Screening asymptomatic siblings for vesicoureteral reflux: sound science or religious rhetoric?

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Introduction: *Many urologists endorse the concept of screening asymptomatic siblings of children known to have vesicoureteral reflux. Others oppose screening until there is better evidence to justify the cost and potential morbidity of adopting a widespread screening program.*

Methods: *A literature review of the following topics was carried out: 1) screening programs in general; 2) reflux in general; 3) familial reflux; and 4) screening for familial reflux.*

Results: *The evidence supporting our traditional surgical and medical management strategies for reflux is weak. The evidence supporting screening is lacking. Public Health organizations do not address the issue of screening for this condition. Despite this, there is a significant body of peer reviewed literature and compelling expert opinion, in support of screening. Possible reasons for this are explored.*

Conclusions: *A randomized controlled trial to definitively assess the utility of screening would be larger and more challenging to perform than any ever done in the history of this condition. Until such time that high quality evidence exists, screening of asymptomatic siblings will continue to be based upon our individual clinical experience and teachings, the morbidity of the index case, and socioeconomic factors. We must continue to re-evaluate our management strategies for this condition in light of new information as it accrues.*

Key Words: vesicoureteral reflux, screening programs, evidence based medicine

Introduction

Many pediatric urologists in North America believe that screening asymptomatic siblings of children who have been identified with vesicoureteral reflux following febrile urinary infection is a worthwhile endeavor. This is controversial. Some experts believe that there is ample data to support such an approach. Others support screening based on intrinsic beliefs, and still others are strongly opposed to screening until there is better evidence to justify the cost and potential morbidity of adopting widespread screening. We review the current evidence and beliefs. We have approached this controversial topic according to four categories:

1. Screening programs in general
2. Reflux in general
3. Familial reflux
4. Screening for familial reflux

This manuscript should be regarded as an evidence based opinion piece. The authors have been deliberately provocative.

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Screening programs in general

All screening programs do some harm

Whether patients undergo a urethral catheterization for a voiding cystourethrogram (VCUG), a venous puncture to measure prostate specific antigen or the potential radiation harm from a screening CT scan,

screening requires an intervention with potential harmful consequences. The emotional impact on patients is another form of potential harm.

Some screening programs do some good

Overall, it is agreed that screening benefits selected groups of patients who are at increased risk for breast cancer, familial colon cancer, and cervical cancer.[1]

Some screening programs do more harm than good

If a screening program requires expensive, invasive testing with a low yield, and questionable health benefits it likely does more harm than good.

Some screening programs do more good than harm

The ideal screening program does more good than harm at a reasonable cost.[2] This cost can be measured in terms of money spent, time required, health care resources consumed and in terms of the emotional resources of patients and their families.

Screening programs should be potentially endorsed only if the following general criteria are met:[3,4]

1. There is a greater prevalence and severity of the condition in the population screened in comparison to the general population. (i.e. high pre-test probability)
2. An available and appropriate screening test exists.
3. There is a significant burden if the condition goes untreated.
4. The screening program can be shown to improve the outcome of the condition in question.

As we have heard regarding the high profile debates that surround screening for prostate cancer and breast cancer, it is often difficult to prove that these criteria are satisfied. What of screening for vesicoureteral reflux?

Reflux in general

Reflux is one of the founding pillars of the subspecialty of pediatric urology. It is the most common inherited anomaly of the genitourinary tract.[5] The relationship between reflux and pyelonephritis was first described in paraplegics by Hutch in 1952.[6] We now know that Dr. Hutch's findings represented observations on secondary reflux as a result of high bladder storage pressures. Today we know that primary reflux is a common finding in young children who present with febrile urinary infections. The younger the child, the more likely it will be found.[7] Our best estimates are that it has a low prevalence in otherwise healthy children, although there are few studies looking at VCUG's in healthy asymptomatic children.[5,8,9]

Our management of reflux is based on 4 time-honored premises:[10]

1. Reflux predisposes to pyelonephritis.
2. Renal scarring is secondary to reflux plus infection.
3. Antibiotic prophylaxis prevents infection and scarring until the reflux either resolves or it is surgically corrected.
4. Treating children with antibiotics after diagnosing pyelonephritis is inferior to antibiotic prophylaxis in terms of renal preservation.

