October | 2010

New Effusion Alternative Test

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Client: Dr. Steven Yale, Marshfield Clinic

Advisor: Professor Chris Brace, University of Wisconsin – Madison

October 20, 2010

Abstract

Pleural effusion is excess fluid that accumulates in the fluid-filled space between the lungs and chest cavity. The condition is diagnosed approximately 1 million times each year in the United States; however, the ability to determine if the fluid is transudative or exudative in a quick and concise way still remains a challenge. We will create a bedside method that allows for the differentiation of the two types of pleural effusions. Our team considered varying methods and received client input to accomplish this goal. The methods we determined to differentiate between transudative and exudative fluid include pH, glucose, and catalase. We evaluated the options giving us the most feasible and efficient design. Successful completion of the design will decrease the time waiting for results and increase the convenience of the test.

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BACKGROUND

MOTIVATION

Approximately 1 million pleural effusions are diagnosed in the United States each year (EMedicine Pulmonology, 2010). Depending on the cause, the excess fluid may be either protein-poor (transudative) or protein-rich (exudative). These two categories help physicians determine the cause of the pleural effusion. Most of effusions are caused by congestive heart failure, malignancy, infections, and pulmonary emboli. Normal pleural space contains approximately 1 mL of fluid due to a balance between hydrostatic and oncotic forces in the visceral and parietal pleural vessels. In contrast, pleural effusions can exceed 1500 mL in volume. When the fluid reaches around 500 mL, it can restrict breathing by limiting the expansion of the lungs during inspiration (Heart & Vascular, 2010). The seriousness of the effusion depends on the primary cause, which can be determined by the fluid type. Thus, making it imperative for a quick, easy, and reliable test for the type of fluid.

PLEURAL EFFUSION

Pleural effusion is excess fluid that accumulates in the fluid-filled space between the lungs and chest cavity as seen in Figure 1. There are two types of pleural effusions, transudative and exudative, which can be identified by the contents of the fluid. The criterion used to distinguish between the two is known as Light's criteria. A pleural effusion is said to be exudative if at least one of the following is true (Pleural Effusion, 2000):

1. The ratio of pleural fluid protein to serum protein is greater than 0.5
2. The ratio of pleural fluid LDB and serum LDB is greater than 0.6
3. Pleural fluid LDH is greater than 0.6

Causes of pleural effusion are dependent on whether the fluid is transudative or exudative. The most common causes of transudative effusions are heart failure, pulmonary embolism, and cirrhosis. Furthermore, exudative effusions often are the result of pneumonia, cancer, kidney disease, and inflammatory disease (Heart & Vascular, 2010). Most effusions do not have

symptoms until it reaches about 500 mL; some symptoms include chest pain, dry coughing, and uneasy breathing.

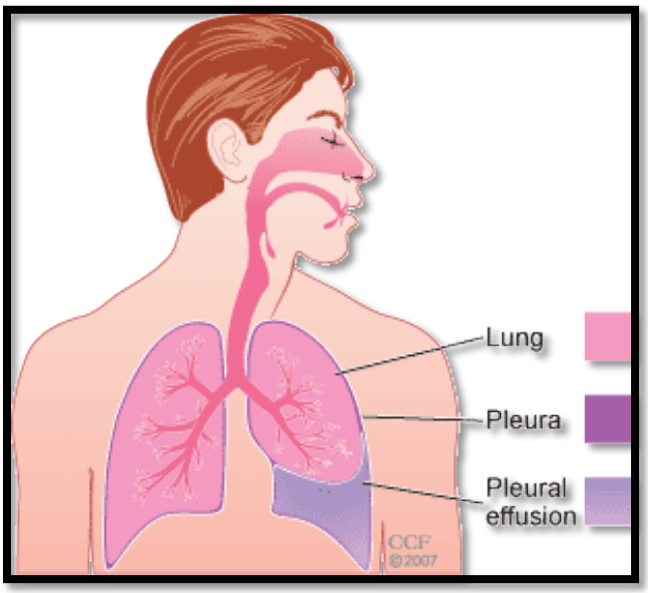

Figure 1. Animated pleural effusion between the lung an chest wall.
http://www.clevelandclinic.org/THORACIC/Chest/imgages/pleural-effusion_airway.gif

