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Running Head: PROPHYLATIC ANTIMICROBIAL THERAPY

Prophylactic Antimicrobial Therapy in Children with Hydronephrosis

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Abstract

Objective: The goal of this literature review was to examine the efficacy of prophylactic antimicrobial therapy in children with hydronephrosis.

Methods: Research articles from 2005-2011 were reviewed to identify primary studies on children with documented hydronephrosis. A total of 20 articles met these criteria, however only 10 of these articles were used in this review, focusing specifically on studies, which examined the need for treatment with prophylactic antimicrobial therapy for children with hydronephrosis, or looked at antibiotic resistance patterns in children receiving prophylactic treatment for hydronephrosis.

Results: The literature review revealed conflicting data about the efficacy of prophylactic antimicrobial therapy in preventing infection in children with hydronephrosis. A majority of the studies found that the risk for antibiotic resistance outweighed potential kidney damage and concluded that children with hydronephrosis should be placed on prophylactic antibiotic therapy. However, others concluded that the potential for antibiotic resistance places the child at a higher risk due to the inability to combat infections with the appropriate antibiotics.

Conclusion: Current literature supports the concern about the impact of prophylactic antimicrobial therapy in children but yet, there is not enough evidence-based research to change the current treatment method used for children with hydronephrosis. -Recommendations point to the best treatment for children with hydronephrosis should be to manage each case individually based on the severity of the renal impairment. The various grades of hydronephrosis and the underlying condition should be treated as separate conditions because ultimately they have a different outcome.

Introduction

Hydronephrosis is dilatation of one or both kidneys, and affects 1% to 5% of all pregnancies (Delaney, 2006). It is one of the most common anomalies detected during fetal ultrasound, and with improvement in fetal ultrasound and modern technology, infants are diagnosed at an earlier age than ever before with congenital urological anomalies. Despite early detection, studies have shown that the rates of reoccurring urinary tract infections (UTI) have not changed. This plateau in the rates of UTI's can closely be linked to the fact that current follow up and treatment regimes do not offer health care providers conclusive guidelines for how to uniformly treat infants with varying grades of hydronephrosis (Nguyen et al., 2010). Current clinical practice suggests the use of prophylactic antimicrobial therapy is based upon individual institutional preference and guidelines. Unfortunately insufficient evidence-based data for the treatment of hydronephrosis and the wide range of management and treatment options create inconsistent guidelines between providers in determining the best practice for treatment of children with hydronephrosis and ultimately the best treatment method for these infants.

Identification of the Issue

The renal system is in charge of regulating the body's fluid volume, mineral composition, and acidity through absorption and excretion of water and inorganic electrolytes. It is around the 5th week gestation that a fetus's ureteric buds arise from the posterior portion of the mesonephric ducts (Nguyen, 2010). They grow posteriorly in the sacral portion of the mesoderm, called the metanephric blastema. This complex interaction between the two structures leads to development of the fetal renal system, which is complete just before the 36th week of gestation (Nguyen et al, 2010).

Polyhydramnios and oligohydramnios are directly correlated with antenatal kidney disorders or obstructions, and are one of the most important predictive factors for postnatal pathology (Nguyen et al., 2010). Throughout pregnancy, kidney growth and development can be

monitored through measurement of the kidney and observation of amniotic fluid levels called the amniotic fluid index. Levels resulting in too much fluid, defined as amniotic volume greater than 1500ml is called polyhydramnios; where as fluid volume of less than 500ml is called oligohydramnios (Nguyen et al, 2010). These fluid levels allow providers to recognize the increase in urine production or an inability of the kidneys to properly absorb fluid *in utero*, which increases the risk of postnatal renal anomalies.

Congenital urological defects are often suspected in utero based on fluid levels, but a confirmatory ultrasound of the kidneys and bladder should be performed 48 hours after birth (Lidefelt & Herthelius, 2008). The ultrasound is delayed because of the low glomerular filtration rate and relative oliguria in the newborn period. This lack of urine production may underestimate or misdiagnose the degree of renal dilatation. The ultrasound findings are generally considered abnormal when renal pelvic dilation is >7mm on examination (Lidefelt & Herthelius, 2008). This abnormal urological diagnosis is called hydronephrosis.

Hydronephrosis is defined as the dilation or swelling of the collecting system in one or both kidneys. The collecting system is the structure that collects urine directly from the kidney tissue and routes it through the ureter into the bladder (Delaney, 2006). The dilation occurs when a blockage somewhere in the urinary tract causes urine to back up into the kidneys. In mild cases and even some moderate cases of hydronephrosis, children will have no symptoms and the condition may disappear on its own within the first year of life. In more severe cases, when kidney function is affected the infant or child can experience pain, bleeding, and frequent urinary tract infections. These symptoms may not develop until months or years after hydronephrosis is first detected (Delaney, 2006).

