Differentiating Acute Otitis Media (AOM) from Otitis Media with Effusion (OME) using the Autofluorescence of Neutrophils

(Technical Paper)

In the Context of Antibiotic Resistance, How does the Placebo Effect Impact Antibiotic Overprescription in the United States?

(STS Paper)

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

By
Caroline Anderson

December 6, 2022

Technical Team Members:
Layth Popp
Esha Tulsian
Dreyden Wedertz

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

ADVISORS

William Guilford, PhD, Department of Biomedical Engineering

Bryn E. Seabrook, PhD, Department of Engineering and Society

Introduction

"The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted." These are the words of Alexander Fleming spoken in a 1945 interview, shortly after he had been awarded the Nobel Prize in Medicine for his discovery of penicillin, the first antibiotic (Drexler, 2019). The "evil" Fleming alludes to, which is nowadays referred to as antibiotic resistance, is a phenomenon where bacteria evolve in response to antibiotic exposure, resulting in bacterial strains that are no longer responsive to the antibiotics that used to kill them (*Antibiotic Resistance*, 2020). According to the Center for Disease Control and Prevention, antibiotic resistance was the direct cause of 1.27 million deaths worldwide in 2019 (*About Antibiotic Resistance*, 2019). The modern worsening of antibiotic resistance is often attributed to the overuse of antibiotics, specifically the overprescription of antibiotics by medical professionals to patients whose condition does not require them. Overprescription can result from both a patient being misdiagnosed with a condition that is treatable with antibiotics, and a patient receiving antibiotics despite the given diagnosis not indicating antibiotics.

This document includes proposals for two independent projects, which together will aim to reduce antibiotic overprescription by targeting the aforementioned root causes: misdiagnosis and prescription despite medical indications. Otitis media (OM) is one example of a disease that is prone to misdiagnosis and thus overprescription. OM has two primary types, between which there is a 50% misdiagnosis rate among general practitioners (Pichichero & Poole, 2001). The technical project will focus on addressing misdiagnosis by designing an attachment to the traditional otoscope that enables infection detection by visual contrast. The STS project will focus on the patient prescriber interactions that lead to antibiotic prescription in cases where they

are not medically indicated by assessing how the social construct of the placebo effect impacts antibiotic overprescription. Together, the two deliverables will aim to holistically address the issue of antibiotic overprescription.

Differential Diagnosis of Otitis Media Using Autofluorescence

OM is one of the most common childhood illnesses worldwide, and is the leading cause of pediatric hearing loss (Schilder et al., 2016). The two primary subtypes of OM are acute otitis media (AOM), which is characterized by an accumulation of infected middle ear fluid (MEF), and otitis media with effusion (OME), which is a mechanical malfunction that inhibits MEF drainage. The goal of this technical project is to improve diagnostic standards of care by identifying a measurable biological marker present in MEF that can noninvasively be used to differentiate AOM and OME.

Neutrophils are a subtype of white blood cells that migrate to sites of inflammation and are known to be found in higher numbers in AOM MEF in comparison to OME MEF (Elbistanli et al., 2017; Nassif et al., 1997). When a neutrophil encounters a pathogen, it will phagocytose it, then neutralize it with reactive oxygen species. The pathway that neutrophils utilize to synthesize reactive oxygen species requires levels of NADPH that are much higher than in other cell lineages (Nguyen et al., 2017). These characteristics, taken together with the autofluorescence of NADPH, makes NADPH a promising biomarker for distinguishing between AOM and OME. However, using NADPH as a biomarker would require a detector that is sensitive enough to accurately measure NADPH at physiologically relevant concentrations (Bauldry et al., 1992). Therefore, the goal of this project is to develop a diagnostic method capable of measuring NADPH autofluorescence levels with a degree of sensitivity that enables differentiation between the concentrations of NADPH found in healthy, AOM, and OME MEF. Our project is divided

into two phases: designing a diagnostic instrument to detect NADPH, and validating and applying the instrument.

The first phase will begin with performing a literature review to establish the exact concentrations of NADPH that are present in the MEF of healthy, AOM and OME patients. The literature NADPH concentrations will then be used, in conjunction with the known parameters of the optical system developed last year by UVA alumni, to determine what autofluorescence values should be expected to obtain from a given concentration. Predicting autofluorescence output measurements may also include refining the arrangement of the optical equipment, and purchasing more sensitive components.

Phase two, validating the model, will entail demonstrating preliminary system functionality through the accuracy of the detection of NADPH concentration in free solution. Previous results from UVA alumni have measured a concentration 10,000-fold larger than the expected concentration. A biologically relevant model will then be developed in order to compare the accuracy of our model in measuring NADPH within a neutrophil suspension to its ability to measure NADPH in a free solution.

Through the design of a diagnostic method that takes advantage of the autofluorescence of NADPH, it is expected that the differentiation of AOM and OME among medical professionals will increase in accuracy. Current diagnostic techniques are incapable of accurately differentiating between an infected and non-infected fluid-filled ear. Using NADPH as an indicator of disease will lead to a reduction in misdiagnosed cases, unnecessary surgeries, and prescriptions. Once the developed instrument proves that NADPH can be used as a marker to detect concentrations of neutrophils, new research will develop in an attempt to reduce the size of the electronics to fit inside a handheld model. Having a device capable of detecting

concentrations of neutrophils will allow a physician to rule fluid as "infected" or not for more accurate diagnoses.