Pleural Effusion can be diagnosed using varying methods including chest x-ray (Figure 2), computerized tomography (CT) of the chest (Figure 3), and ultrasound of the chest. Once it has been diagnosed, the patient may undergo a procedure called thoracentesis, in which a needle is inserted between the ribs to remove a sample of fluid. The fluid is then taken to a lab and analyzed for levels of different metabolites to differentiate between transudative and exudative (Pleural Fluid Analysis, 2010).

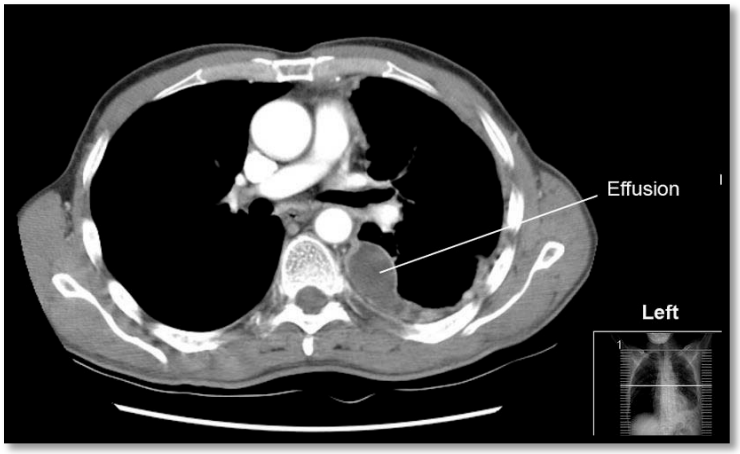

Figure 2. CT scan of chest showing left sided pleural effusion
http://upload.wikimedia.org/wikipedia/commons/thumb/a/a2/Pleura_effusion.jpg/220px-Pleura_effusion.jpg

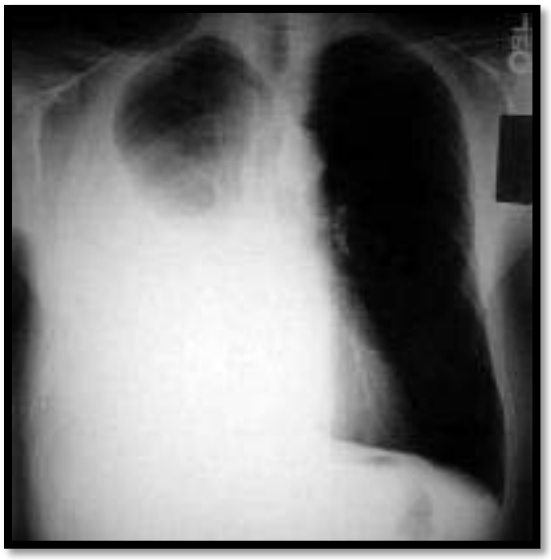

Figure 3. Chest x-ray of the chest showing a right-sided pleural effusion
http://img.medscape.com/pi/emed/ckb/pulmonology/295571-299959-127tn.jpg

CLIENT INFORMATION

Our client is Dr. Steven Yale, who is the director of clinical research at Marshfield Clinic**.** He specializes in internal medicine and is interested in improving the diagnosing process of pleural effusion.

PROBLEM STATEMENT

Dr. Steven Yale has requested a clinical method that is cost efficient, convenient, and quick for the characterization of fluid properties to determine if the effusion is transudative or exudative.

Current methods for the determination between the two types of fluids are expensive, time inefficient, and complicated. The team's model will be simple so that any clinician can use it at the bedside. In addition, the model will be small for portability.

COMPETITION

Our team came across three methods that compete with our design: magnetic resonance spectroscopy (MRS), ultrasounds of the chest, and pleural fluid laboratory analysis.

