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Vesicoureteral reflux and antibiotic prophylaxis: why cohorts and methodologies matter

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Abstract

Purpose—Published cohorts of children with vesicoureteral reflux placed on antibiotic prophylaxis differ in baseline characteristics and methodology. These data have been combined in meta-analyses to derive treatment recommendations. We analyzed these cohorts in an attempt to understand the disparate outcomes reported.

Materials and Methods—Eighteen studies were identified from 1987 to 2013. These either retrospectively or prospectively evaluated children with VUR who were on long-term antibiotic prophylaxis. The presenting demographic data, criteria and methods of evaluation were tabulated. Outcomes were compared—specifically recurrent urinary infection and renal scarring.

Results—Significant differences in baseline characteristics and methodology were identified: gender, circumcision status, grade of reflux, evaluation of bowel and bladder dysfunction (BBD), methodology of urine collection, definition of urinary infection (UTI), measurement of compliance, means of identifying renal scarring. Cohorts with larger numbers of uncircumcised boys had more breakthrough UTI's. Both infection and renal scarring rates were higher in series with higher grades of reflux. Bagged urine specimens were allowed in 6 series, rendering the data suspect. Children with BBD were excluded from 3 cohorts; only in 1 was BBD correlated with outcome. Compliance was monitored in only 6 studies.

Conclusions—Sub-populations as well as methodologies vary significantly in published series of children with VUR on anti-biotic prophylaxis. It is inappropriate to combine outcome data from these series in a meta-analysis, since this serves to blur distinctions between these sub-populations. Broad recommendations or guidelines based upon meta-analyses should be viewed with caution.

Introduction

The diagnosis and treatment of vesicoureteral reflux (VUR) in children remains an unsettled issue, despite numerous prospective and retrospective studies. Vesicoureteral reflux can be associated with recurrent urinary infection, pyelonephritis and renal scarring. Long term antibiotic prophylaxis has been the mainstay of treatment, based upon studies comparing prophylaxis with anti-reflux surgery. A majority of children with reflux--primarily with lower grades I, II & III—will outgrow the condition and appear at less risk for recurrent infection and renal involvement. Identification of those most at risk remains a challenge and

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no clear methodology exists to definitively segregate those who do not require either medical or surgical intervention. Most recently, meta-analyses which include series comparing long term prophylaxis to no treatment have led to recommendations and guidelines against evaluation of all infants and children after a first urinary infection and against antibiotic prophylaxis for all children discovered to have VUR. [1, 2] Meta-analyses which include the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial come to the opposite conclusion. [3] It may be inappropriate, however, to combine data from disparate studies, since the populations in each cohort differ.

We evaluated series that span 3 decades and represent investigations of diverse populations internationally, evaluating the outcomes of children with VUR on long term antibiotic prophylaxis. The study populations differ from one another in many crucial demographic aspects: age of presentation, grade of VUR, gender distribution, circumcision status. Furthermore, these studies also differ in methodology: definition of urinary infection, standardization of radiographic interpretation, radiographic evaluation of renal scarring, assessment of bowel and bladder dysfunction and compliance with taking medicine. It is possible that the conflicting and muddled conclusions of these studies are due to the underlying differences in study populations and methodology. We examined 18 studies which evaluated the outcome of children on long-term antibiotic prophylaxis, in an attempt to understand the differing outcomes. This is not intended to be a meta-analysis, as the data from these studies is not combined, but rather examined separately.

Materials and Methods

A literature search was performed using the Ovid MEDLINE data base. Eighteen studies were identified from 1974 to 2013. [4–25] These all either retrospectively or prospectively evaluated children with VUR and included a cohort who were on long-term antibiotic prophylaxis. No studies were excluded. The presenting demographic data, criteria and methods of evaluation were tabulated. Outcomes were compared—specifically recurrent urinary infection and renal scarring—when the data allowed.

