CE CONTINUING EDUCATION

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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. To become aware of the morbid condition requirements for newborn screening (NBS).
2. To become familiar with the different methodologies used to screen for genetic disorders, particularly tandem mass spectrometry.
3. To know the limitations of NBS testing.
4. To learn what factors can cause false-positive alerts for amino acids on NBS.
5. To become aware of the commonly measured acylcarnitines and their associated disorders.
6. To be aware of the pitfalls in the interpretation of acylcarnitine profiles by NBS labs when evaluating fatty-acid metabolism disorders.
7. To learn that interlaboratory comparison of results for acylcarnitine analysis is severely limited.
8. To learn what needs to be done to optimize cutoff levels for various analytes for identifying patients that warrant further investigation.
9. To gain an understanding of the short and long term cost involved in false-positive NBS results.

CONTINUING EDUCATION

Potential and pitfalls of NBS, and the reference lab’s role

By Dennis William Bartholomew, MD

Among the most notable advancements in public health in the 21st century has been the expansion of newborn screening (NBS) for the early detection and treatment of heritable disorders. Breakthroughs in technology, particularly the use of tandem mass spectrometry (MS/MS), have allowed for the development of fast and inexpensive protocols to quantify amino, organic, and fatty-acid metabolites as markers for inborn errors of metabolism on a scale amenable to population screening. Individually, most of these disorders are quite rare, but taken together, they represent a significant proportion of the identifiable genetic conditions with a strong potential for mental retardation, morbidity, and mortality.

There is no existing federal mandate regarding state obligations for newborn screening. An up-to-date summary of the current policy for individual states, including diseases screened for and financing strategies, can be found at http://genes-r-us.uthscsa.edu.

A formal set of recommendations to Congress for a universal core and supplemental panel of disorders to be screened for by all states was made by the Health Resources and Services Administration and the NBS Committee of the American College of Medical Genetics in 2005, though compliance is currently voluntary. In Ohio, an effective screening strategy has been implemented for all but one of the targeted conditions.

To be suitable for newborn screening, a disorder should meet the minimal criteria as outlined in Table 1. Paramount in this discussion is the understanding that NBS is not meant to be diagnostic in itself. For some disorders, repeating the NBS test following an “alert” is inappropriate and potentially misleading, and urgent consultation with the state or regional metabolic-disease consultant is strongly recommended to determine the most efficient approach to evaluate a suspected disorder. It is the role of the reference laboratory to provide confirmatory testing or recommendations for more specialized testing procedures. A detailed understanding of the potential and the pitfalls of follow-up testing is critical to the rapid resolution of NBS “alerts.”

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MS/MS usefully innovative

NBS laboratories utilize a variety of technologies to screen for genetics disorders, though all rely on the filter-paper blood spot as the biological source for analytic testing. High-performance liquid chromatography (HPLC) and isoelectric focusing are the principal methodologies for identifying sickle-cell disease and other hemoglobinopathies. Direct analysis of enzyme activity is used in testing for galactosemia (galactose-1-phosphate uridyltransferase deficiency) and biotinidase deficiency. Immunofluorimetric techniques are commonly employed in screening for congenital hypothyroidism (TSH) and 21-hydroxylase deficiency (17-hydroxyprogesterone), as well as cystic fibrosis (immunoreactive trypsinogen, or IRT). Targeted DNA-mutation testing has been proven useful as an adjunct to IRT in identifying newborns most at risk for cystic fibrosis. The commercial use of tandem mass spectrometry, however, has been the single most useful innovation introduced for NBS in the last 10 years, largely as a consequence of its ability to simultaneously assay a large number of critical analytes as markers for rare metabolic disorders in an extremely rapid, reproducible, and inexpensive fashion.

The overall process is a highly specific way for detecting specific substances in complex mixtures. It can be coupled to an HPLC system, which acts as an autosampler and can provide the ability to separate compounds with the same nominal masses using a column. The combined system is called LC-MS/MS. Column-separation techniques involve significantly more processing time per sample, and are of limited clinical utility in an NBS laboratory that may be analyzing 500 or more samples per day. To save time and expense — and to be practical for large-scale screening — NBS blood-spot-sample derivatized eluents are injected directly into the tandem mass spectrometer.