MRS is a non-invasive technique that is used to measure concentrations of different metabolites in the body tissues. The difference between and Magnetic Resonance Imaging (MRI) and an MRS is that the latter detects the chemical composition of the scanned tissue (Magnetic Resonance Spectroscopy, 2010). Generally, an MRS is done in combination with an MRI (Figure 4). The information given by an MRS is displayed in a graph that can be seen in Figure 5. An MRS gives information needed to determine between transudative and exudative; however, it is neither cost effective nor convenient to perform at the patient's bedside.

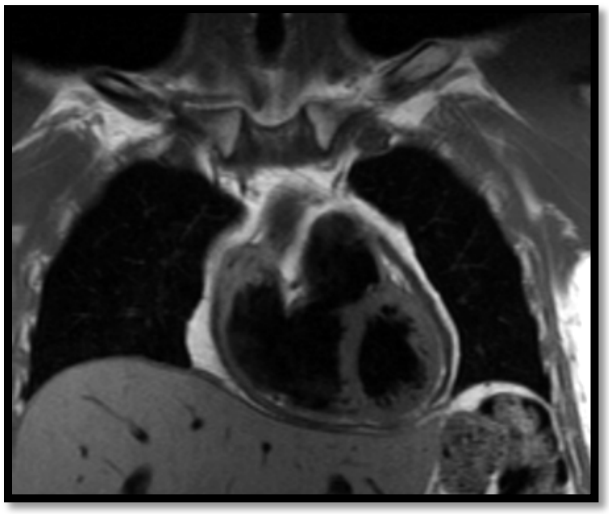

Figure 4. Magnetic resonance imaging scan of a patient's chest. http://www.bmj.com/content/337/bmj.a2042/F1.medium.gif

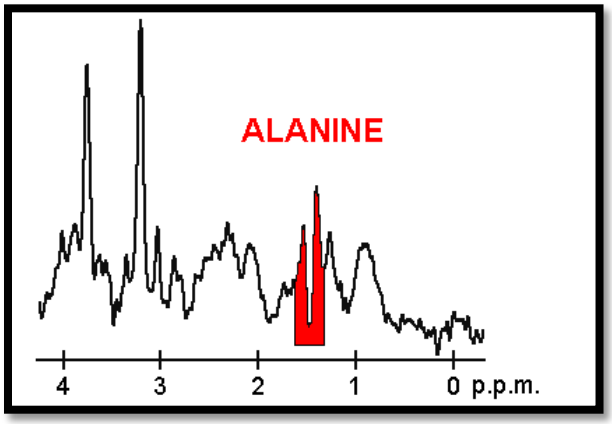

Figure 5. Graphically displayed information from an MRS. http://upload.wikimedia.org/wikipedia/en/a/a0/MRS_spectrum.gif

The next competing method is an ultrasound of the chest (Figure 6). This allows for visualization of the fluid location and volume. Additionally, it is useful in determining where to insert the needle for thoracentesis. A disadvantage of this method is that it does not provide any useful information regarding fluid content, which is necessary for differentiating between exudative and transudative pleural effusions.

Figure 6. Patient receiving an ultrasound to detect pleural effusion http://www.bayareachest.com/PS_Pictures/ultrasound.png

The final competing method is pleural fluid analysis (Figure 7). First, thoracentesis is used to get a sample of the pleural fluid. Once the fluid is obtained, it is sent to a lab to be examined for malignant cells, cellular makeup, chemical content, other organisms that can cause disease, and Light's criteria (Pleural Fluid Analysis, 2010). With this, the fluid can be classified as transudative or exudative. The problem with this method is that the results are not obtained in a timely manner. Our client would like the results immediately at the bedside.

