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Detecting Ventilator Associated Pneumonia Through On-board Endotracheal Tube Diagnostics

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Abstract

Ventilator-associated pneumonia (VAP) is a burdensome healthcare-associated infection which puts 54% of intensive care unit (ICU) life support patients across the United States at serious risk. Half of all antibiotics in the ICU are prescribed for VAP, but due to widespread inadequate treatment (up to 30% of cases), mortality rates remain as high as 24-76%. Inadequate treatment stems from lack of diagnostic and monitoring capacity. The current standard of detection is a non-specific complete blood count (CBC) completed every 24 hours. CBCs may take up to an additional 24 hours to process, allowing the infection to grow and become more difficult to treat for a total of 48 hours. To address these issues, this study conceptualizes a passively operated, high-fidelity, and high-frequency bacterial monitoring device to detect the presence and concentrations of bacteria commonly encountered in VAP.

Electrochemical Impedance Spectroscopy (EIS) has been utilized extensively in electrochemical industry applications such as acid battery testing and, more recently, as a sensitive method for biofouling quantification. However, EIS has not been implemented clinically. The selected design will use a specialized EIS sensor to analyze mucosal excretions of intubated patients and quantify the bacteria present. This technology can alert physicians of infection 24-48 hours earlier than currently possible, allowing patients to receive treatment faster and thus potentially reducing their length of stay (LOS) in the ICU by ~6 days. Our findings project that this approach would lower each VAP patient's treatment cost by approximately $24,000 and would save healthcare systems $3,600 per ICU patient (rates and estimates determined in 2019).

Keywords: Ventilator, pneumonia, infection, sensor, endotracheal tube

1. Introduction

Ventilator-Associated Pneumonia (VAP) is defined as an upper-respiratory infection correlated to mechanical ventilation or endotracheal tube (ETT) placement. Clinically, VAP is defined as any pneumonia contracted more than 48 hours post-intubation [1]. Although the exact mechanism of infection is likely multivariable and is not yet fully defined, the probable pathogenesis stems from contaminated oropharyngeal secretions pooling over the ETT cuff and subsequently draining down to the lungs through a hydrostatic gradient made possible by the ETT acting as a bypass of normal physical barriers for pathogen entry (i.e. the larynx, cilia, and gravitational gradient) [2]. This often results in biofilm formation, giving the invading pathogens a protected reservoir to elude antibiotic therapy [3].

According to the World Health Organization, 30% of all ICU patients in high-income countries will contract at least one healthcare-associated infection [1]. VAP is the most common healthcare-associated infection among US intensive care unit life support patients [4]. 54% of all ICU patients are at risk for contracting healthcare-associated pneumonia [5]. An estimated 300,000 contract VAP in the United States annually. VAP is associated with a 38% increase in 30-day mortality and has an overall mortality rate of 28.4% [5]. Viral infections such as the recent pandemic of the novel coronavirus SARS-Cov-2 (CoViD-19) increase the body's susceptibility to infection such as VAP. Immunologically compromised patients are also placed at increased for infection and death.

Despite the large and pressing nature of the disease, there has been no system proposed for the early detection of VAP. Physicians have only limited preventative measures contain the burden of VAP on the healthcare system including: 30 degrees head elevation, cuff pressure monitoring, avoidance of sedatives and muscle relaxants, etc. [6]. The current standard of detection is a daily CBC for leukocytosis or increased white blood cell count. These are only general indicators of infection, and may take up to 24 hours to process, translating to a total possible delay of 24 to 48 hours between infection onset and medical intervention. *The objective of this study is to improve the detection of Ventilator-Associated Pneumonia with a passively operated high-fidelity device that allows for increased monitoring frequency.*

2. Methods

2.1 Design Generation

Market research and clinician interviews were conducted to establish customer requirements and translate them into technical specifications for the design. Each author individually developed a design based on differing mechanisms to meet these requirements. These designs were then refined by the author and collaborators based on more targeted interviews with clinicians to ensure relevancy and feasibility before the selection process began.

2.2 Design Selection

The designs were compared and objectively evaluated for capacity to deliver the technical specifications identified utilizing the House of Quality (HOQ) decision matrix (**Table 1**). Customer requirements were given weighted importance-based clinician input gained in interviews. Correlations were drawn between the customer requirements and technical specifications. Designs were compared directly according to their ability to perform the outlined task. Scoring values were assigned (1, 3, 6 or 9) to allow for an improved scoring granularity. Scores were assigned based on perceived aptitude of the design to meet customer requirements based on literature review. These scores were multiplied by the corresponding percent weighted value and totaled. Each design was ranked based on the total score to select the optimal design to meet the customer requirements.