In the analysis, the metabolites are typically extracted from the dried blood sample on the filter-paper disc or from 3.1 µl of serum or plasma, chemically derivatized, and subjected to analysis by electrospray tandem mass spectrometry. The function of a tandem mass spectrometer is to:

1. produce ions from the compounds in the sample under analysis;
2. select PRECURSOR (PARENT) ions according to their mass in the first analyzer of the instrument;
3. fragment the mass-selected PRECURSOR (PARENT) ions by colliding them with argon gas in the collision cell to give PRODUCT (DAUGHTER) ions — a process called COLLISION-INDUCED DISSOCIATION (CID); and
4. analyze the PRODUCT (DAUGHTER) ions according to their mass in the second analyzer of the tandem instrument.

MS/MS’ limited effectiveness in certain areas

In the NBS setting, MS/MS is employed to screen for disorders of amino, organic, and fatty-acid metabolism, as well as several urea-cycle abnormalities. It is equally important to emphasize what it cannot do. MS/MS has proven to be ineffective in reliably identifying deficiencies in the urea-cycle enzymes ornithine transcarbamylase (OTC) and carbamyl phosphate synthetase (CPS1) through the quantitation of citrulline, though is considerably more useful when detecting elevations in this analyte in newborns with a deficiency in argininosuccinic acid synthetase (ASAS) or argininosuccinic acid lyase (ASAL). Glycine has not been shown to be so consistently elevated at 24 hours of age as to make this useful in screening for nonketotic hyperglycemia, or NKH. Preliminary clinical research studies suggest that quantitation of tyrosine in the first two days of life is extremely unreliable in ascertaining infants with tyrosinemia type 1 (fumarylacetoacetase deficiency). It is incumbent upon physicians to know the limitations of NBS testing, and not to blindly assume that a normal comprehensive profile effectively excludes an inborn error of metabolism.

Amino acids quantitated at 24 hours of age for NBS using MS/MS typically include citrulline, arginine, leucine/iso-leucine, valine, methionine, tyrosine, and phenylalanine. Cutoffs to establish “alert” notifications vary between laboratories, and are commonly set between three and six standard deviations (SDs) above the newborn population mean. Since tandem mass spectrometers separate and quantify compounds of interest based on their molecular weight (or more precisely, their mass/charge ratio), amino acids with identical weights cannot be separated using MS/MS alone. Leucine, isoleucine, alloisoleucine, and hydroxyproline all have molecular weights of about 131 and are quantitated together for this reason. Therefore, follow-up testing by the reference lab requires the use of ion-exchange column chromatography rather than MS/MS when maple-syrup urine disease is suspected. Further, an amino-acid elevation that seems relatively trivial at 24 hours may be markedly abnormal by three days of age, as the protective influence of materno-placental circulation is no longer present. For example, the state of Ohio NBS protocol sets an alert level of 120 µM (about 2 mg%) for phenylalanine at 24 hours. Levels in classically affected patients are invariably normal at birth but typically exceed 1,200 µM within several days. Accurate quantitation of phenylalanine and tyrosine using an amino-acid analyzer is preferable to repeating the NBS test.
Complicating factors resulting in false-positive alerts for amino acids on NBS include the early use of total parenteral nutrition, hepatic immaturity, sepsis, and other neonatal disorders. For most NBS laboratories, a typical ratio of false-to-true-positive results ranges between 10 to 1, to 20 to 1. Some analytes, especially methionine and arginine have a significantly higher incidence of false-positivity. It is important to emphasize the limited clinical utility of methionine as a marker for homocystinuria. Pyridoxine-responsive cystathionine beta-synthase deficiency, and most homocysteine remethylation disorders are unlikely to result in significant elevations in methionine in otherwise healthy term infants at one day of age, while prematurity and hepatic dysfunction are notorious for false-positive alerts. A serum amino-acid profile and total reduced homocysteine assay should be used to clarify any abnormal methionine NBS results.

