

To Resist or Not to Resist? That is the Dangerous Situation: A Look at Antimicrobial Stewardship in Pediatric Care in North America

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Abstract

This article will explore the impact of antibiotic resistance on pediatric care in North America, specifically focusing on how it negatively affects patient health outcomes. The mitigation of this issue in everyday health practice will be outlined. Antibiotics are one of the most commonly prescribed medications in children, with a significant number of them being used inappropriately. Considering the growing global threat of antibiotic resistant superbugs, it is vital to develop strategies and programs for decreasing antibiotic misuse and combating antibiotic resistance. Antimicrobial stewardship is one such method of reducing antibiotic resistance and has already shown evidence of improving patient outcomes, such as decreasing risk of future invasive infections, decreasing hospitalization and decreasing mortality. With more awareness to this dangerous issue, we are beginning to see the development and implementation of a variety of practices aimed at using antibiotics judiciously in pediatric patients across North America. This article will address the severity of the issue of antibiotic resistance in pediatric care in North America and highlight how this can be managed using antimicrobial stewardship principles that are practical, evidence-based and easily implementable in healthcare practices. Although there is still much work to be done, small improvements in resistance rates show that we are moving in the right direction.

Introduction

While the COVID-19 pandemic is on the forefront of most minds, there is another dangerous public health threat lurking in the shadows – the rising resistance of bacteria to available antibacterial agents. Although antibiotics are life-saving medications, their escalating inappropriate use is leading to increased resistance among bacteria.^{1,2} Among children in North America, antibiotics are the most common class of medications that are prescribed.¹ Amoxicillin continues to be the most prescribed medication in children aged 0 to 11 years.¹ Although its usage has decreased by roughly 14% since 2002, there still continues to be over 18 million prescriptions filled each year for amoxicillin.¹ It is estimated that almost a third of these prescriptions are unnecessary, with some prescribed for viral infections (instead of bacterial) and others prescribed for more days than needed to adequately treat the infection.^{1,2} As a result of using antibiotics such as amoxicillin inappropriately, we

are seeing an increasing number of bacteria developing resistance to these agents.^{1,2} In hospitals, there has been a trend of using broad spectrum antibiotics when a patient becomes unstable and the causative organism is unknown.^{1,2} This is giving rise to a new breed of superbugs that cannot be treated with “big gun” agents, leaving us with limited options for treating these organisms.² This problem may be solved with mindful prescribing. Antimicrobial stewardship is the practice of ensuring appropriate use of antimicrobial agents so that they continue to be effective at treating infections and is one way to decrease the alarming rates of infection resistance and superbug development.⁹

The Problem

In hospitalized Canadians, we are seeing a 6.25% risk of developing a bacterial superbug.³ Since 2012, there has

carbapenems, a class of wide spectrum antibiotics often used in hard to treat infections.³ These statistics include pediatric patients, who are specifically noted to have increasing cases of hard to treat *Staphylococcus aureus* and *Enterococcus sp* over the last decade.¹⁵ In a 2014 study from the U.S. Military Health System, MRSA resistance to clindamycin increased from 9.3% to 16.7% in the span of nine years in a pediatric population.⁶ What does this translate to? An increased death toll.¹⁵ Without effective antibiotics, infections can become fatal. For example, MRSA bacteremia in Canada led to 20% of infected patients dying within 30 days between 2014 and 2018.⁴ Mortality rate within 30 days increased to 31% for vancomycin-resistant *Enterococcus* (VRE) bacteremia.⁴ These numbers are a reflection of both adult and pediatric patients, with the rate of increase in deaths from hard to treat infections steeper in pediatrics compared to adults over the last decade.⁴ Pediatric-specific data from the US has demonstrated an increase in VRE infections leading to ICU admissions, with 120 cases per million leading to ICU admissions in 2012 but only 53 cases per million in 1997.^{15,17} In children, we are seeing an alarming rate of antibiotic resistant organisms (AROs) among oncology and transplant patients who would otherwise die without effective antibiotics.¹⁵ Currently, carbapenems are one of the strongest antibiotic groups in North America due to their broad spectrum and relatively low resistance. In a recent study looking at over 87,000 *Pseudomonas aeruginosa* isolates from U.S. children, carbapenem resistance increased from 9.4% to 20% between 1999 and 2012.^{15,18} This is very concerning due to the lack of alternative antibiotics available if resistance becomes common with these “big gun” agents. Overall, we are seeing an increase in MRSA and VRE infections in children and rapidly increasing rates of resistance of bacteria to beta-lactams, fluoroquinolones and macrolides.¹⁵