Unfortunately these four premises are very difficult to prove. In fact, recent studies have suggested that looking for reflux, even in children who present with febrile urinary infection, may not be a clinically worthwhile endeavor. For example, the group at Great Ormond Street Hospital in London, England published a meta-analysis of 12 studies involving over 1000 kidneys in children who presented with pyelonephritis. Their data suggested that reflux is neither sufficient, nor is it essential for the development of renal damage in the presence of a febrile urinary tract infection.[11] Other authors have questioned whether reflux in fact really predisposes to renal scarring at all. What available literature there is suggests that DMSA detected renal scars after a presentation with acute pyelonephritis occur at a similar rate in children who are subsequently found to have reflux as they do in those without the condition.[12] Although we have all been taught that antibiotic prophylaxis reliably prevents urinary infection, there is scant data to support this time-honored urological practice. A recent systematic review of existing randomized controlled trials revealed considerable uncertainty about whether long-term low-dose antibiotic use prevents urinary infection in children. Well-designed randomized placebo controlled trials are still required to evaluate this commonly used intervention.[13]

Granted these opinions represent the conservative end of a spectrum regarding the investigation and management of reflux. Nonetheless, they come from reputable institutions, published in high impact journals. If there is skepticism regarding the utility of investigating children for reflux when they present with urinary infection, it is difficult to argue convincingly for screening asymptomatic children.

Common clinical questions

QUESTION #1: "IS PROPHYLAXIS SAFE DOCTOR?"

Answer: "Yes I think so…. I mean we have been doing this for over 40 years now!"

Parents are increasingly reluctant to put their children on long-term low dose prophylaxis. They are concerned about the emergence of resistant strains of bacteria and the long-term side effects of antibiotics. They worry that their child might become "immune". These fears are not entirely groundless. For example, Allen et al examined over 1600 urinary isolates in just under 1000 children with urinary infection at the Children's Hospital of Eastern Ontario.[14] Bacterial resistance rates to commonly used antibiotics, such as Ampicillin, Cotrimoxazole or both, were upwards of 30%-40%. The children most at risk for having resistant isolates were those who had been on prophylaxis for urinary tract infection with an odds ratio of 24:1. This is not an isolated study. Other authors have shown that the long-term use of antibiotics places selective pressure on endogenous flora and promotes emergence of resistant bacteria.[15,16]

Recently, epidemiologists in Washington State looked at the impact of long-term antibiotic use in a large case control study of over 10000 women subscribing to a health maintenance organization (HMO).[17] The antibiotic prescription patterns of over 2200 women with primary invasive breast cancer were compared to nearly 8000 randomly selected female controls who were also health plan members. Increasing cumulative days of antibiotic use registered within the HMO were associated with an increased risk of breast cancer. The authors concluded that use of antibiotics in adult females is associated with increased risk of incident and fatal breast cancer. There is also emerging evidence that long-term antibiotic use may increase the severity of otitis media in children, and frequency of upper respiratory tract infections in adults.[18,19] While one should not confuse correlation with causality, these findings do reinforce the need for prudent long-term use of antibiotics.

Parents are aware of this sort of information. They acquire it from the internet. They want reassurance that long-term antibiotic use is unequivocally safe. Currently, we don't have the evidence to do this.

QUESTION #2: "CAN'T WE JUST STOP THE PROPHYLAXIS AND SEE WHAT HAPPENS?"

Answer: "Perhaps when your child is no longer at risk for pyelonephritis and kidney damage regardless of the status of the reflux".

More and more parents are requesting a "trial of life" for their child with reflux. In other words, after a period of antibiotic prophylaxis in well children, they'd like to see what happens when we stop the medicine. Typically this refers to children with low to moderate grades of reflux, and morphologically normal kidneys, older girls with normal voiding function, or perhaps the antenatally detected boy who has never had a urinary infection. Pediatric urologists recognize that the data supporting this approach is limited. There are currently only three published studies detailing the benign outcome of children who have had antibiotic withdrawal in the face of known persistent reflux.[20-22] All of these are retrospective studies on older children with normal voiding function and low to moderate grades of reflux. At this time these findings should not be generalized to all children with reflux without careful consideration and caution.