Patterns of elevated levels of particular analytes

The detection of potential organic and fatty-acid metabolism disorders is contingent upon MS/MS analysis of acylcarnitine derivatives. L-carnitine is intrinsically involved in the transport of long-chain fatty acids (C16 and C18) across the mitochondrial membrane following esterification of the lipid moiety to carnitine. Carnitine, however, is also esterified to a wide variety of shorter chain and unsaturated fatty acids as well as organic acids, and these can easily be measured in the blood. Elevations in particular acylcarnitine species suggest abnormal accumulation of the organic or lipid precursor due to an interruption in the normal degradative pathway for that compound. For example, newborns affected with medium-chain acyl-CoA dehydrogenase deficiency (MCAD), one of the commonest inborn errors of metabolism, will show a marked increase in octanoylcarnitine (C8) by 24 hours of age. This reflects the interruption in the mitochondrial lipid beta-oxidation pathway for medium-chain-length fatty acids.

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The elevation of different acylcarnitine species in other disease states is the basis for employing this technique as an effective screening tool for NBS programs. Table 2 summarizes commonly measured acylcarnitines and their associated disorders. It is clearly apparent that elevated levels of a particular analyte may indicate risk for more than one condition, and that several disorders are associated with a pattern of elevated acylcarnitines. Recognition of this change from the standard “one-marker, one-disease” model represents a paradigm shift in risk assessment with the use of MS/MS as a screening technology, and emphasizes both its power and limitations for NBS. Further evaluation of an abnormal acylcarnitine result in this setting will almost invariably require additional diagnostic testing such as amino- and organic-acid analysis, enzyme activity assay, or DNA-mutation detection by a reference laboratory.

Pitfalls abound in the interpretation of acylcarnitine profiles by NBS laboratories. The identification of elevated acylcarnitine species suggestive of fatty-acid oxidation disorders is of particular concern. In the immediate post-partum state, a neonate will mobilize lipid stores as an energy source until adequate carbohydrate and protein intake is established. During this brief period, abnormal acylcarnitines are consistently elevated in affected infants, and NBS samples acquired at one day of age are highly likely to be informative. Such elevations, however, will gradually decrease in unstrained and well-fed affected infants, and may appear to be within the normal range within a week. The reference range or cutoff for acylcarnitine “alerts” in an NBS laboratory is likely to be different than that of a reference lab, since the normative data to establish the mean and SD in the former is typically derived almost exclusively from samples obtained in the first two days of life. Therefore, repeating the newborn screening test for an initially elevated C14:1 (monounsaturated 14-carbon fatty acid associated with VLCAD deficiency) at seven days of age is inappropriate, since a “normal” result on the repeat screen may mislead a clinician into believing the initial test was a false-positive. Consultation with a metabolic-disease center will be necessary to determine if more detailed fatty-acid oxidation studies are indicated. A similar pattern can be seen with patients at risk for LCHAD, CPT II, or carnitine translocase deficiency. On the other hand, consistent elevation in butyrylcarnitine (C4) is a marker for short-chain acyl-CoA dehydrogenase (SCAD) deficiency, though most of these elevations, while real, are associated with polymorphic changes in the ACADS gene and are of little clinical significance.

The establishment of a uniform methodology for acylcarnitine analysis by MS/MS remains a long-sought but elusive goal for state and private laboratories. Differences in extraction methods, derivatization of samples, availability of radio-labelled standards, and determination of acceptable alert levels has severely limited the potential for interlaboratory comparison of results. Each laboratory must establish its own normative values from internally generated population data, and adjust mean values and SDs for individual analytes on a continuous basis to optimize cutoff levels for identifying patients that warrant further investigation.

High costs of false-positive NBS results

Screening for rare metabolic disorders entails significant cost on several levels. The establishment of cutoff levels, values above which prompt recommendation for urgent follow-up testing are largely arbitrary, and reflect the conflicting necessity of limiting the number of false-positive results while ascertaining that no true-positives evade identification. For some analytes, such as octanoylcarnitine, the lowest level ever associated with true MCAD deficiency is sufficiently elevated above the unaffected population mean as to allow for a cutoff that results in fewer than half of “alert” samples being false-positive. On the other hand, glutarylcarbnitine (C5DC) is much less sensitive, and affected patients may have values within three SDs of the population mean. Any attempt to completely eliminate the possibility of missing a true case of glutaric aciduria type 1 may come at the cost of establishing a cutoff so close to the mean as to result in an unacceptably high number of alerts.

