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https://reachmd.com/programs/cme/topics-and-controversies-newborn-stem-cell-medicine/7760/

Released: 12/03/2015
Valid until: 12/30/2017
Time needed to complete: 45 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Topics and Controversies in Newborn Stem Cell Medicine

Narrator:
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Dr. Weinthal:
Hello, I'm Joel Weinthal, and we're going to be talking about Topics and Controversies in Newborn Stem Cell Medicine. The history of cord blood transplantation dates back to 1974 when cord blood was identified as a source of stem cells. In 1988, the first successful cord blood transplant was done in a child who had a genetic form of anemia, called Fanconi's anemia. The field rapidly advanced over the next several years with the first sibling cord blood transplant done for a malignancy in 1992, and in 1993 the first unrelated cord blood transplant for a child with acute lymphoblastic leukemia was reported. A great majority of the unrelated transplants in children are now done utilizing unrelated cord blood.

This cartoon shows the basics of cord blood and stem cell medicine. You can see on the slide that the stem cell can differentiate into red blood cells, white blood cells, and platelets. And this stem cell, which is the hematopoietic stem cell, the cell that grows up to form blood cells and immune cells, can come from peripheral blood, bone marrow, or in our subject of interest, umbilical cord blood. And taking that one step further, you can see our stem cell in the middle from cord blood which can grow up, divide, and proliferate, and make the blood system, shown here as red blood cells, white blood cells, and platelets, but also within this stem cell component are stem cells which can differentiate into liver cells, nerve cells, and many other types of cells. These rare stem cells within the cord blood unit are the basis for the growing and exciting new field of Regenerative Medicine which we're going to talk about in just a few minutes.

This cartoon shows the basics of how we do a cord blood stem cell transplant in 2015. The top panel shows a patient in need of a stem cell transplant. The patient undergoes high-dose chemotherapy and/or radiation therapy to wipe out their blood and immune system. A cord blood unit which has been identified as being suitable for that patient is then thawed and delivered to the patient after they've received the high-dose chemotherapy and radiation, and given to them through an IV infusion. The stem cells then migrate to the bone marrow, grow up and divide, and reform an entirely new blood and immune system. Cord blood and hematopoietic stem cell transplants are life-saving procedures for many patients who have no other medical therapy to treat their underlying diseases. Unfortunately, many patients do not have a brother or sister or a histocompatible family donor available to treat their disease.

This slide illustrates that three-quarters or 75% of patients do not have a compatible family donor, so we have to rely on alternative donors to do a transplant. Many patients do not have this compatible family donor and have to rely on registry matches and many patients are unable to identify a suitable match, despite the fact that over 20 million adults have been tissue typed in the National Marrow Donor Program Registry. This has led the way for umbilical cord blood stems cells to become another important source of stem cells for transplantation and life-saving procedures in patients.

Umbilical cord blood stem cells are slightly different than stem cells that come from the bone marrow or peripheral blood. They have pluripotent properties as I illustrated in one of the previous slides. Not only do they have hematopoietic properties but they have

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mesenchymal properties and this is often even more prevalent in cord blood tissue, and we'll talk a little bit about this down the line, as well as neural properties. The cord blood stem cells are readily available since every time a baby is born there is a cord blood unit available potentially. It is estimated that there are over 4 million births annually, so this makes over 4 million potential cord blood donor units available, at least in theory. And cord blood units are a noncontroversial source of stem cells.

They're available with every single delivery or birth that's done throughout the world. The advantages of cord blood stem cells over the traditional bone marrow stem cells are that it is a very simplified collection process; it does not require a surgical harvest; there is reduced time-to-treatment; certain infections are less common since the fetal blood or cord blood has been exposed to virtually nothing while inside the mom; there are less stringent HLA requirements since this is immunologically very immature tissue or cells; there is a lower risk of graft versus host disease, a dreaded complication of doing stem cell transplants; and we have noticed throughout the years that there's increased long-term immune recovery in patients receiving cord blood stem cell units as opposed to other sources of stem cells.

And with all this information and data throughout the many years now, you can see that the number of cord blood stem cell transplants done throughout the world continues to increase and can now be considered a standard of care as opposed to a research or experimental process. The last complete yearly data from the end of 2013 that we have available says that over 30,000 cord blood transplants have been done throughout the world.

One of the questions that's often asked is can this be done in adults since much of the early data was in children, and the answer is yes. This early report from Dr. Laughlin that was published in the New England Journal in 2004 showed outcomes of transplant from either cord blood or bone marrow in adults who had leukemia, and Dr. Laughlin and her colleagues concluded that HLA-mismatched cord blood could be considered an acceptable source of stem cell grafts for adults if they did not have an HLA-matched conventional adult donor.