2.3 Risk Analysis

To comprehensively predict and prevent adverse outcomes of the selected design, a Failure Modes and Risk Analysis (FMEA) and the Failure Tree Analysis (FTA) models were utilized. Utilizing both methods predicted and classify the potential failures of each component of the device and which

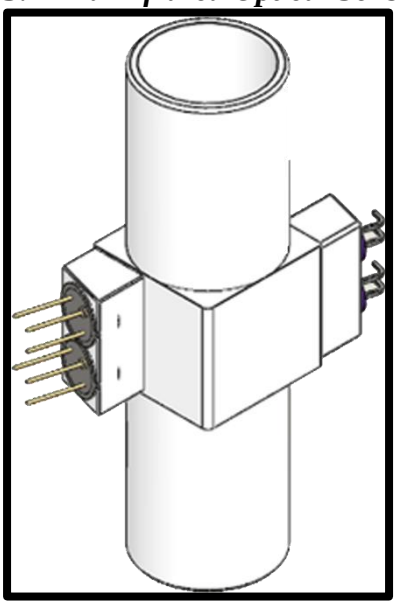
component malfunctions or combination thereof would lead to failures identified. Updates to our selected design were implemented with information gained from both models of risk analysis to maximize risk mitigation.

2.4 Commercialization

Market opportunity was identified and defined based on the patient population likely to benefit from the device. The total addressable market and beach-head market were outlined to be targeted for initial distribution. With the beachhead market fully defined, the competitor landscape was assessed, and the value added of the design calculated. Business models were drafted and selected with this information. Finally, a cost and distribution model were created to estimate the entry market pricing and capital investment required to begin manufacturing. Based on this market analysis, the device was determined to represent protectable intellectual property. A provisional patent was filed through the University of Texas at San Antonio Office of Commercialization and Innovation.

3. Results: Design Generation

3.1 Mid Infrared Optical Sensor

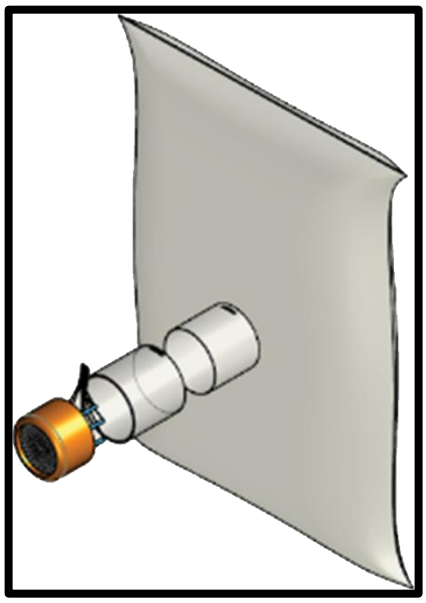


The infrared biosensor design includes 4 components: 2 infrared light sources, a linear multipass absorption cell, and a detector. The device itself would be inserted into the ventilator tubing immediately distal to the y-split where exhaled breath passes from the patient to the environment or a collecting chamber. Dispersive light is focused from the infrared source placed on the exterior surface of the exhaled-breath tubing into the multipass absorption cell inside the tubing where the light would interact with the patient's breath. The multipass cell serves to increase the path length of the light and therefore the amount of interaction with molecules in the breath; this allows for a higher sensitivity to be achieved. The light will pass back out of the tubing and into the detector where the absorbances of the separate wavelengths are measured. The output signal would be sent to a computer module for display and comparison to reference values.

Figure 1: *Infrared Biosensor Isometric View*

The design utilizes 3.0μm and 3.4μm light sources to quantify the C-H and C-O bonds present in the exhaled breath and elucidate the presence of ethanol, a known biproduct of bacterial metabolism. The path length of the infrared light through the sensor is 5.7cm, comparable to pathlengths in similar sensors [7]. This is achieved by directing the light entering the sample cell at an angle of 15.5 degrees. 98% of the light is transmitted through each of the silicon windows and 96% is reflected off the gold-plated mirrors. Full strength signal of the detector receiving light from the 3.0μm source was 0.36V. The detector for the 3.4μm infrared light outputs 0.82V with no gas interference. With a basic computational sensor, this results in a high-resolution output read from the 3.0μm source and 170 for the 3.4μm source. This is sufficient for determining a change in gas present in exhaled breath but is limited by the quality of light sources or detectors.