There is no existing federal mandate regarding state obligations for newborn screening.

False-positive NBS results are annoying for clinicians, frightening to families, and financially burdensome to the healthcare system. Every alert for an elevated phenylalanine that prompts a serum amino-acid profile will cost a family or insurance payer about $120. In Ohio, about 200 alerts for phenylalanine per year are called, and about eight to 10 true phenylketonuria, or PKU, cases are ascertained. This results in a minimum initial cost of $24,000, and excludes clinic visits, biopterin testing, and ongoing care of the few affected patients. An elevated propionylcarnitine (C3) often necessitates an immediate patient evaluation, a repeat acylcarnitine analysis, and urine organic-acid assay. The total cost of this initial assessment may exceed $600. In early 2007, over 160 abnormal results indicating high risk for cystic fibrosis were
In summary, the scientific potential for long-term financial encumbrance that states of clinical utility, presents both a short- and assay added to the NBS panel, regardless addition to the supplemental panel. Every taken, and likely represent the next major storage diseases have already been under- 
up care. Clinical trials of NBS protocols to identify infants with treatable lysosomal- 
ility, presents both a short- and long-term financial encumbrance that states and hospitals must be prepared to meet.

Identification of heritable disorders
In summary, the scientific potential for expanded automated newborn screening is vast. Innovations in analyte detection and microsample analysis will continue to offer options for identifying risk for many disorders outside the traditional realm of inborn errors of metabolism. Our experience with the first major technical advance, tandem mass spectrometry, has educated us on many of the perils as well as benefits of its clinical application. Reference laboratories will continue to play a major role in the early identification of heritable disorders among infants classi- 
ished at risk by this emerging technology. As we push forward into the next stage of newborn screening, the questions — more philosophical than technical — to be answered are these: How much do we really want to know, and how much can we afford to know? 1

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Pain reduction during infant and pediatric phlebotomy

By Dennis J. Ernst, MT(ASCP)

Throughout human history, pain and its alleviation have been at the heart of healthcare. The cruel irony is that some- 
times we have to inflict a little pain to prevent an appreciable amount of pain. Such is the case with phlebotomy. When performed on infants, the pain not only affects the patient but also can be distressing to the collector and parents. It is no small wonder then that pain during infant phlebotomy has been so intensely researched and has led to the development of myriad prac- 
tices, therapies, and devices to minimize it.

Sensitized to pain?
Researchers at the Hospital for Sick Children in Toronto, Ontario, wanted to see if babies subjected to repeat heelsticks would learn to anticipate pain. To measure infant pain, they graded the intensity of grimacing and crying as pain indicators.1 Babies of diabetic mothers — who were subjected to repeat heelsticks in the first 24 to 36 hours of life because of their mothers’ condition — were used as the study group. The control group was comprised of babies from non-diabetic mothers (i.e., those not sub- jected to repeat heelsticks). When venipunc- 
tures were later performed on both groups, the babies who were subjected to repeat

heelsticks demonstrated lower pain scores. The researchers concluded babies learn to anticipate pain. Other researchers have come to similar conclusions.2

But forget venipunctures for a moment. Two studies attempted to determine what happens to an infant’s pain response when the number of heel- 
sticks to which he is subjected increases. Does he become sensitized to heelsticks or not? While one study showed infant pain increases proportion- 
ately with the number of heelsticks performed (as measured by heart rate and behavioral respons- 
es), the other study concluded the frequency of heelsticks may actually lower pain scores.3,4

Oral analgesics
One of the most intensely researched areas of infant pain reduction during phlebotomy has focused on the analgesic effects of pacifiers, oral solutions, and breastfeeding. Several stud- 
ies prove the use of pacifiers during heelsticks and venipunctures on term and preterm infants reduces pain responses.5 While pacifiers may be helpful, dozens of studies have measured the benefits of various concentrations of sugar solu- 
sions given orally in reducing pain during blood sampling.5,7,10 Research conclusively deter- 
mined that glucose, sucrose, and dextrose solu-
tions administered before or during heelsticks and venipunctures significantly reduce pain scores on term and preterm infants. With the exception of one of the studies,7 the effect of the solutions does not seem to be a function of the type of sugar solution or its concentration, but was found to be universal when adminis- 
tered just minutes before the procedure.