Many methods are currently used to determine the severity of the dilation in hydronephrosis, but in 1993 the Society of Fetal Urology proposed a five-point grading system

based on the appearance of the renal pelvis, calyces, and renal parenchyma (Nguyen et al, 2010). Grade 1 hydronephrosis has normal parenchymal thickness and only renal pelvis splitting, while Grade 4 demonstrates distention of the renal pelvis and calyces in addition to parenchymal thinning (Nguyen et al, 2010). Despite efforts to make the grading system consistent, it is difficult to classify a kidney with calyceal dilation or renal parenchymal thinning. This inconsistency in the grading of the defect is one of the many reasons that treatment methods vary with hydronephrosis, suggesting that providers may unknowingly be treating the same defect differently based on an inaccurate grading system (Nguyen et al., 2010).

Common causes of hydronephrosis include posterior urethral valve, vesicoureteral reflux, and pelvic junction obstruction. Posterior urethral valve is an abnormal flap of tissue in the urethra, which prevents urine from flowing out of the bladder (Lee et al., 2006). Vesicoureteral reflux occurs when the valves, which are located where the ureter attaches to the bladder, fail to close properly and allows urine to back up from the bladder into the kidneys (Lee et al., 2006). Lastly, pelvic junction obstruction consists of various defects, which can cause a blockage where the ureter connects to the kidney. Ultimately the severity and outcome of hydronephrosis is based on the underlying cause of the dilation and the level of difficulty in treating the underlying condition (Lidefelt & Herthelius, 2008).

Maturation and development are the key features in the neonatal period, thus any insults suffered by the kidney during this phase can profoundly affect the structure and function of the kidney. The overarching goal of early detection and treatment for infants with hydronephrosis is to decrease the incidence of complications such as urinary tract infections, kidney stones, or renal dysfunction. Infants and children with hydronephrosis are more at risk for recurrent urinary tract infections, which is defined as two infections in a 6-month period. The increase in

infections can most closely be correlated to urinary stasis in children with hydronephrosis (Seung-Hun & Kim, 2008).

Urinary tract infections are identified as the presence of bacteria in urine, in addition to symptoms of infection (Seung-Hun & Kim, 2008). Infants and young children often have nonlocalizing symptoms, which make early diagnosis and detection difficult. The most common organism of infection is *Escherichia coli*, accounting for approximately 80% of infections. Other pathogens include Staphylococcus and Streptococcus species, a variety of enterobacteria and *Candida albicans* (Seung-Hun & Kim, 2008). Typically, the presence of a single type of bacteria growing at high colony counts is considered a positive urine culture. For clean-catch samples, cultures with greater than 100,000 colony forming units/mL of one type of bacteria indicates infection (Seung-Hun & Kim, 2008).

Renal parenchymal infection and scarring are well-defined complications secondary to infections of the upper urinary tract in children. This type of infection is called pyelonephritis, and can lead to renal insufficiency, hypertension, scarring, and renal failure. Parenchymal scarring develops in 10 to 15 percent of children with UTIs (Lee et al., 2006). Children less than one year of age with a UTI are at much greater risk for renal scarring than older children. Each subsequent episode of pyelonephritis increases the child's risk for more scarring and future kidney damage (Seung-Hun & Kim, 2008).

It has been previously recommended that children who are considered at risk for recurrent UTI's should receive prophylactic antibiotic treatment (Koyle & Caldamone, 2007). The aim of the treatment is to provide sufficient levels of antimicrobial agent in the bladder, to prevent bacterial multiplication resulting in infection. Various recent studies support as well as refute the effectiveness and need for prophylactic antibiotic therapy. Although antimicrobial therapy has been recommended empirically, there is currently no data available to suggest that

antimicrobial therapy has a better outcome in infants with congenital hydronephrosis compared to those without (Koyle & Caldamone, 2007).

The World Health Organization has discussed antibiotic resistance as one of the world's most pressing problems (WHO, 2011). Since the introduction of antibiotics in the 1940's, misuse and overuse of antibiotics has accelerated the spread of bacterial resistance. One of the main ways in which bacteria becomes resistant to antibiotics is by developing beta-lactamase enzymes. Certain antibiotics such as penicillin and cephalosporin's have a four-atom beta lactam ring structure that kills bacteria. Bacteria with beta lactamase enzymes break this ring open and deactivate the antibiotic (Nguyen et al, 2010). This resistance complicates the treatment of patients who become infected with an antibiotic resistance organism (Koyle & Caldamone, 2007).

