Correlation not Causation: Looking Back at the History of VUR

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Vesicoureteral reflux (VUR) is a medical condition where urine flows retrograde from the bladder superiorly, and has traditionally been considered a risk factor for kidney damage in children. However, over the past decade and a half, several randomized controlled trials have shown the risk of kidney damage in the presence of VUR is low, and any treatment for VUR does not change that risk. Here, we review the history of VUR as a pathologic condition, how the interpretation of that history led to possibly overestimating the danger, and how current findings should be seen in the context of that history. UROLOGY 193: 231–236, 2024.

BEGINNING OF MODERN ERA

John Hutch, a physician at the VA hospital in Richmond, VA, is generally considered one of the first to regard VUR as a pathologic condition. In a review of men rendered paraplegic in World War II, he stated. "We also believe that reflux is a great destroyer of renal tissue in the later stages of the paraplegic patient".[1] In 1952, he reported the correlation between reflux and renal dysfunction in his series of 55 adult paraplegic patients, of whom 17 required nephrostomies and 2 underwent ureterostomy to preserve renal function.[2]

Hutch cites previous urologists who "have come to regard reflux as a definite danger to the upper urinary tract," and mentions the possible implication of ascending urinary tract infection (UTI), but does not provide—or indeed, aim to provide—direct evidence or a mechanistic explanation other than expert opinion.[2] Rather, his paper aimed to present a new surgical technique for correcting VUR performed on the basis of having already "convinced ourselves" that VUR "constitutes a grave danger to the function of the upper urinary tract".[2]

Thus, in one of the seminal papers where VUR is reported as a pathologic condition, a correlation—reflux in the setting of renal deterioration—was assumed to be a causation. Hutch states, "That reflux is damaging to renal function is illustrated by the fact that of 14 deaths on our paraplegic service due to urologic causes, 9 were due to reflux and its complications".[2] Yet, no further elucidation on the mechanism is given. This is important, given how Hutch's observations about VUR were limited to paraplegic patients with neurogenic lower urinary tract dysfunction (LUTD), patients who today would likely be considered to have secondary reflux due to a high-pressure, low-compliance bladder, the true "cause" of the renal deterioration.

FURTHER INVESTIGATION

The radiologic findings characterizing pyelonephritis presumably caused by VUR were first described by C. John Hodson and David Edwards, who reported the association between "chronic pyelonephritis," and focal renal scarring[3] in their 1960 case series of 20 pediatric and adult patients with reflux on voiding cystourethrogram (VCUG). In some of these patients, VUR was seen initially, then pyelonephritis subsequently developed, though 10 patients had already been diagnosed with chronic pyelonephritis when the diagnosis of VUR was made. The authors concluded that these observations confirmed the close association between VUR and pyelonephritis, and that VUR represented a separate pathologic condition.[3] However, in their discussion, even they conceded that the timing of the reflux is not clearly defined relative to when renal changes occur, and again the issue of correlation versus causation becomes apparent. Regardless the framing of VUR as a strong factor in the development of chronic pyelonephritis and renal scarring that required proactive treatment had begun to cement.

LABORATORY STUDIES

Subsequent clinical and experimental reports further associated VUR to pyelonephritic scarring, seen as radiographic and histologic focal loss of renal parenchyma in the areas of "intrarenal reflux." Yet the question remained whether VUR, infection, or a

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combination of the 2 was responsible for renal scar formation.[4,5] Key pig studies were performed in the 1970s, one of which surgically induced unilateral low- or high-grade reflux and divided animals into infected versus sterile urine subgroups, with each contralateral kidney serving as a control. In pigs with sterile urine, scar formation was not seen in low- or high-pressure reflux systems. When urine was infected, scars were seen in all refluxing kidneys.[6]

Here is where a direct causative mechanism could be imputed, at least in theory. However, the authors astutely pointed out the difficulty of translating findings to the clinical setting. They write:

"The major problem is the rarity with which a pyelonephritic scar is observed in previously unscarred kidneys (in humans) which is necessary for a complete analysis of the possible factors involved. A corollary of this is that most children with vesico-ureteric reflux who are destined to form pyelonephritic scars have already done so by the time of presentation".[6]

Indeed, many previous clinical reports linking VUR and renal damage faced the very same limitation of renal scarring being already present in most children at initiation of the study.[7] Further complicating the ability to extrapolate the findings in pigs were the conditions in which reflux and pyelonephritis were induced, with porcine *Escherichia coli* introduced into the bladder via a wax foreign body (which remained in the bladder), and the infection not treated for up to 4 weeks—not exactly closely mimicking clinical reality.[8]