QUESTION #3: "IS SURGERY BETTER THAN MEDICINE, DOCTOR?"

Answer: "Hard to say".

Whenever assessing management options for reflux, one must be careful to specify what outcomes are being measured. Uncomplicated urinary infection, pyelonephritis, renal scarring, hypertension and end-stage renal disease have at various times, all been assessed in relation to the management of reflux.

There have been only eight published randomized controlled trials involving 859 children with reflux since 1966. A recent meta-analysis of trials comparing antibiotics and surgery for reflux provides less than a ringing endorsement for surgical management.[23] Urinary infection rates at 1, 2 and 5 years of follow up were no different between surgically and medically treated patients. There appears to be no difference in the rates of new scar formation or progressive renal damage after 5 years under each management strategy. The only advantage that surgery confers is a 60% reduction in *febrile* UTI's over antibiotic use alone. The authors concluded *"it is uncertain whether the identification and treatment of children with reflux confers clinically important benefit . . . the assumption that reflux is a modifiable renal risk factor is not based on strong evidence from existing randomized controlled trials . . ."* These conclusions underscore the fact that our evidence for current management strategies is weak. Most of our care is based on clinical experience and what we were taught.

Evolutionary phases in our management strategies for reflux[24]

1. In the 1960's and 1970's it was felt that reflux did not occur naturally and therefore all reflux required surgery. If a VCUG demonstrated reflux, an operation was recommended to correct the anatomic defect.
2. Subsequently, owing in large part to the investigative works of Jean Smellie and others,

we learned that children outgrow reflux over time.[25] Therefore, reflux became equated with the use of prophylactic antibiotics and observation in many children until they outgrew the condition. Surgery was reserved for a select group failing this approach.

3. We now believe that only children with reflux who are at risk for pyelonephritis and renal damage actually benefit from surgery. Therefore, reflux presently equates to prophylactic antibiotics and observation in many until an age when the infection risk resolves and then we stop the antibiotics. Controversy surrounds the age at which antibiotic withdrawal is safe. Surgery is reserved for a select few failing this management strategy.
4. There may be a fourth phase in this evolution. Parents won't give antibiotics to their children indefinitely (if at all!). Therefore if reflux can be reliably cured by a non-invasive outpatient procedure such as endoscopic injection therapy, why not avoid the long-term follow up on antibiotics and inject everyone up front at the time of diagnosis? This recent approach is a trend that is both market-driven and patient-driven. For the first time ever there is an FDA and Health Canada approved substance in the form of hyaluronic acid dextranomer (Deflux®). Deflux has been approved in Europe for over 10 years, and in the United States and Canada since 2001. It is easy to inject with low morbidity as a quick outpatient endoscopic procedure. In the United States, Deflux® has been enthusiastically endorsed by urologists. The number of cases of reflux treated in hospitals has increased 143% in the last 3 years.[26] Despite this initial enthusiasm, the jury remains out on whether this will be a lasting cornerstone in the management strategy of reflux.

NIHILISM?

While it could be argued that there are no longer any indications for the surgical correction of reflux, this would be regarded as an extreme view. The authors' own current indications for surgical intervention include the following:

1. Breakthrough febrile urinary infections while on prophylactic antibiotics.
2. A failed trial of conservative management with persistent high-grade reflux in a patient with demonstrable renal jeopardy (e.g. renal scarring, decreased GFR, solitary kidney).
3. Non compliance with medications and/or follow up in conjunction with high grade reflux in a patient with demonstrable renal jeopardy (e.g. renal scarring, decreased GFR, solitary kidney).
4. High grade reflux and advanced age at presentation with a febrile UTI.
5. Socioeconomic factors/parental preference.

The last is probably the most compelling indication for surgery. If parents have neither the means nor desire to maintain contact with the health care system because of geography, finances, neglect, or paranoia, we have a low threshold for recommending a surgical approach.