As a primary care provider, one must question the appropriateness and effectiveness of placing a child with hydronephrosis on prophylactic antimicrobial therapy while factoring in the child's risk for future antibiotic resistance. In addition, a consensus for treatment or evidence-based guidelines for treatments would promote better consistency in assuring positive outcomes for children with hydronephrosis.

Literature Review

A review of the literature was performed using OVID, CINDHAL, PubMed, and the Cochrane library database searching for articles after 2005 that related to the keywords hydronephrosis, prenatal hydronephrosis, postnatal hydronephrosis, prophylactic antibiotics, and prophylactic antibiotic resistance. Reference lists of the research articles and reviews were searched to ensure all appropriate articles were discovered. While a total of 20 articles were

obtained as potentially relevant, only 10 were used in this review because they contained specific pertinent information that met the criteria for the search.

Seven of 10 articles first discussed the diagnosis and grading of hydronephrosis. These studies revealed that early diagnosis was beneficial to the positive outcome for the urological condition, yet Song, Lee, Park, & Kim (2006) and Nguyen et al (2010) both drew upon the points that there has not been a change in the outcome of patients with hydronephrosis despite early diagnosis. Nguyen et al (2010) review of the literature included an in-depth examination of 410 articles, and correlated this stagnation to the inconsistency in provider practice associated with the lack of comprehensive prospective studies that correlate pathology with varying degrees of hydronephrosis. Lee et al. (2006) found major variations in the method of screening and diagnostic follow-up. Their logistical regression of the data demonstrated significant variability in the timing of the postnatal ultrasound, which can significantly change indicators of the diagnosis. Ultimately they suggested that because of various external factors, providers grade hydronephrosis differently, which affects consistent treatment.

Seven articles focused on the various treatment plans for hydronephrosis. Six of the seven articles concluded that there were an inadequate number of prospective studies confirming the need for prophylactic antimicrobial therapy, yet the risks of long-term antibiotic use outweighs the risk for recurrent UTI's (Lee et al., 2006). Song et al (2007) performed a retrospective study of 105 patients diagnosed with hydronephrosis between 1995-2005. They specifically looked at UTI rates in patients with grade III-IV hydronephrosis, and concluded that 36.2% (38 patients) developed UTI occurring mostly (92.8%) before 6 months of age. Seung-Hun & Kim (2008) determined that recurrent UTIs are observed in 30-50% of children with hydronephrosis after their first urinary tract infection, using the diagnosis criteria of greater than 100,000 colony forming units/mL in a clean catch specimen of the urine. This elevated risk is the

reason that Seung-Hun & Kim (2008) recommend prophylactic antimicrobial therapy in children that are considered at risk for recurrent UTIs and potential scarring.

Nguyen et al. (2010) recommended antimicrobial use for children with “moderate” hydronephrosis, yet fail to discuss what they defined as “moderate”. Of the 410 studies reviewed by Nguyen et al (2010), none were prospective randomized trials between antibiotics and no antibiotics in children with hydronephrosis; therefore the efficacy of prophylactic antimicrobial therapy cannot be proven. Alconcher and Tombesi (2005) similarly reported no statistical difference in the incidence of UTI in children with hydronephrosis while taking the antibiotics compared to those that were not. In addition, Nguyen et al (2010) acknowledged the high rates of urinary tract infections in children receiving antimicrobial therapy for hydronephrosis.

Lidefelt, & Herthelius (2008) suggested that the number of infections was lower when children were placed on prophylactic antimicrobial therapy, but several children still did get a urinary tract infection. The research study followed 106 infants over two years, diagnosed at birth with various grades of hydronephrosis. At birth, all infants were given prophylactic antibiotic called Trimethoprim 1 mg/kg/day, and UTI rates were monitored. The study concluded that long-term prophylaxis couldn't be recommended in this case because 50% of the newborns studied with hydronephrosis ran the same risk of developing UTIs as the normal population (Lidefelt, & Herthelius, 2008). A weakness in the research study is that the statistical significance of the results was not discussed, creating opportunity for error or coincidence in the findings. Ultimately the authors felt that newborns with hydronephrosis should be carefully examined by ultrasound postnatally to determine the severity of their anomaly and treated accordingly (Lidefelt, & Herthelius, 2008).