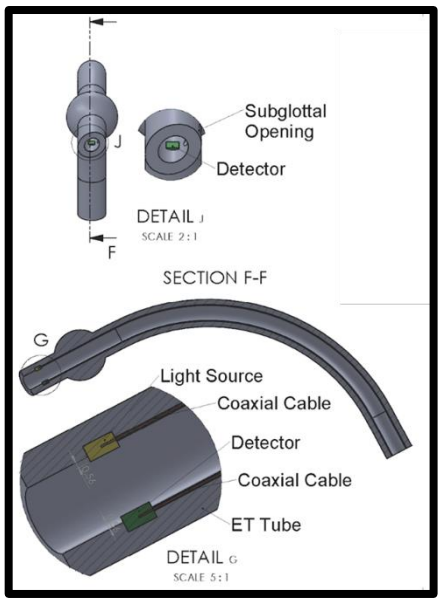
3.2 Semiconductor Gas Sensor



The semiconductor design includes of 7 components including an MQ3 ethanol sensor, a fixture component, a Tedlar bag to collect the expired gas, six leads connecting the sensor to the Printed Circuit Board (PCB), the PCB, an alarm system, and a graphic user interface. The MQ3 sensor is placed in the fixture that connects the bag to the expiratory limb of the ventilator. The fixture will have an opening to allow for the leads from the sensor to connect to the PCB. This establishes power for the sensor by connecting the 5V and GND terminals respectively. The other 2 connections are the analog and digital output of the sensor. When exhaled air flows through the expiratory limb of the ventilator, it will be collected in the Tedlar bag. The MQ3 sensor will be able to continuously read the amount of ethanol present. When the ethanol concentration reaches 1mg/L, the alarm will alert a healthcare professional.

Figure 2: *Semiconductor Biosensor Isometric View*

3.3 Optical Mucus Sensor



The design would propagate a beam of visible light transversely across the intraluminal space of the patient's endotracheal tube. Upon crossing the space, the light would shine on a photocell which would generate an electrical current and translated into a digital signal. The intensity of light interacting with the detector would be directly proportional to the current supplied to the system, and a voltmeter would transmit this data to a user interface such as an LED alert system.

To generate clinically relevant data, this device must detect changes in the amount of purulent mucosa present distal to the ETT cuff. Since purulent mucosa is characterized as "green-yellow" in color, it would attenuate this light frequency more than clear, white, or cream-colored mucosa, which have been strongly associated with absence of microbial content [8]. The photocell selected would generate 3.5 mA of current per lumen. With a high-resolution voltmeter, the system sensitivity is adequate to measure a variable biological target.

Figure 3: *Optical Biosensor Sectional View*

Placing components in the ETT presents a unique challenge of maintaining the conditions of oxygen delivery to the patient despite changes in the interior surface of the ETT to accommodate the source and sensor. In our preliminary design, both additional components obstruct < 2% of the ETT cross-sectional area.

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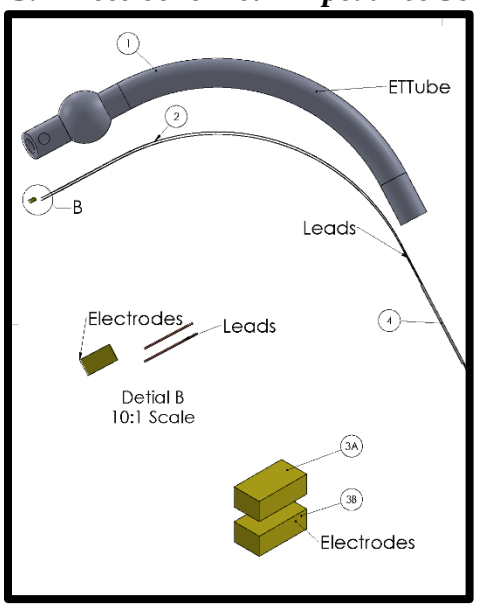
3.4 Electrochemical Impedance Sensor (EIS)



The design uses mucus which accumulates at the distal end of the ETT and analyzes it for bacterial colonization with electrodes connected to a biosensor.

