congenital anomalies.

Clearly the late effect of most concern is relapse. Parents often ask when they can consider their child definitely cured of ALL. In general, the answer to this question is a qualified "never." Most relapses occur within the first few years of beginning therapy: The risk of relapse decreases rapidly after the first year of treatment and becomes negligible at five and one-half years from diagnosis.

A child who has completed chemotherapy for ALL generally visits the clinic every month for the first year. Visits drop to every three months the second year, every six the third, and yearly thereafter into

adulthood. Each visit includes a careful physical exam and a review of the peripheral blood smear. In between, the pediatrician should handle sick visits and other health-maintenance concerns. The family should be strongly encouraged to continue to see the pediatric oncologist.

Future directions

Although major advances in the treatment of children with leukemia have fostered optimism among pediatric oncologists, work remains to be done. Current research efforts are directed at children who have a particularly high risk of relapse. Risk-directed treatment, stratified by high-risk features at diagnosis and by early response to chemotherapy, is limited by acute and long-term drug toxicity. Alternative sources for hematopoietic stem cell transplants from the marrow or peripheral blood will potentially make transplant an option for more than just the one-third of patients who have matched sibling donors.

The focus also is shifting to the biology of ALL. Biotherapy and immunomodulatory techniques, including the use of biologic response modifiers such as interleukin-2, monoclonal antibody therapy, retinoids, and inducers of apoptosis, are making the transition from the laboratory to the clinical armamentarium of oncologists at major treatment centers.

Another approach to lowering the risk of relapse is to lessen the development of drug resistance by leukemic clones. Early identification of poor response to chemotherapy and efficient detection of minimal residual disease will allow rapid modifications in therapy that may prevent full-blown relapse. Another avenue is to determine individual sensitivity to particular drugs, which could help minimize unnecessary toxicity. Finally, besides searching for new agents that are effective against cancer, investigators are studying techniques such as gene therapy to increase tumor-cell sensitivity to today's chemotherapeutic agents while decreasing

systemic toxicity.

Because of current multidisciplinary treatment approaches to ALL, cure rates have skyrocketed over the last three decades. We hope to continue that improvement so that all children with ALL will grow up to lead happy, healthy lives.

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the public schools.

I accept all consults whether they are done electronically or written on a paper towel. If you need me to see a patient sooner than what I have available, I would be happy to accommodate. I appreciate all the support and referrals over the years and want to continue to provide a good service. Unfortunately, with all the consults I have, therapy is not something that I provide. At present Wilford Hall has six speech pathologist and offer a limited number of therapy slots.

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