At the end of 2013 a review was published in the American Society of Hematology Journal, Blood. This was celebrating the 25th anniversary of cord blood transplantation throughout the world and this reviewed the experience in both children and adults over the several decades of cord blood transplantation. And you can see in these cartoons, comparing the results in Europe and North America as well as children and adults that success rates have continued to improve throughout the time period of doing transplantation utilizing cord blood stem cell units. Particularly in children less than 16, both in Europe and North America, success rates are approaching 60% long-term survival in childhood leukemia and myelodysplasia, diseases which would otherwise be fatal.

So, a summary of the umbilical cord blood transplant literature, at this point in 2015, is that utilizing cord blood to do transplants is clinically effective in selected patients. The overall survival is approximately equal to bone marrow transplants and it will add peripheral blood stem cell transplants as well. There is less graft versus host disease, the immunologic complication of transplants utilizing cord blood, and certainly better survival, if you're lucky enough to have a related umbilical cord blood unit. There are limitations to using cord blood. It takes longer to engraft compared to bone marrow or peripheral blood and this is because the units are quite small. Some units are too small for adults and this has led to studies trying to come up with ways to utilize these small cord blood units in larger recipients. This has included using double cords, or 2 cords at once in doing a transplant, and many other different types of stem cell expansion studies which continue to this day. Graft versus host disease, the immunologic complication of doing a transplant, is less than utilizing bone marrow, but still a significant problem that needs to be overcome and requires expertise in dealing with when doing these complicated procedures.

The advantage of utilizing related umbilical cord blood stem cells is quite evident to people that do the transplants since they ar readily available and accessible, there is increased histocompatibility, since within a family the match will be very, very close, there's a known family history, and each unit is genetically unique to a given child and family. There is decreased morbidity and mortality utilizing related umbilical cord blood stem cells and at this point in time related cord blood stem cells are the preferred source for Regenerative Medicine applications. Most of the related stem cells utilized for Regenerative Medical applications to date have been autologous, or someone's own cells.

This cartoon shows 2 different types of collection kits and methods. One can collect cord blood either while the placenta is still in utero, after the baby is delivered, or ex-utero and just simple harvest the cord blood through the umbilical vein after the placenta is delivered. It's a simple procedure requiring anticoagulant and a syringe and needs to be done in a sterile fashion. As stated at the bottom of this slide, the health of the mother is always considered first, since this is the primary important medical need within the delivery room. To collect cord blood stem cells, collection kits have been put together by many different cord blood banks, both private and public banks.

The collection kit protocols and sterility vary somewhat with each bank but, in general, are fairly similar utilizing a needle to catheterize the umbilical vein, anticoagulant, and a collection bag to store the blood in. Some components can be placed on the sterile field and when you enter the Labor and Delivery Room, or the Operating Room, you want to make sure you know where the kit is, and familiarize

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yourself with the specific kit. Cord blood collection methods involve double-clamping close to the baby's body, holding the pitocin, especially if it's a C-section until the cord blood collection is done, collecting the cord blood before the hospital blood, and sometimes some fundal pressure can help in getting as much cord blood as you possibly can so that the unit can be as large as possible for future use.

When you're using a bag collection method, you want to hold the needle still and when the cord is collapsed, you're done collecting. Empty the chamber, safety cap the needle, and tie off the tubing. The cord blood segment is requested; there is usually a cup within the kit, and this segment can be cut and placed in the kit. After the delivery, finish all the packaging and paperwork, hand the kit to whoever is responsible -- often the dad or other relative -- and the kit can be shipped overnight to a storage facility for processing. Most cord blood banks require receiving the specimen, the cord blood unit, within 1 to 2 days after collection; 24 to 36 hours is usually the optimal amount of time. After that, there is concern that the cord blood stem cells, essentially a live organ, will start to deteriorate and the unit will not be as viable for future use.

One of the questions asked is, how long are these cord blood stem cells good after they're collected? Well, there've been several studies published in the literature and Dr. Broxmeyer, one of the pioneers of cord blood stem cell transplant biology, updated a publication several years ago to say that there were units that are viable and engrafting not only after 15 years, but greater than 20 years after collection. So, in theory, a cord blood unit, if stored properly, should last forever and certainly the lifetime of a donor.

Now I'd like to shift gears a little bit and talk about some potential uses of cord blood.