Signal Relay

The signal begins in the function generator then passes through silicone insulated leads into the ETT probe. Impedance characteristics of the mucus alter the current and amplitude of the signal. Two separate leads bring this signal into a protoboard for signal separation into waveforms representing current and voltage. The oscilloscope then receives the waveforms and calculates impedance values based on the frequencies, amplitudes, and phases measured. Normalized resistance and changes of phase at a range of frequencies are tracked for differences over time, which indicates the presence of VAP.

Figure 4: *EIS Biosensor Exploded View*

Electrode Placement

The leads connect the biosensor to the contacts adhered to the inner surface of the ETT as shown in Figure 4. Alternate placements of the electrodes (such as the interior of the pressure cuff and/or placement of a reference electrode set in the proximal end of the ETT) have been considered to reduce potential noise-to-signal ratio, but optimal placement of the electrodes was not testable due to the COVID-19 pandemic. Depending on the results of optimization testing, further iterations of the device may include electrode placement not in the ETT tube itself, but in the suctioning, system designed to periodically remove subglottal secretions from the end of the ETT. This would provide a more controlled environment for the sensor to operate in but would potentially limit the sensing frequency to the frequency of bronchoalveolar lavage to every 1-2 hours.

Mechanism of Action: Electrochemical Impedance Spectroscopy

In alternating current (AC) circuits, voltage is affected by resistance as well as other additional factors. Capacitance and inductance are frequency-dependent properties which effect voltage. The combined effect of resistance, capacitance, and inductance is referred to as impedance. AC signals are often represented as sine waves. If a resistor (with an influence independent of frequency) is applied to this AC signal, then the amplitude of the sine wave is decreased proportionally to the resistance applied. However, if the circuit includes components such as inductors and capacitors, then not only is the amplitude changed, but the time at which the current flows in relationship to the voltage applied also gets translated horizontally. This translation in time is referred to as a “phase shift”. EIS is the monitoring/measurement of both phase and resistance change in a system. This means substances are characterized not just by their resistance, but also by their capacitance and inductance, which allows EIS designs to blueprint complex systems much more accurately than ever before. EIS is a tri-variable assessment of a substance’s electrical properties and can be used to differentiate between mixtures of differing concentrations.

3.5 Design Selection

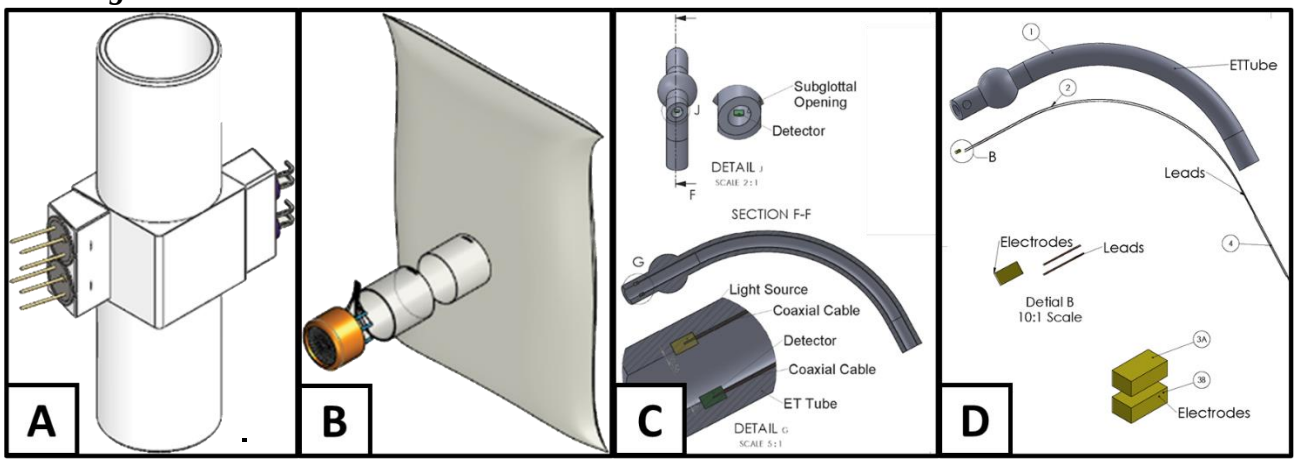


Figure 5: A) Infrared Sensor B) Semiconductor Sensor C) Optical Mucus Sensor D) EIS Sensor