Four of the articles reviewed raised the concern for antibiotic resistance; when children were placed on prophylactic antimicrobial therapy. Landhani and Gransden (2005) performed a

5-year retrospective study to identify organisms isolated from the urinary tract in their sample population, of 2815 healthy children and 1314 children with underlying renal disorders. The children with varying degrees of renal impairment were placed on prophylactic antibiotic therapy while those with normal function were not. The study found that the isolates from the children with the underlying renal disorder were generally more resistant to commonly used antibiotics compared to those of healthy children who were only treated with antibiotics for common childhood illnesses. Specifically Trimethoprim resistance increased from 24.1% to 31.6% in the community group (chi squared for trend= 4.1, p= 0.04). The increase in trimethoprim resistance was much great in children with underlying renal problems from 37.4% to 62.5% (chi squared for trend = 17.9, p <0.0001). In this same population, resistance to Cefuroxime (chi squared for trend= 13.4%, p<0.001) and Gentamicin (chi squared for trend = 5.4, p= 0.02) both gradually increased over a 5-year period. This study reiterates the concern of children receiving prophylactic antimicrobial therapy, as this article found the high-risk population of children was more resistant to antibiotics.

Cheng et al (2010) reviewed data retrospectively from children diagnosis with vesicoureteral reflux in two hospitals during a five-year follow up period. The authors specifically looked at 324 children in one hospital, and 99 children in another hospital who were treated prophylactically with the antibiotics co-trimoxazol, cephalexin, or cefaclor. A χ^2 analysis was used to assess the differences in recurrence rates between groups and changes in the frequency of bacterial resistance with each regimen. Groups were analyzed with calculations of RRs and 95% confidence intervals. *P* values of <0.05 were considered to be statistically significant. The study determined that the children receiving cephalosporin prophylactically were more resistant to multi-drug resistant uropathogens than healthy children (CI 95%, p<0.0001). By limiting the options for antibiotic therapy, the child is at risk for more severe

infections in the future when antibiotic treatment is essential. These antibiotic-resistant bacteria can quickly spread to the child's family members, schoolmates, and co-workers, which in turn creates risk for the community with a new strain of infectious disease that is more difficult to cure and more expensive to treat (Cheng et al., 2010).

A study by Koyle and Caldamone (2007) analyzed current data and found that 30-50% of children with hydronephrosis treated with prophylactic antimicrobial therapy will have a urinary tract infection within 5 years of initial diagnosis. They performed a clinical comparison of urinary tract infections rates in children receiving prophylactic antibiotic therapy versus those not receiving therapy, the results revealed similar rates of urinary tract infections in both groups (12.9 vs. 1.7%, $p= 0.0291$). Despite this evidence, Koyle and Caldamone (2007) concluded that prophylactic antibiotic therapy is recommended for most children with hydronephrosis, because of the lack of credible data to refute this existing practice. The study addressed that current clinical guidelines should be revisited to include evidence based research. But despite the potential for development of antibiotic resistance due to overutilization and patient noncompliance, it was found to be more beneficial to prophylactically treat patients than not.

Two research studies suggested symptoms management as an approach to treatment of hydronephrosis. Lee et al (2006) and Lidfelt and Herthelius (2008) discussed the long-term implications of hydronephrosis: grades I-II often times resolves independently and grades III-IV hydronephrosis requiring long term or surgical treatment. By managing the child's symptoms of an active urinary tract infection, it could potentially decrease the child's exposure to unnecessary antibiotics. They conclude that primary care providers are equipped to manage children with mild hydronephrosis but those children with grade III-IV should be referred to a nephrologist. This is because of the close monitoring need for additional problems that could potentially be correlated with severe renal disease, and the likelihood of the child needing surgical repair to

correct the underlying disorder (Lee et al, 2006). By allowing the specialist to create a treatment plan, it could create more consistency in patient management to determine the need for prophylactic therapy, as well as monitor the child more closely with frequent renal ultrasounds.

Discussion of the Findings

The current literature was summarized and general recommendations were developed based on current clinical evidence to offer guidance to primary care providers when treating patients with hydronephrosis. As a primary care provider, the inconsistency within research and between current research articles makes it difficult to determine when to place a child with hydronephrosis on prophylactic antimicrobial therapy. Ultimately the literature review determined that there is no current guideline for providers to use when treating patients with this common renal disorder. The only consistency between researchers is that their needs to be more evidence based, prospective research studies to determine the best treatment plan for children with grade I-IV hydronephrosis.