The left side of this diagram shows treatments that are being utilized today. This is my everyday practice as a Pediatric Hematologist/Oncologist and Stem Cell Physician. We utilize cord blood to treat blood cancers, metabolic diseases, immune diseases, and some solid tumors; however, the exciting new field of Regenerative Medicine are the treatments that are being researched and potentially changing the entire field of medicine for many diseases which have had no treatments in the past and no good medications even being researched at this time. Regenerative Medicine uses include: brain injury, hearing loss, congenital heart disease and even autism. I will review some of these in the coming slides, and it is important to understand that these are research protocols at this time, not clinical state of care, as is the case in transplant medicine.

So, this cartoon shows that autologous stem cells can be used for Regenerative Medicine trials and these are nonhematopoietic uses. Some of them include: heart disease and angiogenic trials, diseases of the eye, diabetes, brain/spinal cord injuries, stroke recovery, Parkinson's disease, amyotrophic lateral sclerosis, and muscular dystrophy. All this research and excitement related to the field of Regenerative Medicine led to a statement by the United States Department of Health and Human Services. They define Regenerative Medicine as the next evolution of medical treatments. The revolutionary technology has the potential to develop therapies for previously untreatable diseases and conditions.

Examples of diseases Regenerative Medicine can include: diabetes, heart disease, renal failure, osteoporosis, and spinal cord injuries. I'd like to review a few of these studies briefly. The references are provided and are available and certainly the field is evolving very quickly.

Cord blood stem cells in Regenerative Medicine have included clinical trials in diabetes. Diabetic mouse models have shown that mice transplanted have lower blood and urine glucose levels and significantly longer life spans. A clinical Phase I/II trial has been underway at the University of Florida and full trial results are awaiting full reports, but second and followup trials are now being designed and hopefully we will have some human trial data coming down the road.

Cord blood stem cells have been used in various cardiology trials including valve replacement where cord blood stem cells are seated on biodegradable scaffolds and the cord blood is differentiated into functional valves. Many papers have come out using 3D printing technology using cord blood stem cells and other stem cells in trying to come up with functional valves with longer potential uses, not only for children, but in adults as well. Myocardial infarction trials, where cord blood stem cells have been utilized after a myocardial infarction to try to save cardiac tissue and muscle from the necrotic injury of the infarct, have been done in animal models as well as some human trials. Animal models have thought to be successful secondary to a paracrine or bystander effect by decreasing inflammation and coming up with regulatory effects on the inflammatory and potential damaging effects of the insult in myocardial infarctions. Hopefully this trial data will continue and we'll have more to report on in future lectures. Congenital heart disease has also been studied utilizing cord blood stem cells and other autologous cells in an effort to improve cardiac function in this critical and often fatal disease in young children.

Brain injuries are familiar to everyone taking care of children, particularly neonates. There have been large trials, mainly at Duke University, but in other universities throughout the country in cerebral palsy where pediatric patients have been infused with autologous cord blood. The safety has been well documented and we await efficacy results down the road. Traumatic brain injuries, an often

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devastating problem not only in children and adults, have also been investigated using cord blood to try to ameliorate the effects of these often-debilitating problems, both in children and adults. There is an ongoing trial in Texas at this time, in Houston, utilizing autologous cord blood to treat traumatic brain injury. And finally, hypoxic ischemic encephalopathy, a significant problem in neonates, is now being investigated utilizing cord blood after delivery in children, trying to minimize brain injury and hopefully improving their longterm outcomes.

Studies are also being done in hearing loss in many parts of the world, including in the United States, once again in Houston, evaluating the safety and efficacy of autologous stem cells to treat acquired or congenital hearing loss.

Other trials are ongoing in cartilage defects, utilizing the mesenchymal stem cell component within the cord blood and cord blood tissue, in an effort to repair and treat degenerative joint disease and cartilage injuries.

Regenerative applications also include studying spinal cord injuries. This has been investigated not only in animal models but in human trials where cells have been delivered directly to the spinal cord. Once again, these are clinical trials, not the standard of care in medicine. No serious adverse events have been reported and we await formal clinical trial results and progression to larger clinical trials, with the hope to treat spinal cord injuries and many other diseases which have no other effective therapies.

Other regenerative applications include treating chemically-induced liver damage, ischemic injuries, particularly strokes. Many animal models have been studied and functional improvements were demonstrated in an early Phase I trial in stroke patients receiving autologous mesenchymal stem cells.

This cartoon again shows utilizing mesenchymal stem cells from the cord blood component to treat myocardial infarction. Many trials are going on, not only in the United States, but throughout the world.