Figure 7. Protein analysis of fluid http://www.microbiologylaboratory.biz/untitled.jpg

DESIGN ALTERNATIVES

Due to the broad range of possibilities and interests our client presented to us at the beginning of the semester, we had numerous options to consider for this project. Dr. Yale was interested in both locating the pleural effusion fluid and analyzing it to differentiate between exudative and transudative effusions. By researching and brainstorming we came up with four different design options. To evaluate where the fluid is located an EIT belt can be used. There are several options to evaluate the properties of the fluid which include a FastEEM Probe, rapid protein test, and multi-variable bedside test.

EIT BELT

An EIT belt uses a bioimpedance technique to evaluate pleural fluid location. Current is applied to the surface of the body using electrodes and the resulting voltage is measured. In order to analyze the data, a system such as the CardioInspect PulmoTracePro or similar programs can be used. Finally an image similar to Figure 8 is produced. Although this method is able to locate the fluid, there are some concerns regarding its accuracy and functionality. One problem with this method is that the measurement is a global average of lung resistivity and does not allow for separate thoracic compartments. Bioimpedance techniques are also unable to differentiate between pleural effusion and pulmonary edema, decreasing its reliability (Arad 2009). Specific to our project, there is the concern of characterizing the fluid. The bioimpedance method is unable to differentiate between transudative and exudative fluids (Webster 2010). Despite its downfalls the EIT belt provides a design that is lightweight, portable and noninvasive.

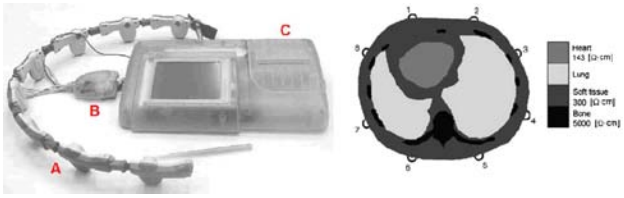

Figure 8: EIT belt and image created in PulmoTrace Pro
http://iopscience.iop.org/0967-3334/30/4/006/pdf/0967-3334_30_4_006.pdf

MULTI-VARIABLE BEDSIDE TEST

After reading numerous articles about singular tests for the differentiation of pleural fluid, we brainstormed the idea of combining these tests into one rapid bedside test. By

combining the tests we could improve upon the specificity and sensitivity. Although some tests, such as protein, could yield accurate diagnosis using Light's criteria, the process was time consuming. Currently, in order to quantify the protein levels, the sample is sent to lab (Yale 2010). A rapid bedside test would shorten the time between the thoracentesis and the clinician's diagnosis so that treatment could begin more rapidly. The main downside of this design is that a sample would still have to be obtained using thoracentesis. Despite this fault, the rapid bedside test is portable, inexpensive, easy to use, and can analyze the fluid in a short amount of time.

FASTEEM PROBE

One way to determine the characteristics of a fluid in vivo is by using a FastEEM approach. A probe with a fiber optic tip is inserted into the body, and then a sequence of ten laser pulses and two white pulses are emitted. By analyzing the reflectance the presence of certain metabolites can be determined (FastEEM, 2010). This design utilizes cutting edge research making it difficult to undertake in a semester. It is less invasive than the standard thoracentesis needle and has accurate results; however, there are some problems with this design. The FastEEM equipment is very expensive and the results are complicated to interpret.

RAPID PROTEIN TEST

Currently after a thoracentesis the pleural fluid specimen is sent to lab for a plethora of tests including protein analysis (Yale 2010). The protein concentrations are then used in conjunction with Light's criteria to determine if the pleural fluid is exudative or transudative. A rapid protein test would cut down the time between the thoracentesis and diagnosis, and thus treatment. We researched multiple methods. The Biuret test was the fastest and most accurate (Braun, 2001). Unfortunately, the quantification equipment needed for that test is not as portable as we would like it to be to transfer from room to room.

DESIGN MATRIX

In order to evaluate the different design options, a design matrix (Table 1) was used to determine the best design. The design matrix allowed us to choose a design quantitatively with

minimal subjective bias. The following six criteria were used to rank the four design alternatives.

Sensitivity was weighted the highest due to the need for an accurate test. High sensitivity and specificity are essential to limit false diagnoses. The EIT belt was given the lowest score in this category due to its inability to differentiate between exudative and transudative fluids. The other designs received higher scores because they are able to differentiate between the fluids.