In 2020, the World Health Organization declared antimicrobial resistance one of the top ten global threats to humanity.^{5,6} If we do not take serious steps to decrease inappropriate use of antibiotics, there may come a time when even the most simple of infections will have significant morbidity and mortality risks.^{6,7,8}

Antimicrobial Stewardship

Antimicrobial stewardship is the practice of using antimicrobials only when necessary and, if used, ensur-

ing their appropriate use.⁹ It goes beyond simply telling prescribers not to use antibiotics and focuses more on principles for how to use them judiciously. Literature has shown that antimicrobial stewardship programs (ASP) are effective at reducing antibiotic overuse and improving patient outcomes.⁹ These outcomes include decreased hospitalizations, decreased ICU admissions, decreased risk of invasive fungal disease, improved quality of life and decreased mortality from hard-to-treat infections.^{9,15,16} As such, several committees have created guidelines on how to implement ASP into daily practice with a focus on pediatric populations.^{9,10,11}

Some important ASP principles are as follows (adapted from the Canadian Pediatric Society and American Academy of Pediatrics’ position papers):^{9,10,11}

1. Avoid the use of antibiotics when a virus is suspected.
2. Consider not treating mild and self-limiting infections.
3. Access to appropriate and timely tests for diagnosis and monitoring should be available.
4. Narrow antibiotics once a causative organism is identified.
5. Avoid treating contaminations, especially with urine and wound samples. Instead, treat if signs and symptoms of an infection are present.
6. Confirm allergies to antibiotics. Sometimes, the “allergy” may be a side effect or intolerance.
7. Optimize dosing and administration of antibiotics. In pediatrics, there is typically a dosing range and prescribers are encouraged to dose at the higher end of the range. Ensure the use of the child’s most recent weight when calculating the dose.
8. Use the shortest recommended duration to treat. Parents should be encouraged to complete the full course, and neither stop early nor continue longer than instructed.
9. Do not switch antibiotics early in the course. It usually takes infections several days to subside.
10. Vaccinations are important! They prevent infections and decrease antimicrobial use overall

Barriers and Areas for Improvements

The principles of antimicrobial stewardship are simple enough and look to be relatively attainable on paper. However, when dealing with people issues are never black and white. In order to have successful programs to decrease the misuse of antibiotics, we need to understand three stakeholder groups: healthcare workers, pharmaceutical companies and patients.

Antibiotics in North America are typically available to patients by prescription, which means a healthcare intervention is needed to access them. As such, healthcare workers require education and support in order to prescribe antibiotics appropriately. If medical professionals lack updated information (for example, access to a regularly updated local antibiogram) and tools to identify the type of infection and/or offending organism, inappropriate prescribing may be the outcome.⁶ Medical professionals may also be under pressure from patients' families to prescribe antibiotics when not needed.⁶ Additionally, lack of infection prevention and control measures in clinics and hospitals may increase the spread of infections.⁶ These factors should be addressed in order to decrease the ever growing number of antibiotic prescriptions being written across North America. Some successful solutions include providing healthcare professionals with a local antibiogram updated at least yearly, improving lab turnaround times for reporting cultures and sensitivities so antimicrobials can be narrowed appropriately, as well as imparting regular reminders of the appropriate use of Personal Protective Equipment (PPE) in healthcare settings.^{6,9,10,11} Since 1987, there have been no major discoveries in the antibiotics drug category and this does not appear to be changing.⁶ With other, more captivating, markets, pharmaceutical companies are not incentivized to pour money into the research and development of novel antibiotics.^{6,7} Most antibiotics that exist today have been isolated from a small sample of ecological niches and taxonomic groups, mostly from *Actinomyces* soil.⁸ Some approaches to combat this may be exploring other niches such as the marine environment, exploring synthetic mechanisms or engineering medications with more than one active agent in order to possess dual target activities.⁸ Groups such as the International

Coalition of Medicines Regulatory Authorities (ICM-RA) are focused on helping pharmaceutical companies prioritize the development of new antibiotics.⁷ This is a start, although more funds and supports may be required to provide pharmaceutical companies with the incentives needed to innovate the antibiotic market.