Familial reflux

Like so many aspects of pediatric urology, Mr. Douglas Stevens was a seminal contributor to our understanding of the inheritance of reflux. He was the first to describe the existence of reflux in two sets of twins. The monozygotic twins both had reflux, whereas only one of the dizygotic pair did. He postulated a genetic inheritance pattern.[27] Subsequently, in 1971 a group from Rochester, New York presented a pedigree analysis of 10 affected families to the Society for Pediatric Urology in Chicago. They postulated an autosomal dominant inheritance pattern with incomplete penetrance.[28] Since then there has been a plethora of information published regarding the genetics of familial reflux.[29] Little if any of this data has a direct impact on the day to day practice of urologists, and it remains largely within the realm of basic scientists at this time.

What's been published on familial reflux

If one accesses the Medline search engine, PubMed, and searches using the headings "vesicoureteral reflux and siblings" or "vesicoureteral reflux and familial" from 1975 to 2005 there are 104 hits from the peer reviewed literature over the 30 year time-span.[30] One can see there has been a steady appetite for peer reviewed publications on this topic averaging approximately four publications per year, Figure 1. Most of these studies are small, and are lacking in age stratification of those screened. As a result, the reported incidence of sibling reflux varies widely. Probably the best synopsis of the topic resides in a recent systematic review by Hollowell.[31] Take- home messages included the following:

1. Approximately one third of asymptomatic siblings of refluxers will have the condition if they are screened aggressively.

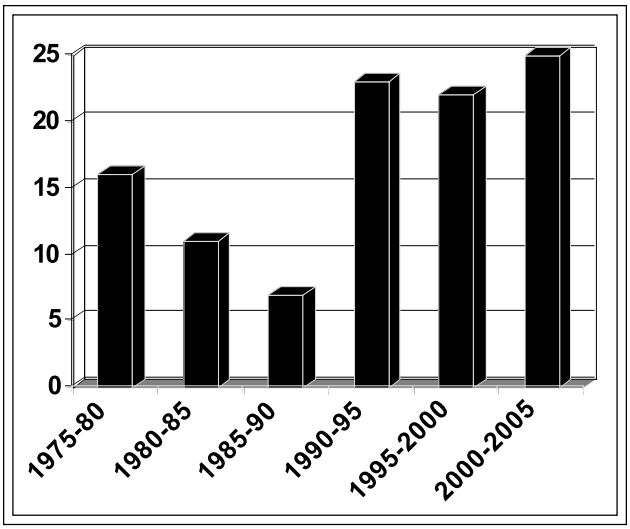

Figure 1. Number of MedLine indexed publications addressing familial reflux in 5 year increments from 1975-2005.

2. The majority of asymptomatic siblings will have low-grade reflux.
3. Sibling age predicts the presence of reflux. It is more common under the age of 2 years and it s extremely rare beyond age 6.
4. If high grade reflux exists in asymptomatic siblings, it is very unusual beyond 1 year of age.

Screening for familial reflux

What the authorities say

If one looks at the Canadian Task Force on Preventative Health Care there is a wealth of information for health care providers, planners and consumers regarding a variety of preventative health interventions using evidence based recommendations.[1] Readers would find if they browse this website that there is discussion on evidence-based vaccination schedules, screening for breast cancer, screening for prostate cancer, and sexually transmitted diseases. Screening for vesicoureteral reflux is not even mentioned. Similarly, in the United Kingdom there exists a national screening committee.[32] England has a variety of screening programs for breast cancer, cervical cancer, cystic fibrosis, as well as some pilot programs for colorectal cancer, diabetes, heart disease and stroke. There is even an antenatal screening subgroup. Nowhere within this organizational structure is there reference to screening asymptomatic family members of known patients with reflux. The Cochrane collaboration is a repository for all of the guidelines, randomized clinical trials, systematic reviews and meta-analyses available in the peer reviewed literature today.[33] The Cochrane Renal Group, a subset of the collaboration is based in Australia. This offers an excellent resource for information on evidence based studies related to urological and nephrological topics.[34] If one accesses the Cochrane database, the reader can confirm the previous statement that in the last 40 years there have been only eight RCT's involving 859 children with vesicoureteral reflux. The focus of these studies was primarily to compare medical and surgical management strategies; none address the issue of screening asymptomatic family members

If one reviews the abstracts of the 104 publications retrieved from MedLine, 41/104 (39%) address the screening of family members. Of these, 38/41 (93%) endorse screening asymptomatic siblings and/or offspring of known refluxers on the unproven assumption that we can prevent renal damage by doing so. If one reviews the current edition of Campbell's Urology, (8th Edition) readers are advised the following: *"…a VCUG is recommended as a (sibling) screening test for reflux in babies and young children, especially those younger than five years of age"*.[5] Interestingly, there is no data provided to support this recommendation.