Several studies herald the benefits of breast- 
feeding during heelsticks and venipunctures as an effective means of reducing infant pain.5,10,11 In one of them,11 researchers studied the reac- 
tions of 180 infants during venipunctures per- 
formed by experienced nurses to the dorsal aspect of the infants’ hands. One group was breast fed, one group was held in their mothers’ arms without being fed, one group was given sterile water as a placebo, and a fourth group was given 30% glucose followed by a pacifier. Behaviors associated with pain were measured according to two acute-pain rating scales. The breast-fed group and those bottle-fed with glu- 
cose showed a significant reduction in pain-re- 
lated responses over the other groups.

The nose knows
Is it possible that aromatherapy has benefits?

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Bibliography
when it comes to reducing pain in infants? Researchers at the Gettysburg College in Gettysburg, PA, think so. They exposed healthy preterm newborns to odors while subjecting them to heelsticks and venipunctures. One-third of the infants were exposed to an odor with which they had been familiarized prior to the draw; one-third were presented with an odor with which they had not been familiarized; and one-third were not exposed to an odor at all. Their response to pain as indicated by crying and grimacing was observed. Those exposed to an unfamiliar odor or no odor at all demonstrated significant increases in their pain responses than those exposed to a familiar odor. The researchers stated the results reinforced prior evidence of early memory and olfactory competence in newborns and fetuses.

Topical anesthetics

Topical anesthetics have long been used to manage minor pain. But are they effective in reducing venipuncture pain? Studies show they might be effective — and they might not be.

One of the commonly known pharmaceutical interventions to the pain of venipuncture is a mixture of lidocaine and prilocaine, often marketed under the brand name EMLA (Abrasalis Pharmaceuticals). Other topical anesthetics include L.M.X4 (4% lidocaine) (Ferndale Labs), and Ametop (Smith & Nephew Healthcare).

Researchers have found that topical anesthetics such as EMLA are as effective as other forms of topical anesthesia in children (e.g., iontophoresis or 4% amethocaine cream), but phlebotomists may be inconvenienced by the 60-minute waiting period required for EMLA to take effect and the complications that can occur when the venipuncture site is selected by someone other than the person performing the procedure. (Because EMLA is a prescription medication, it is usually administered by a nurse, physician, or parent who may not choose the same venipuncture site as would the phlebotomist.) Some researchers found EMLA to be effective for pediatric and adult venipunctures. Others found it to be no more effective in minimizing the pain of venipunctures and heelsticks on infants than a placebo. According to the manufacturer, EMLA is less effective on children under seven years of age than on older children and adults. EMLA is less effective on children under seven years of age than on older children and adults.21

One intriguing study showed EMLA to be effective, however, when inserting 20-gauge needles into the back of the hands of newborns. No explanation was given for the use of 20-gauge needles as opposed to the significantly smaller 23-gauge needles, which are more likely to be used for newborn venipunctures.

Ferndale Laboratories offers a non-prescription EMLA competitor: L.M.X4 (formerly ELA-Max), claiming activation within 15 to 30 minutes. Studies have shown no difference in effectiveness between the two; some report faster onset with L.M.X4. Due to additional side effects of both lidocaine products, however, researchers suggest more studies are necessary to determine their safety and effectiveness. Others suggest the absence of prilocaine in L.M.X4, which rarely causes methemoglobinemia, gives it the edge for neonatal use.

Researchers in Wales found Ametop gel (4% amethocaine) to be more effective than EMLA in minimizing venipuncture pain in pediatrics between one and 15 years old. Another study found Ametop effective in reducing the pain of venipunctures in the newborn but not for heelsticks.