Patients and their families should understand the dangers of inappropriate use of antimicrobials.⁶ Too often do parents pressure prescribers for an antibiotic to treat their child's viral infection or instruct children to stop taking their antibiotics after a few days as they feel better. Just as prescribers should be educated in principles of antimicrobial stewardship, so should the public. The media should be leveraged to showcase the growing threat that looms due to these superbugs.⁷

Hope for the Future

ASP requires a multidisciplinary approach. We cannot rely on just one group to change the course of this dangerous dilemma. Prescribers, nurses, pharmacists, government agencies, pharmaceutical companies and patients need to work together to first, understand the dangers of antibiotic resistance and second, their role in slowing it down. With new promising evidence, ASP programs may significantly decrease the development of AROs and reduce clinical failures when treating various infections.^{9,10} Although some of these principles may sound elementary, they are vital to combat this issue. Various groups require support in order to easily implement these principles in an already stretched healthcare system. Continuous evaluations of ASP programs are also crucial to ensure they continue to benefit their target populations.

People are beginning to be exposed to the severity and depth of this issue with a number of news and media outlets recently reporting on antibiotic resistance. This is an opportunity for public health and science communicators to use these platforms to reach a wide audience.¹² Social media is another tool that may be used to educate the younger generations. If you go on Twitter™, you will not find a shortage of public health and medical influencers educating society. This should be continued, and encouraged, among our public health, science and healthcare colleagues. And we should move beyond this into other social media platforms in order to keep up with

the communication methods and styles of this new age.¹²

Preliminary data from the past 3 years has already started to show a decrease in bacterial resistance to fluoroquinolones and an increase in *Staphylococcus aureus* being susceptible to penicillin.¹³ IDWeek 2020 also highlighted a variety of accomplishments, showing that we are starting to move in the right direction.¹⁴

Conclusion

In North America, resistance of organisms to available antimicrobials is increasing at an alarming rate. In children, this trend has become even more pronounced in the last decade. With the ongoing high use of antibiotics in pediatric patients, it is important to use them appropriately and judiciously so they continue to be effective. ASP is one solution to this dangerous problem. Through a set of guidelines and principles, this program aims to minimize inappropriate use of antibiotics. Evidence has shown that ASP implementation leads to decreased rates of hard to treat bacteria and improved patient outcomes.

Although ASP is one important method of tackling this problem, it doesn't come without its limitations. First, implementing a good ASP requires a lot of time and resources. The program must be comprehensive, involve various clinicians and stakeholders, be region-specific and must be regularly evaluated and updated. Due to its resource-heavy nature, smaller community hospitals may not be able to implement ASP. If not implemented correctly, ASP can be restrictive and limit healthcare professionals' ability to use clinical judgement when treating infections. Rather, these programs should serve as guidelines and assist prescribers when treating infections. They should not prohibit certain antimicrobials from being used if the prescriber feels they are needed or delay a patient from receiving effective treatment while the prescriber gets "permission" to use an agent. Some programs become over-ambitious and have a long list of guidelines and policies. This is resource-heavy and unnecessary. Moreover, this also makes it hard to analyze which part of the program is working well and which requires refinement. Effective ASP are typically narrow in their focus, with less than 15 interventions to promote appropriate antimicrobial use. Although there is emerging evidence of the benefits of ASP in reducing antimicrobial resistance, this evidence is early, not

robust and may be anecdotal (as the studies may not be sufficiently powered to detect these benefits). Further, evidence has not proven any significant decreases in antimicrobial side effects or length of hospital stay, which is a common quality marker in hospitals.²⁰ More high-quality evidence is required to continue to validate APS in our healthcare system and to turn the skeptics into believers. Other strategies targeting healthcare workers, patients and pharmaceutical companies are also essential to this fight against antimicrobial resistance.

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