If one looks at the largest, most current and complete peer reviewed articles examining screening protocols for asymptomatic siblings with reasonable data for analysis some observations can be made.[35-40] Table 1. Authors in these studies generally show that the incidence of reflux in asymptomatic siblings is close to 30%. Generally the incidence of scarring in these siblings is lower than in the index cases who presented with pyelonephritis. Enthusiasts of screening infer that if these siblings had not been screened they would have gone on to develop more scars much like the index cases and, therefore, screening is necessary to prevent this adverse outcome. Scrutiny of this logic, however, suggests several alternative interpretations. For example, the authors may be reporting a form of lead-time bias.[41] Perhaps the asymptomatic siblings are already on a trajectory towards progressive renal damage. Early detection only increases the time to end organ damage and hypertension without altering the natural history. Perhaps the DMSA findings do not represent scarring at all, but rather renal dysplasia, in which case infection or not, reflux or not, the die is already cast. Perhaps the finding of reduced scarring represents a form of length time bias.[41] Screening may only detect indolent, clinically inconsequential, incidental radiographic findings that pose no serious health risk. Perhaps virulent forms of reflux that pose a true risk to kidneys only present with pyelonephritis.

TABLE 1. **Summary of recent MedLine indexed manuscripts examining differential rates of renal DMSA abnormalities between index patients and asymptomatic siblings detected by screening.**

	# screened siblings	% VUR detected	% index scars	% sib scars	Comments/criticisms
Noe 1992	354	34	25	7	Used IVP to diagnose scar Follow up of scars unclear No evidence that screening is affecting the outcome
Bonnin 2001	65	26	50	6	Concluded that screening is not beneficial because adverse outcome is rare
Cascio 2003	226	24	22	7	Cross sectional study, outcome of renal scars found after screening not discussed, recommended RCT to assess the impact of screening
Sweeney 2001			55	33	Heterogeneous patient population including VUR diagnosed based on prenatal U/S and sibling screening Only patients with high grade reflux included
Wan 1996	622	27		14	Cross sectional, descriptive study with no data on outcome of renal scars detected based on sibling screening No statistical analysis provided
Houle 2004	123	36	82	26	Cross sectional study Low number of patients Major statistical flaws and calculation errors No evidence that screening changes the outcome

Potential reasons why urologists might endorse screening for reflux

1. The parents want it.

Parents by nature are anxious about the health of their children. They want to know. There may have been high morbidity associated with the index case. Perhaps the family wants closure. Young families are the most highly mobile segment of our population and they do not want to move from city to city, or job to job with an uncertain health status for their children.

2. Doctors want it.

We believe we can prevent bad outcomes. We believe we can alter the natural history of reflux. Despite the lack of solid evidence to guide us, we have been trained to look for an anatomic explanation for childhood renal infection. Having found a putative reason for infection and knowing that there is an increased prevalence in asymptomatic siblings we believe diagnosing reflux can potentially prevent infection and save renal function.

In some sectors of North America, we are in competition with our peers and we wish to build our practices. We know that if we don't screen the patients for a condition, someone else will. In other words, there is a potential opportunity cost for clinicians who adopt a conservative approach.

3. Industry wants it.

As mentioned, there is a new product for us to inject. Pediatricians, primary care physicians and urologists are being saturated with marketing in support of early endoscopic injection therapy for reflux. Parents are aware of this option. If we can find reflux before it potentially causes infection, and there is a relatively benign and effective correction, why not look for it and treat it?