Table 1: HOQ Competitive Design Selection

Customer Requirements Competitive Assessment	**Weight**	**Infrared Ethanol Sensor**	**Semiconductor Ethanol Sensor**	**Optical Mucus Sensor**	**EIS Mucus Sensor**
Specific to VAP	25%	1	3	1	6
Sensitivity	20%	3	3	6	9
Functionally Inert	15%	9	6	9	6
Biocompatible	15%	9	9	6	3
Quick Turnaround Time	15%	6	6	6	3
Passive/Continuous	7%	6	6	9	9
Compatible w/ current systems	2%	9	6	6	6
Easy to install/use	1%	9	3	9	9
TOTALS		**5.14**	**5.07**	**5.4**	**5.94**

3.6 Risk Analysis

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Component	Function	Potential Failure Mode	Potential Failure Effects	SEV	Potential Cause of Failure	OCC	Current Process Controls	DET	RPN (S*O*D)	Corrective Action					Percent Change in RPN
										Action Taken	SEV	OCC	DET	RPN (S*O*D)	
Endo-tracheal Tube	Serve as a standard ETT	Mechanical Properties Altered	Airflow is altered or blocked	8	Misplacement of the tube	8	Qualified Surgeon	7	448	N/A	8	8	7	448	0.00%
					Chemical Degredation	1	Material Selection	9	72	N/A	8	1	9	72	0.00%
					Change in body position	4	Trained Hospital Staff	5	160	N/A	8	4	5	160	0.00%
	Hold components in place	Components dislodged	Signal Lost	6	PVC Rupture	2	Material Selection	5	60	N/A	6	2	5	60	0.00%
Signal Generator	Provide signal with set voltage and range of frequencies to the electrodes	Output signal different from expected	Spectrums over time are created using different signals (gives incorrect results)	7	Fluctuations in signal intensity (V)	3	Signal Generator Amplitude Control System	7	147	Calibration test cycle	7	3	1	21	85.71%
					Frequency Sweep faster or slower than expected	2	Signal Generator Frequency Control System	7	98	Calibration test cycle	7	2	1	14	85.71%
Coaxial Cables	Connect the electrode to the signal generator	Connection between components is lost	Signal Lost	6	Excessive ETT movement	4	Trained Hospital Staff	3	72	N/A	6	4	3	72	0.00%
					Poor signal generator connection	5	N/A	2	60	Calibration test cycle	6	5	1	30	50.00%
					Poor electrode connection	5	N/A	2	60	Calibration test cycle	6	5	1	30	50.00%
Voltmeter	Calculate voltage of incoming signal and output to single board computer	Voltage detected is different from actual	Erroneous Data Output	7	Voltmeter not calibrated properly	2	N/A	7	98	Function generator signal is split between electrodes and directly to voltmeter to serve as a control	7	2	1	14	85.71%
Alert System	Alert medical staff of detected concentrations of bacteria	Medical Staff do not recieve alert notification	Medical staff is not notified	5	Alert system failure	2	N/A	5	30	Calibration test cycle	5	2	1	10	66.67%
					Connection from device to alert system is lost	3	N/A	3	45	Calibration test cycle	5	3	1	15	66.67%
		Not distinguishable between other normal hospital noises/alerts	Medical staff is unaware of alert	4	Alert is not responded to by medical staff	5	Trained Hospital staff to know when to respond	3	60	New alert system (examples: loudit)	4	3	3	36	40.00%
	Analyze incoming data from voltmeter	VAP incorrectly identified	Erroneous Data Output	7	Unexpected spectrum values	6	N/A	5	210	Index additional strains	7	3	4	84	60.00%
					Over-sensitivity	6	N/A	5	210	Appropriate percent change determined w/ product testing	7	3	5	105	50.00%