The second highest rated category was ease of use. It is important that our design can be used efficiently and effectively by health care professionals. The device should be easy to use and provide clear results. The multi-variable bedside test and the bedside protein analysis would have the highest performance in the category.

Feasibility is another important aspect, although not as crucial as the aforementioned criteria. We want to be able to present our client with a working prototype at the end of the semester. The FastEEM probe is very technical and would take longer than a semester to design and implicate. The other three tests more practically address our objectives.

Size is another design aspect that was considered. The device should be small enough to be included in a thoracentesis kit. This would increase the usability of our product. The only two options that could realistically fit into the kit are the multi-variable bedside test and the bedside protein analysis.

The level of invasiveness is a key aspect of any medical procedure and should be minimized. Ideally the device should be noninvasive, similar to the EIT belt. Although currently the needle used for thoracentesis is small enough to reduce significant complications.

Cost is the last design aspect considered. It was weighted the lowest due to the fact that our client gave us a very large budget. However, we still included cost in the design matrix due to a lower the cost having greater marketability.

	Weight	**Fast EEM/Ramen Probe**	**EIT Belt**	Multi-Variable **Bedside Test**	**Bedside Protein Analysis**

Sensitivity	1	7	2	**6**	7
Ease of Use	0.75	7	7	**9**	9
Feasability	0.5	5	8	**10**	7
Size	0.5	7	7	**9**	8
Invasiveness	0.5	8	10	**5**	5
Cost	0.25	4	6	**9**	8
Total	3.5	23.25	21.25	**27**	25.75

Table 1. Design Matrix

FINAL DESIGN

The final design chosen to characterize a patient's pleural fluid was the Multi-Variable Bedside Test. This test utilizes three biological markers found in pleural fluid to differentiate between transudative and exudative pleural fluid. By combining the three methods, it is our intention to improve upon the sensitivity and specificity of each test. Included in the Bedside Test kit will be an analysis chart (Table 2). It will be used to quantify and compile the results of each test to determine whether the pleural fluid is exudative or transudative.

The pH of the fluid can be used as an indicator for differentiating between types of pleural fluid. Fluid classified as transudative has a pH of greater than 7.3, while fluid with a pH of less than 7.3 is considered exudative (Good, 1980). Explanations of pleural fluid acidosis have not been precisely defined. However, possible mechanisms include a combination of acid production by pleural fluid or an inadequate buffering capacity of the fluid. In the case of empyemas, increased acid generation may be due to the presence of leukocytes and bacteria found within the fluid. This is a result of the metabolism of glucose to its end products, CO_2 and lactate. For malignant effusions, low pH may be due to an increase in acid production by malignant cells. Another explanation is the impaired efflux of H^+ as a result of pleural thickening due to a tumor (Good, 1980). Determination of fluid pH will be conducted with a diagnostic test strip secured to the wall of a cuvette. The reaction portion of the strip will be positioned near the bottom of the cuvette to enable a reaction with a minimal amount of fluid. A colorimetric analysis of the diagnostic strip will be used to determine the pH of the fluid. Reference colors will be given to the clinician on the analysis chart.

An additional biological marker that can differentiate between exudative and transudative fluid is glucose. Glucose levels lower than 60 milligrams per deciliter are correlated with exudative pleural fluid while glucose levels great than 60 mg/dl are associated with transudative fluid (Light, 2002). The cuvette used to identify glucose levels will be found on the end of the testing device due to the need of a glucose monitor to interpret the results of the test. This monitor will be attached in a sealed container next to the cuvette where the fluid is inserted. A small opening between the container holding the glucose meter and the cuvette will be needed for the test strip. Both the test strip and glucose meter will sit at the bottom of the cuvette to ensure that a sufficient amount of fluid is present to identify glucose levels. The results of the glucose test will be displayed digitally on the glucose meter.