THE RISE OF ACTIVE TREATMENT

Subsequently, studies of CAP as a means of preventing pyelonephritis and renal scarring in children with a history of UTI began to accumulate. A 1965 report of 116 children on CAP was one of the first to make claims to its efficacy, and found that among those with history of recurrent UTI, annual incidence was 2.4 pre-CAP compared to 0.26 while on CAP.[9] Another series of 119 cases of patients with VUR assessed outcomes of VUR, infection, kidney growth, and scarring in those without treatment, with CAP only, and with surgery and CAP. Authors found that patients with no treatment had worse outcomes, and that infections persist or relapse with treatment but scarring was prevented in over 80% of patients with long-term CAP.[10] Rounding out research in the field at this time, work published by Edwards et al in 1977 showed that VUR spontaneously resolved in almost three-quarters of children on long-term CAP, and that more severe reflux was less likely to disappear.[11]

AN EMERGING PARADIGM

Having determined that VUR was a pathologic condition meriting proactive diagnosis and treatment, though one that could possibly resolve with time, attempts were made, starting in the 1980s, to determine the efficacy of the 2 primary forms of treatment, CAP and anti-reflux surgery. The International Reflux Study (IRS)[12] enrolled patients 10 years of age or younger with a documented UTI and grades III and IV VUR, and randomized them to CAP or anti-reflux surgery, with CAP continued until documented resolution of reflux. No difference was seen between the 2 arms in new renal damage, though pyelonephritis episodes were significantly fewer in the surgical arm.

Similarly, the Birmingham Reflux Study Group[13] randomized children less than 15 years of age with grade III VUR (6 subjects had grade II with renal scarring) to CAP or anti-reflux surgery, and found no difference in rate of recurrent UTI or new renal scarring. The Southwest Pediatric Nephrology Study Group[14] enrolled patients younger than 5 years with grades I-IV VUR and a first documented UTI for treatment with CAP until the reflux resolved. They found higher rates of VUR resolution in the lower grades, and significantly higher rates of new renal scarring in kidneys with dilating (grade III or higher) VUR. With these studies, the idea that CAP was an appropriate first-line treatment for VUR in the setting of UTI, with surgery reserved for those with breakthrough infection, was galvanized. For the next 15 years, no significant challenge to this paradigm would occur.

A RECONSIDERATION

Despite the coalescing of opinion regarding the need for active treatment of VUR, there were those who still asked the question, what if we did nothing? Craig et al[15] noted the lack of change in ESRD rates due to reflux nephropathy in the age of active VUR treatment, suggesting a theory that while VUR was potentially a pathologic condition, all renal damage occurred prenatally, and postnatal interventions accomplished nothing. They called for randomized controlled trials with a no-treatment arm to provide definitive answers on the benefit of intervention.

Garin et al[16] were the first to answer this call. In their study, children between 3 months and 18 years of age with or without VUR (grades I-III) diagnosed with a first febrile UTI were randomized to antibiotic prophylaxis or no treatment and followed for 12 months. Endpoints were rates and types of UTI, and incidence of new renal scarring. The study found no difference between patients with VUR and those without in terms of UTI recurrence rate, pyelonephritis recurrence rate, or renal scarring. They also found no difference in the same parameters between patients receiving CAP and those not receiving it. This was true when comparing subgroups (VUR +/- prophylaxis, no VUR +/- prophylaxis).

Next were a trio of studies published in 2008. Pennesi et al[17] enrolled patients between 1 day and 30 months of age with a first diagnosed pyelonephritis episode and

documented grades II-IV VUR, and randomized them to antibiotic prophylaxis or no treatment, and followed for 4 years. Primary endpoints were recurrence of pyelonephritis, with incidence of renal damage as a secondary endpoint. CAP was not associated with an improved outcome in either endpoint.

Roussey-Kessler et al[18] enrolled children 1 month to 3 years of age with a first febrile UTI and grades I-III VUR to no treatment or prophylaxis for 18 months. No difference was found between control and prophylaxis groups in terms of febrile UTI and overall UTI recurrence, though they did find boys with grade III VUR benefited from CAP. No evaluation of development of renal scar was attempted.

The third study, by Montini et al,[19] enrolled patients 2 months to under 7 years of age with a first febrile UTI. Both patients without VUR as well as those with grades I-III were enrolled. Patients were randomized to CAP or no treatment and followed for 12 months. Primary endpoint was recurrence of febrile UTI, and secondary endpoint was new renal scarring. The authors found no advantage to CAP in any of the subgroups in preventing new febrile UTI, nor in preventing new renal scarring. They did find, however, an increased risk of new febrile UTI in patients with grade III VUR.