Autoimmune diseases, such as multiple sclerosis and many others, have also been investigated throughout past several decades using stem cell transplantation, and more recently, using cord blood stem cells. Animal models for many of these autoimmune diseases exist and the basic theory is to redo the immune system or immune component, hopefully altering the underlying autoimmune disease. Clinical trials are underway in many different autoimmune diseases, including multiple sclerosis which is shown on this slide.

Other areas of investigation include lupus where pilot trials have been done as well as in animal models of this multiorgan difficult autoimmune problem.

And umbilical cord blood, particularly the mesenchymal stem cell component, has been utilized in augmenting recovery from solid-organ transplants as well as hematopoietic stem cell transplants. These cells have been used to assist in overcoming the difficult immune problems in transplant from donors who are not identical immunologically.

Shifting gears to patient counseling.

I believe that OB/GYNs are on the frontline in talking with patients about cord blood collecting and banking. I think it's important for umbilical cord blood collections to be discussed with expectant parents so that families can know about umbilical cord blood and the options they have, both with public and private banks. Once patients understand the procedure, they can make more informed decisions about banking. This includes understanding how the cord blood stem cells are cryopreserved or saved, and also keeping up with current literature and potential indications for cord blood stem cell procedures. We've talked a little bit about Transplant Medicine as well as the exciting new fields of Regenerative Medicine which are emerging in the literature on an almost-daily basis.

I divide patients into high-risk and low-risk families when thinking about banking. High-risk families including families that have significant cancer history or genetic disorders, high-risk ethnic groups where certain diseases are very prevalent, families where there are unknown health histories or mixed ethnic families or surrogate parentage where it's going to be very difficult to obtain a donor in the future. Low-risk families would include families where there are no high-risk factors identified. I think it's important to provide information to families and counsel them, both about private banking, as well as public donation. Obviously, in my role as a Pediatric Transplant Physician, we need public donation so that we have cord blood units to treat our patients; however, both public and private banking are both reasonable options and I think families need to make an informed decision about what they want to do.

Comparing family banking, or private banking, with public banking is shown on this slide. One of the important differences is that in private banking virtually all samples are cryopreserved or saved. When families donate to a public bank, less than half the samples are actually saved because minimum cell counts and volumes are taken into consideration when public funds are used to save cord blood units. When a unit is donated to a bank, if it is donated to a private or family bank, the ownership is with the family that has sent the unit in. In a public bank, once you release the unit to the bank, you no longer have ownership rights to that; it's within the public domain or within the public bank's ownership rights. So, you'll always have access to your own samples if a unit is donated to a private bank, where it is possible you'll have access in a public bank, but could be unlikely if the unit is used by someone else. There are no costs to

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donating to a public bank but there are significant costs to a private bank. The upfront cost is approximately $1500 to $2300 for upfront costs and then with storage fees running about a $100 to $130 per year. Once a unit is donated to a public bank there are no more costs involved for any families whatsoever. To release a unit for use for transplant, there is no cost if you own the unit; it's yours. However, from a public bank when we access a unit there are fees from $25,000 to $30,000 to even $50,000 for us to get our hands on that unit to use in transplantation. I should add that this is significantly less than obtaining bone marrow or stem cells where there are operating room costs and many, many other costs related to the donor procurement of the stem cell unit. However, access for families to donor banking is somewhat limited in the public milieu. There are very few public banks available throughout the United States and world and only select hospitals collect for public banks on a routine basis. Family or private banking is virtually available to everyone who delivers in the United States and throughout the world. All one needs is the kit and the ability to send it to the private bank for cryopreservation. Both options address the potential needs for patients in various clinical situations.

So, how do we help people and families make informed choices for the future? This slide summarizes our current thoughts. We believe that all expectant parents should learn about cord blood banking and families with histories of cancer or genetic disorders may have particular needs for education about cord blood banking. These conversations should begin at least at the 24-week prenatal appointments and the earlier one decides about collecting the better, since last-minute stress can be a major issue, not only about cord blood collecting, but about many things related to delivery and their children. This conversation should be initiated within the obstetrical office and educational material should be available for patients and families. I believe that balanced information on all stem cell banking options should be available, including both public and private banking, and the more educational resources that are available, the better. But this is very important because there is only one opportunity to save cord blood stem cells and that is at delivery. One cannot get at these stem cells at any other time than that exact moment. And, as I've mentioned to you, cord blood can be a life-changing or life-saving gift for a child, a family member, or an anonymous recipient who might access cord blood unit stored throughout the world, and have their life saved or changed by this amazing gift.