Furthermore, the level of catalase activity within the fluid can be used to characterize the type of fluid. A unique characteristic of exudative fluid is increased catalase activity (Sarkar, 2009). Due to the ability of catalase to speed the decomposition of hydrogen peroxide to water and oxygen (Chelikan,2004) a simple bedside test can be done to verify the presence of catalase. Therefore, the fluid can be classified as either transudative or exudative. If profuse bubbling occurs within one minute of the addition of hydrogen peroxide, signifies exudative fluid. The bubbling occurs as a result of the decomposition reaction. When hydrogen peroxide is added to transudative fluid, bubbling is not observed. The cuvette using hydrogen peroxide to characterize pleural fluid will contain 10 µL of hydrogen peroxide. To identify the presence of catalase, 200 µL of pleural fluid will be needed. Once the pleural fluid is added to the hydrogen peroxide, profuse bubbling should be seen within one minute. The sensitivity and specificity of this test is believed to be equivalent to the widely used Light's criteria (Sakar, 2009).

Test	Transudative	Exudative
Glucose	> 60 mg/dL	< 60 mg/dL
pH	> 7.3	< 7.3
Hydrogen Peroxide	No bubbles	Bubbles

Table 2. Criteria used to analyze results of tests (Good, 1980; Light, 200;2 Sakar, 2009)

DESIGN SPECIFICATIONS

Each test will be housed within an individual cuvette. Consequently, the final design will consist of three cuvettes attached and set into a base. Each cuvette is manufactured from a clear plastic, allowing for easy interpretation of results from each test. Attached to the glucose test cuvette will be an additional casing to house the glucose meter. Overall specifications for the device are 15cm long x 2.5 cm wide x 4.5 cm high. Individual cuvettes measure at 1.7 cm long x 2.5 cm wide x 4 cm high. The remaining area of the design will be taken up by the base and the glucose meter.

It is important that device is covered as there will be prepackaged hydrogen peroxide in one of the cuvettes. A plastic seal will be placed over the cuvettes to prevent leakage before the device is used. This seal will be removed prior to testing. Additionally, a hard plastic cover will be designed to prevent spillage of not only the testing liquids but also the pleural fluid. This cover will allow for the insertion of pleural fluid via a hole centered above each cuvette. There will be an attachment to allow the syringe containing the pleural fluid to be screwed in, and securely attached to each hole.

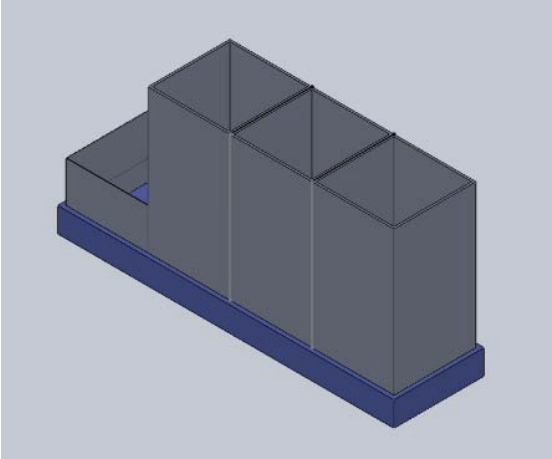

Figure 9. Prototype drawing of the Multivariable Bedside Test (SolidWorks, Dassault Systèmes SolidWorks Corp).

FUTURE WORK

The focus of the rest of the semester will be on improving our final Multivariable Bedside Test. We will use our knowledge of the glucose, pH, and hydrogen peroxide tests to choose the materials best suited for each component of the design. This includes deciding on the best size and material of the small cuvettes, cover, and base. Once we have chosen the proper materials, we will consider incorporating additional tests into the design. In doing so, we may further improve our design's diagnostic value. Tests that will be considered include the analysis of albumin, lactase dehydrogenase, protein concentration, and/or cholesterol concentration in the fluid in question. Additional methods for protein analysis include the Biuret method and the Bradford assay (Braun, 2001).