Finally, tetracaine is also being studied as a topical anesthetic during venipuncture. Two journals published independent studies showing a significant reduction in pain in children using a tetracaine patch when venipuncture was performed 30 minutes after its application compared to a placebo patch. If a phlebotomist does not have the luxury of waiting for an anesthetic cream to take effect or if lathering up the patient with an ointment is
difficult, one of the several available spray-on anesthetic products might be considered. Such products instantly numb the surface of the skin, but how do they compare to the alternatives? One study showed that children upon whom a skin-chilling ethyl-chloride spray was used reported less pain than when Ametop gel was used.32 Others found an ethyl-chloride spray significantly reduced the pain of venipuncture, but not as much as intradermal lidocaine.33 In a third study, researchers let children and teens ages three to 18 rate the pain they felt after being administered a spray-on form of either isopropyl alcohol or ethyl alcohol. The differences were insignificant.34

But how do topical anesthetics compare to orally administered sugar solutions? Researchers in Sweden gave a nod to the sweet. When measuring the pain-reducing effects of oral glucose vs. that of EMLA, the sugar solution decreased pain by 42% as opposed to 19% for the topical anesthetic.20 Those infants who were given oral glucose not only demonstrated lower pain responses but also the duration of their crying was significantly lessened. Since crying in newborns is associated with temporary elevations in white-blood-cell counts, administering oral glucose (under nursing supervision) is a practical way to minimize this pre-analytical effect, which can present an erroneous picture to the physician.35

Iontophoresis
A significant decrease in the time it takes anesthetics to become effective against venipuncture pain can be accomplished with electrical stimulation through iontophoresis. When an anesthetic like lidocaine is delivered — not by the application of an ointment, but by a low-voltage electrical current — the result is a faster and deeper topical numbing. Physicians at Atlanta’s Egleston Children’s Hospital, along with researchers at the nearby Emory University School of Medicine, found lidocaine iontophoresis led to a threefold reduction in pain compared with placebo when applied prior to IV catheter placement.36 Products that utilize this technology for needle insertion include Numby Stuff (Iomed, www.iomed.com), Lidosite (B. Braun, www.bbraun.com), and Needle-Buster (Life-Tech, www.life-tech.com). Some iontophoresis devices are not recommended for children under five years of age. It has been reported that younger children do not tolerate the tingling sensation such devices produce on the skin.37 A fourth company, Algofx Pharmaceuticals, markets ALGRX 3268, a needle-free injection system for accelerating lidocaine into the tissue using helium gas and a triggering device.

Many studies have compared pain responses in infants undergoing heelsticks vs. those elicited during venipuncture. The research conclusively shows venipunctures elicit lower pain responses than heelsticks.

Parental involvement and distraction
The role parents play in minimizing pain during infant and pediatric blood sampling is becoming increasingly obvious. Asking the parent how his child reacts to stimuli similar to a venipuncture, such as a pinched finger, can be helpful. Australian researchers concluded that those who make this inquiry are likely to identify pediatrics who will experience the greatest distress during the venipuncture.38 They also speculated that parents might choose to downplay venipuncture pain to their children in advance of the procedure. For a child who responds strongly to sudden sharp pain, this might help to prevent him from making a scene.

Halfway around the world, researchers at the St. James’s University Hospital in Leeds, West Yorkshire, England, found significant reductions in pain and fear when various forms of psychological interventions were implemented during pediatric venipuncture procedures.42 Researchers there reviewed the literature and found that

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pain and fear ratings decrease with age, and that girls over eight years old are more likely than boys to describe needles as "unpleasant" whereas boys prefer "intensely painful." Predictably, parental factors, including parental anxiety, correlated highly with child distress. The authors reported that parents who were taught and encouraged to use distraction and comforting techniques were more satisfied with the care their child received than those who were present but not taught such techniques. Children who were newly diagnosed with a chronic illness reported higher pain and more fear than those who had a long-term chronic illness. Procedural cues (i.e., seeing samples of blood, hearing the needle being inserted, observing medical equipment) seemed to heighten anxiety in pediatric patients. This author concludes that not enough speci men-collection personnel are properly trained to employ psychological interventions on pediatric patients. Proposed solutions include:

- assessing the child's prior experiences.
- Inquire as to the child's past needle experiences and the circumstances surrounding them that might have been traumatic (e.g., the needle sensation, restraint, the tourniquet, bruising, and so forth).
- preparing the pediatric patient. Articulate the actual steps of the procedure to both child and parent(s) prior to performing the venipuncture. Explaining what the child might feel, sense, smell, see, and hear was believed to be a critical component of preparation including an accurate account of what the sensation of needle insertion will be. This author cautions against the use of topical anesthetics, arguing that the mere application of the anesthetic may generate anxiety, serving as an early warning of an imminent venipuncture. The anticipatory effect may outweigh the potential pain relief the pharmaceutical provides.
- involving the parent. Invite the parent to provide support and distraction.
- allowing the patient to participate in the procedure. Depending on the age of the child, engineer the procedure to be a partnership with the child rather than for the procedure to be something to which the child is subjected. Suggested participation could include having the child choose the cleanse site, sit up or lie down, and similar choices.
- giving the child permission to cry. Such approval was seen to result in less stress than if the child was told to "be brave."

This author does not recommend keeping pediatric outpatients in the drawing area for a prolonged time prior to the procedure. The environment exposes the child to related cues that serve as reminders of the imminent procedure, and affords the child time to dwell on prior traumatic needle experiences. A study published in the Journal of Holistic Nursing reviewed what had been reported on the effect of parental involvement on the pain, fear, and distress children experience when undergoing venipuncture procedures.42 The study's conclusion? Parents who demonstrate high coping skills have children who feel less distress, while highly distressed parents lead to children who cope poorly with the procedure. Also reported in this study was that forcing a child to lie flat during a venipuncture procedure was likely to lead to crying, panicking, and struggling. Positioning the child in a secure parental hug (i.e., with close physical contact), however, promoted the child's sense of control and required fewer assistants.

To determine the effectiveness of parental positioning and distraction on pediatric pain, fear, and distress, the researchers observed 43 pediatric patients between the ages of four and 11 undergoing venipuncture or IV insertion. Children in the control group were only provided with parental presence and an explanation of the procedure. Parents of children in the study group were coached on positioning and distracting techniques to employ during the procedure. Children in the latter group were able to choose between one of three distraction techniques: a kaleidoscope, a book with hidden pictures in multiple graphic designs, and a book requiring the child to open flaps to find hidden objects.

Parents in the study group were instructed to engage the child in questions related to the chosen distraction from the moment the tourniquet was applied until the bandage was placed on the puncture site. Researchers concluded that children whose parents used a positioning-distraction strategy showed less fear. Although not statistically significant, those children reported that they felt less pain and were less fearful than did the children of parents who did not employ positioning-distraction techniques. Another study found the use of a kaleidoscope not to be an effective distraction.44

It comes as no surprise to most mothers that television is a better analog than parental distraction. A study reported in the Archives of Diseases in Childhood found that children watching cartoons on television during venipuncture procedures felt less pain than those whose mothers distracted them during the procedure.45 A second study reinforced the anesthetizing nature of television by reporting that passive distraction provided by movies was more effective in reducing pain during pediatric venipunctures than an interactive toy distraction.46

**Touch therapy**

Many holistic therapists already know the power of the human touch. But can physical contact be a tool in reducing pain during infant phlebotomy? Researchers in Thailand tested the effects of four kinds of non-pharmacologic interventions on pain responses in infants undergoing heelsticks.47 The clear winner: swaddling. Holding the child tightly wrapped in a blanket during the procedure was found to be highly effective in minimizing pain scores. Even leg massage has been found to be effective. Researchers at the University of Calgary found that a gentle massage of the leg prior to heelstick in preterm infants was safe, and decreased their pain responses.48 A skin-to-skin positioning of the baby in the mother's arms called "Kangaroo Care" was also found to be effective analgesic for preterm infants undergoing heelsticks.49 When measured against pain responses in infants placed in a warmer without skin contact, the mother's touch proved superior.

With the wide variety of infant and pediatric pain-reduction strategies, laboratories can lessen the cruel irony of healthcare that requires the infliction of pain in order to prevent suffering. Since negative early-childhood experiences with sharps can lead to a lifelong phobia of needles, healthcare professionals who draw from pediatric patients are in a powerful position to prevent unpleasant experiences resulting in your patient's future avoidance of medical procedures that might seriously affect his health. Employing a combination of pain-reduction strategies helps bring infants and young patients into a kinder, gentler healthcare environment.

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**References**


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