Figure 6: Failure Modes and Effects Analysis of EIS Design

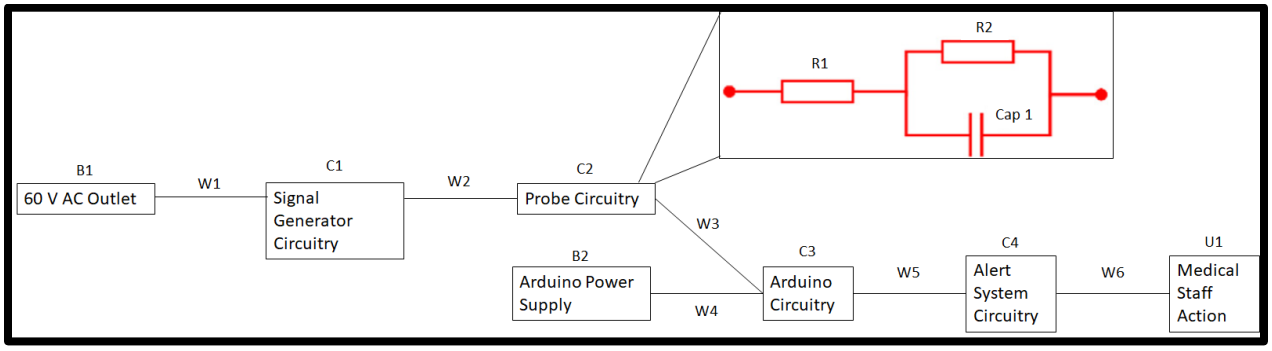

Figure 7: Circuitry Digram of EIS Design for FTA

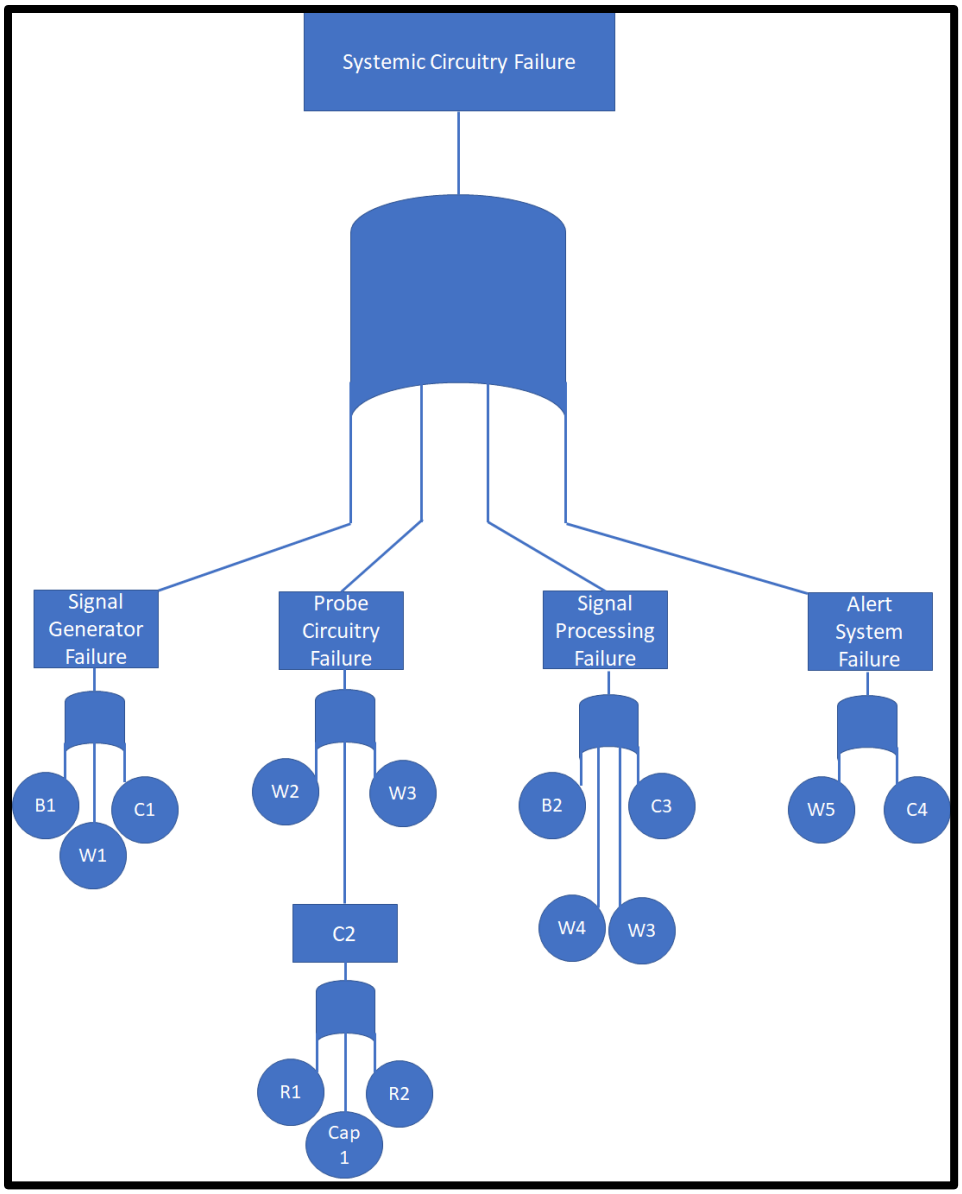

Figure 8: Fault Tree Analysis of EIS Design

4. Discussion:

4.1 Design Selection

The EIS design scored the highest on the HOQ decision matrix largely due to indications it would best serve the customer requirements of specificity and sensitivity. As a result, we elected to construct the EIS VAP sensor, named PneuMed.

