Study title:
Intrapleural DNase and Tissue Plasminogen Activator in Pediatric Empyema (DTPA Trial)

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SICK CHILDREN

Research Consent Form (Parent/Legal Guardian)

Title of Research Project:
Intrapleural DNase and Tissue Plasminogen Activator in Pediatric Empyema (DTPA trial)

Principal/Qualified Investigator:

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Purpose of the Research:
Your child has developed pneumonia (a lung infection). The lung is separated from the chest wall by an area known as the pleural cavity. If the lung becomes inflamed from an infection, such as with pneumonia, large amounts of fluid can leak into the pleural cavity and fluid builds up in this space. This fluid can also become infected and can develop into very thick pus, which is called an "empyema". The antibiotics given to treat the pneumonia have a hard time getting into pus. This means that patients remain sicker for a longer time, and need antibiotic treatment for a much longer period.

To prevent this from happening, usual treatment for an empyema is to drain the pus as much as possible by inserting a small plastic drainage tube (a chest tube) between the ribs into the pleural cavity. The pus can become very thick and solid (similar to a blood clot). This can plug up the chest tube, preventing it from draining all the fluid. This is a common problem, and usually a drug which breaks down the pus is injected through the chest tube into the pleural cavity to prevent this from happening. The drug that is used to do this at SickKids and other hospitals is called tissue plasminogen activator (tPA). The main problem with tPA is that it doesn't always work. The chest tube still gets plugged up, delaying how quickly the child gets better.

Adding another drug called Dornase alfa (DNase) might improve the treatment success of tPA. Pus contains dead bacteria and dead white cells (the immune cells the body produces to fight infection). Both bacteria and white cells contain DNA, which is released when they die. The DNA that is freed into the fluid clumps together, adding to the "clotting" of the fluid that plugs up the chest tube. DNase breaks up free DNA. It doesn't get into living cells, and therefore cannot harm them, but simply works on the DNA released by dead cells.

We think that DNase may add to the effectiveness of tPA in treating empyema. There is currently one study in adults which showed that adding DNase to the pleural cavity after tPA led to a better outcome than tPA alone. Patients in this study had a reduced length of hospital stay, decreased need for further surgery, and improved fever, without any known harmful side effects from the addition of the DNase. However, there are no published studies on using DNase and tPA in children with empyema.

This research study is comparing the time to discharge from hospital after chest drain insertion in previously well children who have pleural empyema, treated with DNase and tPA by chest drain for three doses over two days (48 hours) compared with three doses over 48 hours of tPA alone. We will also examine other outcomes related to effectiveness, safety and cost.

Description of the Research:

Standard of care for children with pleural empyema at SickKids includes inserting a chest drain and adding tPA to break down the organized pus. If you agree to participate in this research study, we will insert tPA into your child's chest drain and then we will insert either a placebo (saline fluid that does not contain any medicine) or DNase. Your child will have an equal chance (like the flip of a coin) of receiving either the tPA and placebo or the tPA and DNase. Neither you nor the investigators will know who has been given which dose until the end of the study. Should it become necessary, that information can be obtained.

Right after the chest tube is inserted, the tPA and DNase or tPA and placebo will be inserted into the chest drain by the medical team caring for your child one at a time (first tPA, then either DNase or placebo). The tPA will be given first while your child is in the procedure suite. This will take an extra 15 minutes and then your child will return to the ward. After the tPA is given, the drain is closed (clamped) for one hour to allow the drug to work in the pleural space. The drain will then be opened for one hour. Then, either DNase or placebo will be given in the same way (with the tube clamped for one hour and then drained for one hour). On the following two days (day 2 and day 3), a dose of the study drugs will be administered in the morning, between 9 and 10 am, in a similar fashion. Thus, your child will receive a total of three doses of either tPA and placebo or tPA and DNase over 48 hours. Your child will not receive any other drugs in the pleural cavity during these 3 days. After the 3 days of treatment, your child will receive standard of care for pleural empyema by his/her medical team. This may or may not include more drugs in his/her pleural cavity.

As part of your child's usual care, the amount of chest tube drainage is recorded. For this study, we would like to collect some of this drainage and store it at SickKids for future testing to look at the cause of empyema. The only change to your child's care will be the randomization (like flipping of a coin) to placebo or DNase. All other parts of your child's care will remain the same as if he/she was not in the study, and will be decided by your child's medical team. Your child will receive standard care for this condition including laboratory investigations, imaging, antibiotics, chest drain care and removal as outlined in the standard care guidelines and as directed by your child's medical team.

We would like to include a total of 98 children for this study from SickKids, BC Children's Hospital in Vancouver, McMaster Children's Hospital in Hamilton, Alberta Children's Hospital in Calgary, the Children's Hospital of Eastern Ontario in Ottawa, and St. Justine Hospital in Montreal. Approximately 49 children will receive tPA and placebo and approximately 49 will receive tPA and DNase. We expect approximately 50 children will be enrolled in this study at SickKids.

We will review your child's health record to obtain information on your child's length of stay and treatments during your child's hospitalization. After your child is discharged home, we will call you in three months to see how your child is doing. We expect that this phone call will take less than 5 minutes. After this, your child's participation in the study is complete.

Although tPA is commonly used at SickKids and other hospitals in children with pleural empyema, Health Canada has not approved its use in children. However, Health Canada has reviewed and has approved the use of tPA and DNase for this study.