Two more studies followed in the next 2 years—the PRIVENT study by Craig et al[20] and the Swedish Reflux Trial in Children, by Brandstrom et al.[21] Craig et al[20] randomized children under 18 years of age with a documented symptomatic UTI to CAP or placebo for 12 months, and found a statistically significant but modest advantage in preventing new UTIs and pyelonephritis in the patients receiving CAP (13% vs 19% and 7% vs 13%, respectively). However, VUR status did not modify these effects. In addition, the authors found no difference in new renal scarring, the rates of which were low. There was a significant increase in resistant organisms in the CAP group compared to placebo.

While the PRIVENT study took all patients under 18 years, the Swedish Reflux Trial in Children specifically focused on children with dilating VUR between 12 and 23 months of age.[21] Most participants were recruited after the first symptomatic UTI and randomized to 1 of 3 arms—CAP, endoscopic anti-reflux surgery, or surveillance—and followed for 2 years. The primary outcomes were recurrent febrile UTI, new renal damage, and VUR status at the end of 2 years. The study authors found an advantage to both prophylaxis and endoscopic therapy in preventing new febrile UTIs as compared to surveillance, though the rates for the last were over double (57%) those found in comparable studies. This advantage did not extend to the prevention of new renal damage, with no statistically significant difference found, though the results did favor treatment versus surveillance (6% vs 12% vs 18% for prophylaxis, anti-reflux surgery, and surveillance respectively).[22]

In 2011, the American Academy of Pediatrics (AAP) released its revised recommendations for a first febrile UTI in children 2 to 24 months of age.[23] Citing the RCTs reviewed above as the basis of its opinion, the AAP recommended against VCUG after the first febrile UTI in the setting of a normal renal ultrasound. While the British National Institute for Health and Care Excellence (NICE) guidelines, released several years earlier and recommending much the same management,[24] did not seem to have much of an effect on practice patterns in younger patients, the AAP recommendations did, with a significant drop in VCUGs performed in this age group after the release of the 2011 guidelines.[25] However, questions about whether CAP prevents UTI recurrence and renal damage still lingered, with the lack of appropriately powered trials the most commonly cited reason.[20]

A DEFINITIVE ANSWER?

In 2014, the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study seemed poised to answer those questions. Specifically, the RIVUR study was designed to compare antibiotic prophylaxis to placebo in preventing new symptomatic UTIs over a 2-year time frame in children from 2 to 71 months of age with a first or second symptomatic UTI and grades I-IV VUR.[26] As secondary outcomes, renal scarring, treatment failure, and antimicrobial resistance were also assessed. The study found a statistically significant advantage in subjects receiving CAP compared to those receiving placebo in the prevention of new symptomatic UTIs. Higher (III-IV) grades of reflux were associated with higher rates of recurrence, though the effect was small (14.3% vs 22.9%, respectively). Renal scarring, however, was not affected by treatment group, either in the setting of total, severe, or new scars.[26]

Based on the RIVUR data, calls were made to revise the AAP guidelines. However, it was noted that arguably the most relevant clinical outcome—renal scarring—had not been affected by CAP, a result in keeping with the findings of the prior RCTs. In addition, the RIVUR study also found that antimicrobial resistance was present in over 3 times the patients in the prophylaxis arm as in the placebo arm, repeating the findings of several earlier studies, and hospitalization and ED visits overall were not affected.

Since the RIVUR study, 2 new studies have been published, largely with similar findings. In 2015, Hari et al[27] randomized children between 1 and 12 years of age with grades I-IV VUR and a first symptomatic UTI to CAP versus placebo, and found an increased risk for recurrent UTI in children receiving CAP, and no difference in renal scarring. Finally, a recent multicenter European study[28] randomizing infants 1 to 5 months of age with no history of UTI and with dilating VUR (theoretically the highest risk population, and the one with potentially the greatest chance at a response) to CAP versus no treatment found a similar impact of CAP on recurrent UTI (though not on febrile UTI) as the

RIVUR trial. Similarly to RIVUR (and every other trial), however, there was no difference in renal scarring.

SLOUCHING TOWARDS A CONSENSUS

Table 1 summarizes the findings of the 9 aforementioned RCTs. While there is at least some evidence that CAP can reduce UTIs (though even this evidence is mixed), there is essentially uniformity in the finding that seems to matter most—no benefit in renal damage. This fact holds true across all grades of VUR and all patient ages. Yet the diagnosis of VUR in asymptomatic children and children with normal kidneys continues. How to explain this? It seems there are several reasons.