4.2 Risk Analysis

With the selected device design, we conducted a Failure modes and Effects Analysis (FMEA) [9] and Fault Tree Analysis (FTA) [10] to identify and implement needed design improvements. Within the FMEA, each potential failure mode was assigned a risk priority number before and after design improvements were made. FTA informed our team of the potential combinations of failures that could result from 1 source or component. Through these two methods of risk analysis, we were able to mitigate many risk factors significantly before entering the prototype phase of the design process.

4.3 Discussion of Functionality

Sensitivity

Sensitivity is one of the first concerns within the design of all biosensors. The pathological definition of infection in a brachial aspirate sample is 10^6 colony forming units (CFUs) per mL [11, 12]. Fortunately, the sensitivity of electrochemical impedance sensors has been well documented for various purposes. For example, EIS systems have been used in battery development and corrosion characterization. More recently, investigators have started to utilize EIS for equally sensitive yet more biologically relevant systems such as water quality and food safety assessments.

However, EIS has not yet been used to characterize disease to any notable scale. In the research and laboratory setting, there is a foundation for developing a scalable EIS biosensing system for disease detection. In fact, one group investigated 3D printed carbon electrodes as an affordable model for detecting bacteria in medical settings [13]. With this protocol, they were able to achieve sensitivity to the minimal concentration required to diagnose and infection, 1.8×10^6 CFUs/mL. The design in this study improves upon the quality of the electrodes, and therefore a correlated increase in sensitivity is expected. Even if testing should prove that these electrodes are inadequate, surface modifications have been shown in other applications to increase sensitivity to as much as 2 CFUs/mL [14] and represent a alternate course for design development in future studies.

Specificity

False positive results were one of the primary complaints expressed by physician during clinical interviews. In order to ensure specificity, not only must the device have high sensitivity and resolution, but this study's selected design utilizes a broad range of frequencies (1Hz – 100 MHz) to generate a comprehensive analysis of a sample's characteristics. By utilizing EIS through a variable frequency AC signal, we gain the advantage of generating a highly specific sample profile as seen with other characterization techniques such as infrared spectroscopy. Ultimately, the specificity of the device will depend on data collection and characterization of interfering or confounding particulates, which may be enhanced using metrics from clinical or laboratory testing.

Biocompatible / Functionally Inert

Ventilators serve a vital role in patient care. No healthy patient is placed on a ventilator and compromising the ventilator's function would be fatal. Therefore, this design has avoided placing any component of the system in a way that would pose a threat to ventilator function or create additional risk for the patient. The materials in direct contact with patient tissue are the same materials as any standard ETT to minimize potential biocompatibility complications, and the electrodes, while exposed to the mucus, obstruct less than 1% of the cross-sectional area of the ETT airway.

Short Testing Period

To generate a single spectrum of Impedance values across a given frequency range constitutes will be treated as the testing period. This period along with any interval between periods determines the testing frequency. The current testing frequency is once per 24-hour period. Our technical specifications dictated that we must have a testing frequency of one result per two-hour period. In our preliminary testing, the average time required to manually collect this data across five frequencies within the range of interest and interpolate the values was less than 30 seconds. We expect this time to decrease with automation of the frequency sweep.

Passive Operation

For this device to effectively reduce hospital costs, the design must account for independent operation, without user interaction between the time of intubation and either extubation or infection. While our current unfinished prototype requires manual frequency adjustment to generate each impedance profile, future iterations of the device will automate this process and remove the need for input except at the above-specified times.

5. Conclusion

Half of all antibiotics prescribed in the ICU are for VAP [12], yet it is still deadly, with mortality rates as high as 76% [15]. VAP is correlated with an average 9-day extension in LOS in the ICU resulting in an average >$40,000 increase in cost per patient [4, 16]. The opportunity for improvement is striking. All healthcare-associated infections are preventable, but up to 30% of ventilator associated pneumonias are treated inadequately [17].