All of the studies concluded that children with hydronephrosis were more at risk for urinary tract infections and pyelonephritis because of the their illness. The authors also agreed that multiple urological infections could leave the children at risk for long-term kidney damage. Six of the ten studies found that the risk for antibiotic resistance outweighed the potential kidney damage; thus concluding that children with hydronephrosis should be placed on prophylactic antibiotic therapy. Nearly half of the studies concluded that the potential for antibiotic resistance places the child at high risk due to the potential for antibiotic resistance. In addition, these studies concluded that children should not be placed on prophylactic therapy or antibiotic therapy should be determined individually based on the severity of renal impairment. Of these four articles, three suggest that children with grade III-IV hydronephrosis are more appropriate candidates for prophylactic therapy.

The inconsistency of treatment regimes found in the studies evaluated creates confusion not only within the healthcare community, but also for families coping with this new diagnosis. Many times families searching to understand a new medical diagnosis will look to researching the topic on their own. Their search may cause confusion because of the inconsistency within the medical community as to the best method of treatment. Lack of consistent information will create an opportunity for primary care providers to educate and counsel families as to the best treatment plan, while alleviating fears and anxiety for the family. As providers, it is important to discuss current research with each family and allow them to play a role in the determination of the treatment for their child. An editorial by Delaney (2005) suggests a good alternative to prophylactic treatment is to educate families of signs and symptoms of UTI, so as to ensure that children be seen in clinic at the first sign of a urinary tract infection to start proper treatment. Modern medicine has created a multitude of options for medical treatment, so it is crucial to encourage families to participate in their child's care to provide the best opportunity for positive outcome.

Current treatment recommendations allow the decision to use prophylactic antibiotic therapy in children with hydronephrosis, to each individual provider. Yet the inconsistencies in treatment could leave one wondering if it should be a provider decision, and what role our government plays in the determination of the treatment. As noted, the World Health Organization has discussed antibiotic resistance as one of the world's most pressing problems, because most types of bacteria become stronger and less responsive to antibiotic treatment when they are used incorrectly or unnecessarily (WHO, 2011). These antibiotic-resistant bacteria can disperse to infect family members, co-workers, and other members of the community. This resistant bacteria threatens the community with a new strain of infectious disease that is more difficult to cure and more expensive to treat. Understanding the role these resistant bacteria play

both financially and medically within our local and global communities, one must question the role our government should play in preventing this spread and monitoring antibiotic use.

Recommendations for Practice

The lack of consistent guidelines for treatment of children with hydronephrosis creates an opportunity for the nurse practitioner to create change within the health care community that will impact future practice areas. Treatment of hydronephrosis is an area within our healthcare system that requires further research to determine best practice. Seventy percent of studies reviewed discussed concern about the impact of prophylactic antimicrobial therapy in children, yet there is not enough evidence-based research to dictate a change in the current standard of practice used to treat children with hydronephrosis. Despite the inconsistent and confusing options for treatment, it is the role of the primary care provider to promote effective and safe management in all aspects of a patients' care. Health care providers can help families navigate through the healthcare system to receive the best treatment options for their child.

Based on the literature review, treatment for children with hydronephrosis would best be managed individually based on the severity of the renal impairment. Children with Grade 4 hydronephrosis who have distention of the renal pelvis and calyces in addition to parenchymal thinning are at a much higher risk for urinary tract infections than children with Grade 1 hydronephrosis who has normal parenchymal thickness and only renal pelvis splitting. The various grades of hydronephrosis and the underlying condition should be treated as separate conditions because ultimately they have a different outcome.

It is important as primary care providers to use outside resources, such as nephrologists or other specialists to help determine the best treatment plan for each individual case. The literature review also points to the need for further research investigation into the use of prophylactic antibiotics for all patients with hydronephrosis. It is important that this topic is

studied further, because each prescription of antibiotics has the opportunity to affect not only the patient but also the community as a whole.

Internet Resources

1. Pub Med Health: Upon searching this topic on the Internet, this is the first website that is present on the topic of hydronephrosis. They gave a very brief, yet thorough and accurate description of the disorder, symptoms, and treatment options. It was easy to comprehend, as it was written in language one can understand without medical background.
2. Mayo Clinic Health Library: Is a reputable resource to offer families, as the website offers a good description of what the disease process was, teaching points/patient education. It was limited in that it gave a vague description about the “treatment depending upon the cause and the severity of the obstruction”. This site is recommended for people looking to understand more about the diagnosis.
3. Up to Date: Up to Date is a great resource for providers looking to understand a disease about which they have little knowledge. It is not free, and the cost ranges from \$200-500 for a subscription. Generally this site is not recommended to the general public. It discusses in great depth the pathology, symptoms, diagnosis and treatment options for children with hydronephrosis, yet could be too technical in medical terminology.

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