Here are two websites which provide excellent information. They are listed here on the slide and they are both available to patients, physicians, and anyone that might be interested. From my last review, there are now 38 public cord blood banks in North America and six of them actually allow for mail-in donations. This takes a little bit of leg work but is possible and, as a provider or health services individual, we can assist our patients in accessing public banks if this is what our patients desire. There are 35 private or family cord blood banks in the United States and many of them offer financial support and aid options to provide assistance so that they can donate cord blood without major financial issues.

With all the excitement and success with cord blood transplant, the Institute of Medicine has recommended patient education, and cord blood legislation has been passed in 27 states representing approximately three-quarters of all pregnancies in the United States. This map of the United States shows areas where cord blood legislation has been enacted, recommending and urging cord blood information be passed on to patients and expectant families so they can make informed decisions.

What factors should be considered when choosing a family bank? Well, my number 1 factor is experience. How many families have donated cord blood to a bank and how many cord blood transplants has the bank facilitated? Saving cord blood and cryopreserving it is a technical procedure which requires significant expertise. It is not just freezing a steak at home in your freezer. So, a bank that has actually facilitated a cord blood transplant, in my mind, has the expertise and has demonstrated the experience in saving cord blood stem cells, having then been thawed and utilized in an actual medical transplant situation. Other factors to consider are illustrated on this slide including what services are offered by the bank, the location of the cell processing and storage facility, to make sure they are in an area that can be easily accessed, and not in a location that might be associated with major disasters or difficulties in getting to the facility or accessing the cord blood units, and finally, financial stability. Unfortunately many cord blood banks have gone into business and then gone out of business and I can't think of anything more devastating for a family than spending money, having cord blood saved, and then having the cord blood bank go bankrupt, and their cord blood unit essentially thrown in the garbage. So, I think it is very important and a real dose of reality to understand how long the cord blood bank has been in business and in operation, and is it likely to be financially stable in the future, if you are trusting them with stem cells for your child or your family?

The American Society of Bone Marrow Transplant came up with a position statement in 2008 about donation of cord blood. It encouraged public donation of umbilical cord blood units. It did not routinely recommend private storage, but did state that family or private banking may be recommended if a newborn has a sibling with a disease treated by hematopoietic stem cell transplantation. Its policy statement also talked about giving accurate information about banking to expectant parents and mentioned the potential for expanded uses of cord blood in the future, and noting that ongoing reviews will be done with potential changes in recommendations. The field of Regenerative Medicine certainly fits that bill and I believe there will be some new position statements coming as clinical data emerges over the next few years.

I'd like to go over a vignette right now which you can review as well with the links that are mentioned. This is a high-risk patient with the

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following characteristics: an ethnic minority of African descent, it utilized donor sperm in a closed-donor situation, there was a same-sex relationship within this patient and neither partner had other children, no other children had been planned from the same sperm donor, and the family was interested in delayed cord blood clamping. This is certainly a high-risk vignette and brings up many things that you may hear about or have to deal with in counseling families and patients who are interested in cord blood banking. I believe that links can be clicked within your presentation to run through the high-risk vignette that we have described.

A second vignette, also accessible through a link that you can access at your leisure, includes an uninformed patient coming to you with a more typical patient, but uninformed about her options in terms of cord blood banking. And you can run that as the second vignette which will illustrate some of the typical questions and suggested answers that you can utilize in your counseling with pregnant patients.

So, to conclude, umbilical cord blood stem cell transplantation has now been a validated procedure over the past 25 years, and the efficacy and safety of cord blood stem cells has been well documented, both in thousands of patients and in the literature. Cord blood stem cells can be easily collected and stored. Long-term cryopreservation has no adverse effects on the stem cells. Cord blood-derived stem cells are clinically useful in a variety of disease states. Banking cells for future therapies has been validated by science, and cord blood stem cells possess significant future potential through studies for expansion, gene therapy, cell-specific therapies, and so much more.

Cord blood-derived hematopoietic stem cells have been shown to be clinically useful in a variety of disease states. There are some advantages and disadvantages of cord blood-derived stem cells compared to bone marrow. I believe that umbilical cord blood remains an underutilized resource. Both family and public umbilical cord blood banks are important and future uses include: cell expansion, amplification of specific cell types for cell therapy, plasticity, specifically sources of stem cell for treatment of a variety of diseases including the topic of Regenerative Medicine which we have discussed, and gene therapy applications which are certainly coming down the road after many years of stopping and starting, but exciting new data being reported in clinical trials throughout the world.

So, I'd like to thank you for your time and hope that you have enjoyed and learned from this presentation. Thank you.

Narrator:
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