Towards an evidence-based approach to screening

It is likely that the first two criteria necessary to support screening for reflux exists: there is a greater prevalence of this radiological finding in asymptomatic siblings compared to the population at large, and we believe that the VCUG is a sensitive test. The questions regarding the third and fourth criteria remain unanswered, i.e. does screening for reflux and its subsequent treatment in asymptomatic family members reduce the burden of the disease? In order to answer this important question a randomized controlled trial needs to be performed. We know from most published studies that the incidence of new scar

formation in children who are on a medical and surgical management protocol is about 10% after 5 years of follow up.[42] If one sets out a priori with a reasonable goal of a 50% reduction in renal damage with screening and intervention, a study that is appropriately powered at 0.80 with type 1 error < .05 could be constructed. One would expect that if screening is in fact beneficial there would be at least a 20% scarring rate in the observational arm of individuals detected by screening. Conservative assumptions would include the following: a 10% dropout rate inherent in any study, 85% of families approached would consent to sibling screening, and all of those found to have reflux would accept randomization. This proposed study would require screening 3400 siblings of index cases.[43] Figure 2. Recall that in the last 40 years less than 900 children have been enrolled in randomized controlled trials related to the management of reflux. A study of the magnitude proposed is therefore unlikely to be performed in the near future.

In the absence of evidence to support screening, we look to eminence.[44] The American Academy of Pediatrics section on Urology (AAP) is the august organization to which pediatric urologists belong. This group of individuals has pursued additional post-residency fellowship training in pediatric urology and has focused their practice on the care of childhood urological diseases. These are the experts. A recent practice pattern survey of AAP members was carried out related to reflux.[45] With a 61% response rate, 83% of respondents indicated they screen asymptomatic siblings up to approximately age 10 years.

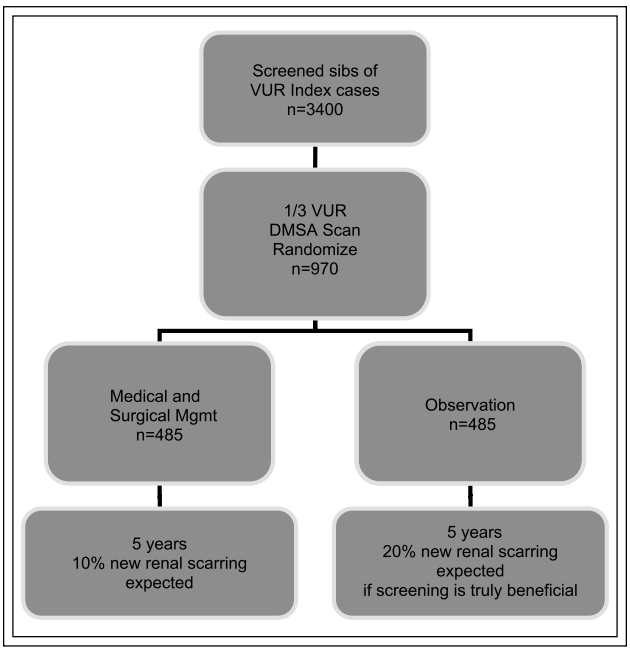

Figure 2. Proposed randomized clinical trial required to answer the question: "Does screening asymptomatic siblings improve renal outcome?" powered at 0.80, p<.05.

So if the published literature recommends that screening is a good thing and eminent experts endorse the same, should we ignore the absence of evidence, and adopt screening whole heartedly? Not necessarily.

Take home message

Some children with reflux have infections. Some children with reflux have no infections. Some children with infections have no reflux. This is because reflux is only one factor related to urinary infection and renal damage. The evidence supporting our traditional management strategies for reflux is weak. The evidence for systematic screening in asymptomatic siblings is lacking. Despite this, screening is endorsed by many North American pediatric urologists and it is criticized by a vocal minority.[46]

Fortunately (or not), medicine is still an art. When evidence to guide us is lacking, we should continue to individualize our approach to patients. Our approach to familial reflux should be a balance between perceived harm and benefit based upon the following variables:

1. Personal experience. The outcomes of patients we see and treat invariably influences our perspective on a particular condition.
2. The morbidity of the index case. Parents and referring physicians will advocate strongly for screening if the index case had a complicated course resulting in recurrent hospitalizations for pyelonephritis and/or renal impairment.
3. Socioeconomic factors. (e.g. parental wishes, your local medical culture, hospital resources and access to care.)

As with all conditions we must continue to re-evaluate our management strategies in light of new information as it accrues. □

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