After fabrication, we will determine the effectiveness of each individual test within the design. By using predesigned, control fluids, we can evaluate the accuracy of each test. We will use fluids with known concentrations of sugar to identify the proper calibration of the glucose meter. Determining the sensitivity of the glucose meter will be critical in evaluating the effectiveness of the fluid's glucose analysis. In addition, fluids with known concentrations of acid will be used to test the pH aspect of the device. In the same manner, fluids with known catalase concentration will be used to assess the accuracy of the qualitative hydrogen peroxide test.

Each individual test within our design has reported values of sensitivity and specificity based on a specific analysis of the test. However, linking these tests together into a single device will benefit the overall diagnostic accuracy. For this reason, our testing must determine the sensitivity and specificity of our incorporative design. This will be the most significant evaluation of our design's accuracy.

Finally, we will incorporate our device into the current thoracentesis procedure. This integration into the current standard protocol will be planned in such a way as to not detract from the ease or effectiveness of the procedure. Ideally, utilizing our design in the process will improve the efficiency of the procedure. The end goal of our project is to incorporate our design into each thoracentesis kit for the convenience of physicians and others using this diagnostic tool.

CONCLUSIONS

The creation of an incorporative multivariable bedside test for the characterization of pleural effusions will allow for the more rapid determination of the fluid type. Consequently, this will shorten the time before a diagnosis is made and treatment options can be considered by eliminating the need for time-consuming lab work. Furthermore, by unifying several methods of effusion characterization, our design will offer increased diagnostic accuracy. Not only will this device decrease diagnostic time but will benefit hospitals around the world that may be less equipped to conduct standard diagnostic tests.

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Appendix A. Project Design Specifications

#22- Non-invasive method for detecting pleural effusion form air-filled pleural space
September 10, 2010
Team: Carmen Coddington, Kelsey Duxstad, Bryan Jepson, Christa Wille
Client: Dr. Steven Yale
Advisor: Professor Chris Brace

Function:
Dr. Steven Yale has requested a non-invasive, clinical method for the detection of pleural effusion in air-filled pleural space that will be an inexpensive alternative to sonographic devices.

Client Requirements:
• To be determined
Design Requirements:

Project Design Specifications

#22- Non-invasive method for detecting pleural effusion form air-filled pleural space

September 10, 2010

Team: Carmen Coddington, Kelsey Duxstad, Bryan Jepson, Christa Wille

Client: Dr. Steven Yale

Advisor: Professor Chris Brace

Function:

Dr. Steven Yale has requested a non-invasive, clinical method to characterize the fluid properties of the pleural effusion to determine whether the pleural effusion is exudative or transudative.

Client Requirements:

- Cost effective
- Portable
- User friendly
- Accurate

Design Requirements:

1) Physical and Operational Characteristics
    a) *Performance requirements*
        i. To determine the fluid properties of the pleural effusion (pH, glucose, catalase, and protein content)
    b) *Safety*
        i. No negative biological effects
    c) *Accuracy and Reliability*
        i. Must accurately detect properties of the fluid
        ii. Differentiate between exudative and transudative effusion
    d) *Life in Service*
        i. 5-10 years
    e) *Shelf Life*
        i. 15-20 years
    f) *Operating Environment*
        i. Patient hospital rooms
    g) *Ergonomics*
        i. Easily maintained
    h) *Size*
        i. 15cm long x 2.5 cm wide x 4.5 cm high
    i) *Weight*
        i. Less than 2 pounds
    j) *Materials*
        i. No latex
        ii. Medical grade plastics
    k) *Aesthetics*
        i. Easy to read results
2) Production Characteristics

a) *Quantity*
    i. One model
b) *Target Product Cost*
    i. $50-100

3) Miscellaneous
a) *Standards and Specifications*
    i. FDA approval is required if placed in the market
b) *Customer*
    i. Medical schools
    ii. Hospitals
c) *Patient-related concerns*
    i. Minimally invasive
d) *Competition*
    i. Magnetic resonance spectroscopy
    ii. Ultrasound
    iii. Protein analysis