Pregnant or nursing women are not eligible to participate in this study. If your child is female and able to get pregnant, a urine pregnancy test will be done. The results of the pregnancy test are confidential and a doctor or a nurse will explain the results of the test to your child in private. There can be many reasons why potential research subjects do not qualify for this study, one of which is pregnancy. Privacy laws mandate that the pregnant woman be told in confidence that she is pregnant, and appropriate supportive counseling should be offered at the same time. It is the pregnant woman's choice to reveal the pregnancy to her family and the duty of the physician is to support her in any decision she makes. Therefore reasons why your child cannot participate or, if enrolled, why she can't continue to participate, may only be revealed to you as 'your child's screening reveals she cannot continue with/be part of the study' or 'your child's condition no longer fulfils the criteria for the study'.

Potential Harms:
Side effects of DNase include chest pain, fever, upset stomach, hoarseness, sore throat, shortness of breath, laryngitis, runny nose, decreased lung function, rash, hives, and inflammation of the eye. Side effects to DNase are rare (less than 1 in 1000 people), and are usually mild and temporary. The most common side effect of tPA is bleeding, especially when it is inserted into the bloodstream. In this study the drug will be inserted into the pleural cavity. Therefore, the risk of bleeding due to tPA is low. In an adult RCT examining the effectiveness of tPA and DNase compared to tPA alone for empyema, there was no difference in the occurrence of side effects between the groups that received tPA alone and those that received tPA and DNase.

Potential Discomforts or Inconvenience:
The only anticipated inconvenience will be the time it takes to complete a short questionnaire by telephone, 3 months after your child is discharged. We expect this phone call to take less than 5 minutes.

Potential Benefits:

To individual subjects:
Your child may or may not benefit directly from participating in this study. We can provide the results of the study to you after the study is completed if you are interested.

To society:
This study will ultimately help the care of children hospitalized with pleural empyema by informing medical teams of the best way to treat the condition.

Alternatives to participation:
If you choose for your child to not take part in this study, your child will receive standard treatment as directed by his/her doctor. This will likely include insertion of a chest tube and insertion of tPA into the chest tube.

Confidentiality:
We will respect your privacy. No information about who your child is will be given to anyone or be published without your permission, unless the law requires us to do this. For example, the law

requires us to give information about your child if a child has been abused, if your child has an illness that could spread to others, if you or someone else talks about suicide (killing themselves), or if the court orders us to give them the study papers.

SickKids Clinical Research Monitors, employees of the sponsor or funder, The Applied Health Research Centre (St. Michael's Hospital), Canadian Institutes of Health Research, or the regulator of the study may see your child's health record to check on the study. For example, people from Health Canada Health Products and Food Branch, if necessary, may look at your child's records.

By signing this consent form, you agree to let these people look at your child's records. We will put a copy of this research consent form in your child's patient health records. We will give you a copy for your files.

The data produced from this study will be stored in a secure, locked location. The data will also be entered into a secure, password protected database stored at The Applied Health Research Centre located at St. Michaels Hospital. Only members of the research team (and maybe those individuals described above) will have access to the data. This could include external research team members. Following completion of the research study, the data will be kept as long as required and then destroyed as required by SickKids policy. Published study results will not reveal your identity.

Reimbursement:
There will be no reimbursement for participation in this study.

Participation:
If you choose to let your child take part in this study you can take your child out of the study at any time. The care your child gets at Sick Kids will not be affected in any way by whether your child takes part in this study.

New information that we get while we are doing this study may affect your decision to take part in this study. If this happens, we will tell you about this new information. And we will ask you again if you still want to be in the study.

During this study we may create new tests, new medicines, or other things that may be worth some money. Although we may make money from these findings, we cannot give your child any of this money now or in the future because your child took part in this study.

In some situations, the study doctor or the company paying for the study may decide to stop the study. This could happen even if the medicine (or treatment) given in the study is helping your child. If this happens, the study doctor will talk to you about what will happen next.

If your child becomes ill or is harmed because of study participation, we will treat your child for free. Your signing this consent form does not interfere with your legal rights in any way. The study staff, any people who gave money for the study, or the hospital are still responsible, legally and professionally, for what they do.

Sponsorship:
The sponsor of this study is Dr. Eyal Cohen and The Hospital for Sick Children. The funder of this research is the Canadian Institutes of Health Research (CIHR) and Physician Services Incorporated (PSI).

Conflict of Interest:
Dr. Eyal Cohen and the other research team members have no conflict of interest to declare.

Consent:

By signing this form, I agree that:
1) You have explained this study to me. You have answered all my questions.
2) You have explained the possible harms and benefits (if any) of this study.
3) I know what I could do instead of having my child take part in this study. I understand that I have the right to refuse to let my child take part in the study. I also have the right to take my child out of the study at any time. My decision about my child taking part in the study will not affect my child's health care at Sick Kids.
4) I am free now, and in the future, to ask questions about the study.
5) I have been told that my child's medical records will be kept private except as described to me.
6) I understand that no information about my child will be given to anyone or be published without first asking my permission.
7) I have been given sufficeient time to read and think about the information in this consent form.

Printed Name of Parent/Legal Guardian	Parent/Legal Guardian's signature & date
Printed Name of person who explained consent	Signature & date
Printed Witness' name (if the parent/legal guardian does not read English)	Witness' signature & date

If you have any questions about this study, please call Dr. Eyal Cohen at 416-813-7654 x202626.

If you have questions about your rights as a subject in a study or injuries during a study, please call the Research Ethics Manager at 416-813-5718.