Likely some of the persistence is governed by the fear that febrile UTI in the setting of VUR carries too high a risk to simply do nothing. After all, medicine continues to pursue interventions in diseases where we have made little progress in mortality over the years, such as pancreatic cancer.[29]

But VUR is not pancreatic cancer. Based on the available RCTs, the incidence of new renal scarring is low.[16,17,19,20,22,26-28] And even in the highest risk population for which we have long-term data—the 10-year IRS data—the overall risk for poor health outcomes appears to be very low. Out of 252 children followed for a decade, only 1 had a subnormal GFR, and 2 were started on hypertensive medication that they were still taking at study close, one of those being the child with a subnormal GFR at study entry.[30] In a meta-analysis of 20 cohorts, including most of the above-cited RCTs, Toffolo et al[31] found that patients with normal kidneys and a history of UTI have a low risk for decline in renal function - roughly 0.4%. Combine this observation with the significantly increased rates of bacterial resistance in patients receiving CAP, the cumulative effects of VUR and UTI treatment on children,[32] the unchanged rates of ESRD due to reflux nephropathy over the "era" of VUR,[15] as well as the invasiveness of the diagnostic and surgical therapeutic regimen, and an argument can be made that diagnosing and treating VUR in most children is an active harm.

Another rejoinder put forward has been that the relevant studies were not powered adequately to detect a difference in renal damage. This is a hard argument to understand—are we to believe that a difference of less than 1% (the difference in renal scarring in the majority of the studies that did not overtly favor no treatment—see Table 1) is clinically meaningful, and we just need to prove it statistically? Or is the expectation that with larger numbers, that 0.2% difference will become 10%, or 15%, or whatever is clinically significant in the reader's mind? If the latter is the case, that would imply an overall flawed original study (how else to account for such a significant change?) and thus all the findings would have to be abandoned.

An argument has also been put forward that the prevention of pyelonephritis, and its attendant costs both in financial and hardship terms, merits continued diagnosis and treatment of VUR. After all, pediatric UTI-related hospital admissions number in the tens of thousands annually,[33] and in an analysis published in 2010, Spencer et al[34] estimated the average cost of UTI-related hospitalization at over $10,000 per admission, a number that has almost certainly risen in the interim. Clearly, reducing the burden associated with these admissions would be a desirable goal. However, again looking at the results of the RCTs is illustrative—in the aforementioned studies that had hospitalizations and ED visits as an endpoint, no statistically significant difference between groups was found, with observed differences ranging from 2%-5%.[20,26,28] So even with this narrowly defined outcome as the goal, in the highest quality studies, intervention has not been shown to make a difference.

Finally, continued screening for VUR has been advocated for based on the ability to risk stratify—namely the ability to identify those patients most at risk for clinically significant VUR, thus creating a "targeted" approach to diagnosis. This thinking, however, leaves central the belief in the paradigm of VUR + UTI = renal damage. Our position, however, is that this paradigm is wrong, and that, more importantly, the high-quality evidence regarding this paradigm is virtually uniform in its findings that it is wrong. Simply put, there

Table 1. Empty cell indicates no result.

Study	Intervention Decreases All UTI Recurrence	Intervention Decreases Pyelonephritis/ febrile UTI	Absolute Decrease in Recurrence Risk (%)	Intervention Decreases Renal Damage	Difference in Renal Damage Treatment/No Treatment
Garin et al[16]	NO	NO	No decrease	NO	Favored no treatment
Pennesi et al[17]		NO	No decrease	NO	Fewer scars in non-treatment
Roussey-Kessler et al[18]	NO	NO	No decrease		
Montini et al[19]		NO	No decrease	NO	0.8%
Craig et al[20]	YES	YES	6%	NO	1%
Brandstrom et al[22]		YES	38%	NO	12%
Hoberman et al[26]	YES		12%	NO	0.2%
Hari et al[27]	NO		No decrease	NO	0.1%
Morello et al[28]	YES		14%	NO	Favored no treatment

is no risk stratification program that can predict patients in whom intervention will reduce risk of renal damage, because the ability to reduce renal scarring in any population has never been proven. So, again, risk stratification in the setting of VUR has no impact on the finding that matters—renal scarring.

CONCLUSION

The history of the development of VUR as a pathologic condition leading to pyelonephritis and renal damage is one of clinicians faced with the limitations of experimental technique, working as best they can to identify and mitigate a potential danger to children—a higher calling is hard to imagine. Yet, in the light of the recent studies, it can also be seen as demonstration of what happens when correlation is conflated with causation, and the unintended consequences of creating a treatment paradigm that does not incorporate the null hypothesis.

Declaration of Competing Interest

The author declare that they have no conflict of interest.

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