This study conceptualized a device that will serve as a warning to physicians to initiate antibiotics and call for a sputum sample analysis, increasing the efficacy of treatment by eliminating the systemic delay in treatment initiation and increasing treatment specificity. This will reduce the poor outcomes associated with the disease. Compared to common antibiotic prescription practices, a random rotation was found to increase efficacy of treatment by 30% and reduce mortality by 23% [17]. Based on these figures, the study's design is estimated to lessen the ICU LOS by 6 days, lowering each VAP patient's treatment cost by an average of $24,000 and saving healthcare systems an average of $3,600 for every ICU patient.

In summary, the bacterial monitor conceptualized in this study is capable of monitoring bacterial growth as it develops rather than after patients present life-threatening symptoms, reducing the burden on the healthcare system and saving millions of lives from preventable and treatable disease.

6. Acknowledgments

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References

1. Organization, W.H., *Report on the Burden of Endemic Health Care-Associated Infection Worldwide; Clean Care is Safer Care.* World Health Organization. 2011, Geneva: World Health Organization.
2. Mietto, C., et al., *Ventilator associated pneumonia: evolving definitions and preventive strategies.* Respiratory care, 2013. **58**(6): p. 990.
3. Fernandez-Barat, L. and A. Torres, *Biofilms in ventilator-associated pneumonia.* Future Microbiology, 2016. **11**(12): p. 1599-1610.
4. Reed, D. and S.A. Kemmerly, *Infection control and prevention: a review of hospital-acquired infections and the economic implications.* The Ochsner journal, 2009. **9**(1): p. 27-31.
5. Ibn Saied, W., et al., *A Comparison of the Mortality Risk Associated With Ventilator-Acquired Bacterial Pneumonia and Nonventilator ICU-Acquired Bacterial Pneumonia*.* Critical Care Medicine, 2019. **47**(3): p. 345-352.
6. Choudhuri, A.H., *Ventilator-Associated Pneumonia: When to hold the breath?* International journal of critical illness and injury science, 2013. **3**(3): p. 169-174.
7. Popa, D. and F. Udrea, *Towards Integrated Mid-Infrared Gas Sensors.* Sensors, 2019. **19**(9): p. 2076.
8. Johnson, A.L., D.F. Hampson, and N.B. Hampson, *Sputum color: potential implications for clinical practice*, in *Respiratory Care*. 2008. p. 450+.
9. Standardization, I.O.f., *ISO 12132:2017(en)*. 2017.
10. Smith, D.J., *Chapter 8 - Methods of Modeling*, in *Reliability, Maintainability and Risk (Eighth Edition)*, D.J. Smith, Editor. 2011, Butterworth-Heinemann: Oxford. p. 103-131.
11. Kollef, M.H., *Silver-Coated Endotracheal Tubes and Incidence of Ventilator-Associated Pneumonia.* JAMA, 2008. **300**(7): p. 805.
12. Vincent, J.L., et al., *The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee.* Jama, 1995. **274**(8): p. 639-44.
13. Ward, A.C., et al., *Identification and characterisation of Staphylococcus aureus on low cost screen printed carbon electrodes using impedance spectroscopy.* Biosensors and Bioelectronics, 2018. **110**: p. 65-70.
14. Barreiros dos Santos, M., et al., *Highly sensitive detection of pathogen Escherichia coli O157:H7 by electrochemical impedance spectroscopy.* Biosensors and Bioelectronics, 2013. **45**: p. 174-180.
15. Charles, M.P., et al., *Ventilator-associated pneumonia.* Australas Med J, 2014. **7**(8): p. 334-44.
16. Cocanour, C.S., et al., *Cost of a ventilator-associated pneumonia in a shock trauma intensive care unit.* Surg Infect (Larchmt), 2005. **6**(1): p. 65-72.
17. Inweregbu, K., J. Dave, and A. Pittard, *Nosocomial infections.* Continuing Education in Anaesthesia Critical Care & Pain, 2005. **5**(1): p. 14-17.
18. Association, A.H. *Fast Facts on U.S. Hospitals, 2020*. 2018 [cited 2020 4/14/2020]; The American Hospital Association conducts an annual survey of hospitals in the United States. The data below, published in 2020, are a sample from the 2018 AHA Annual Survey (FY 2018).]. Available from: https://www.aha.org/statistics/fast-facts-us-hospitals.
19. Vespa, J. *The U.S. Joins Other Countries With Large Aging Populations*. 2018; Available from: http://hispanicad.com/agency/research/us-joins-other-countries-large-aging-populations.