The Placebo Effect in Antibiotic Overprescription

In 2020, a study conducted by researchers at Johns Hopkins School of Medicine found that patient demand for antibiotics is the singular most common reason physicians cite for why they prescribe antibiotics that they know are not medically indicated (Kohut et al., 2020). Despite ample research on how the physician can "approach" such patients, there is a lack of research dedicated to exploring why patients make such requests, and why physicians grant them. The placebo effect describes the phenomenon wherein a patient perceives a positive health outcome from a treatment that was designed to confer no therapeutic benefit, due to the patient's anticipation that an intervention will help (*Placebo Effect*, 2021). It has been suggested that the placebo effect plays a role in antibiotic overprescription in the form of action bias: even if a patient knows that an antibiotic will not help their condition, the patient may feel that the action of taking the antibiotic will aid in their healing (Thorpe et al., 2020).

Employing the Framework of the Social Construction of Technology

The theoretical framework that will be employed in this paper is the social construction of technology (SCOT), which argues that social constructions shape technological development. Sociologist Trevor Pinch and philosopher Wiebe Bijker are credited with developing the SCOT framework in the 1980s, and describe the framework as having four main pillars: interpretive flexibility, relevant social groups, closure and stabilization, and wider context (Klein & Kleinman, 2002). According to the principle of interpretive flexibility, the social environment in which a technology is designed has a profound impact on the state of the final design. In the context of antibiotics, analysis of the impact of the social environment of development will begin

with assessing how the design and public perception of antibiotics was shaped by its World War II origins (*Penicillin: Opening the Era of Antibiotics*, 2018). It will be assessed how the rate of production, development of the drug for initially exclusive military use, and current state of the medical field impacted antibiotic development. Further, it will be explored how the initial public perception of penicillin as a "miracle drug" affected antibiotic usage and patient desire for antibiotic prescription in its early years.

Two primary relevant social groups will serve as the focus for analysis: patients and prescribers. The definition of relevant social groups as groups that share a set of meanings attached to an artifact will be used to assess how patients and prescribers perceive antibiotics differently. The identified differences in antibiotic perception between the two groups will inform the analysis of how interaction and negotiation between the groups led to closure and stabilization of the meaning of antibiotics. One criticism of the SCOT framework is that it does not account for power differentials; relevant social groups may not possess the same amount or type of power in impacting closure and stabilization (Klein & Kleinman, 2002). This will be kept in mind as the process of stabilization is considered, particularly taking into account the power patients and physicians have over each other in a free market healthcare system. In this way, the SCOT framework will structure a history and relations based analysis of how the construct of the placebo effect shapes the meaning and use of antibiotics as a technology.

Research Questions and Methods

Research Question: In the Context of Antibiotic Resistance, How does the Placebo Effect Impact Antibiotic Overprescription in the United States?

Documentary resources and discourse analysis will be the primary methodologies utilized to answer the above research question. Employing the framework of SCOT will require research

into the history of the development of antibiotics to understand the social context in which they were developed, as well as research into the views and contributions of relevant social groups. Documentary resources in the form of survey papers on the history of antibiotic usage, physician surveys on prescribing habits, physician interviews on the impact and perception of patient requests for antibiotics, and academic papers on the psychological factors at play in the patient prescriber interaction will all be instrumental in achieving this end. Sources will be drawn from PubMed and other peer reviewed databases, and studies published after 2000 will be favored to ensure conclusions are drawn based upon modern conditions and leading theories. Key search words and phrases will include “patient prescriber interactions”, “patient expectations”, “antibiotic prescription patterns”, “placebo effect in prescription requests” and “action bias in prescription requests”.

To explore relevant social groups and how they contribute to closure, it will also be paramount to put the views of the two primary social groups, physicians and patients, in conversation with each other. Discourse analysis will fill in the gaps left by the documentary resource methodology by allowing for nontraditional sources, which will serve as primary sources on patient perspectives, to be included in analysis. Sources will include the mom Reddit page, blog posts, and public reviews of outpatient primary care offices.

Conclusion

Antibiotic resistance is an urgent public health threat that has become entrenched in our society’s expectations of treatment and recovery. Addressing antibiotic resistance necessitates both ensuring that inaccurate diagnoses do not cause unnecessary antibiotic use, and ensuring that antibiotics are not used in cases where they are known not to be needed. The successful completion of the technical project will result in an otoscopic attachment that aids in differential

diagnosis by non-invasively determining if infection is present. As a result, only cases in which infection is part of the pathology will receive antibiotics, thus lowering unnecessary antibiotic usage. Answering the STS research question will lead to a more nuanced understanding of how the social construction of a placebo effect contributes to patient expectations and desire to be prescribed antibiotics, independent of medical indication. It is the goal that investigating this relationship will reveal ways in which desire for antibiotic prescription can be systematically reduced.

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