Results

Presenting Demographics

The presenting demographics are shown in Table 1: Nine studies were from Europe; 4 from North America; 1 from Europe and North America; 1 from South America and North America; 1 from South America; 1 from Australia; 1 from Japan. Greenfield [15] and Skoog [4] were retrospective studes, while the remainder were prospective. The gender distribution differed widely. The percentage of boys varied from none to 79%. Studies from Europe, Asia and Australia had a greater percentage of boys. Studies from North America were predominately female—72 to 100%. [4, 5, 9, 15] Males were overwhelmingly dominant (80%) in the one study from Japan. [6] Males comprised 30 to 50% of the cohort in 8 studies —all from countries were routine neonatal circumcision is not practiced. [8,13,14,16,17,18,19,23,24] In the four studies wherein circumcision status was provided, the vast majority were not circumcised—63 to 97%. [9,10,13,14,17] Notably, in the US RIVUR study, among the small number of male patients, 63% were not circumcised. [9]

While not indicated in the manuscripts, it can be assumed that the majority of boys from countries were neonatal circumcision is not routinely practiced were not circumcised. The age distribution varied widely, mainly in limiting the upper age included. Four studies included children only up to age 3 years; 1 included children up to age 6 years; 12 included children as old as 18 years.

Presenting Clinical Characteristics

The presenting VUR grades are shown in Table 2. The older studies did not use the International Scale (IS). VUR was described as dilating or non-dilating or graded on a scale of I, II or III. Dilating VUR was considered grade III or above for the purpose of this analysis. In the 3 point system grade I is equal to grade I (IS); grade II is equal to grades II,III (IS); and grade III is equal to grades IV, V (IS). 3 studies included children with grades III (IS) or less; 8 studies included children with grades IV or less and 6 included grade V or less. Five studies either completely excluded grades I and II or were predominantly—greater than 75%--grades III to IV VUR.

Febrile urinary tract infection was the sole reason for presentation in 4 series (Table 3). Febrile, non-febrile, non-specified or symptomatic UTI was the reason for presentation in the remainder. Two studies also included children who presented without UTI, but with voiding dysfunction or prenatally detected hydronephrosis. [13, 14, 15] Minimum colony counts were required for inclusion in 7 series, while in the remaining 11 no colony counts were mentioned. A urinalysis with pyuria was required in 6 studies, while no mention of urinalysis results was made in the remaining 12 studies. The means of specimen collection was not specified in 9; by collection bag in infants in 6; by catheter only in infants in 3. Bowel and bladder function (BBD) was assessed in toilet trained children in 5 studies and in 2 of those children with BBD were excluded from analysis. In 13 studies BBD was not assessed.

Presenting Radiographic Upper Tract Findings

Presenting radiographic modalities and findings are shown in Table 4. Children in 11 studies underwent radionuclide scanning (RS) at the outset; five had intravenous pyelograms (IVP), 1 had a renal ultrasound and in 1 no initial assessment of parenchymal status was performed. Of those in whom initial renal scarring was assessed, the incidence of scarring in the cohort was < 10% in 4 studies, 10 to 25% in 1, 25 to 40% in 1 and >40% in 8. Renal ultrasound was performed adjunctively in 4 studies—3 also had a renal scan and 1 had an IVP.

Clinical Protocols

Salient details of the clinical protocols are shown in Table 5. Follow up was 2 years or less in 8 studies, 5 years in 4, greater than 5 in 4 and not specified in 2. The prophylactic medication was not specified in 7, TMP/SMZ or Nitrofurantoin in 5, TMP/SMZ in 3, Nitrofurantoin in 1, Cefaclor in 1, Trimethoprim or Augmentin in 1. Attempts to measure compliance with medicine taking were made in 6 studies, while in 12 no method to assess compliance was reported.

Outcomes

The major outcomes tabulated while on antibiotic prophylaxis were recurrent UTI, renal scarring and resolution of reflux. These are shown in Table 6. Recurrent UTI while on prophylaxis was not stated in 3 studies and overall ranged from 7 to 50%. When specified, the majority were febrile. The gender of those with recurrent UTI was specified in 3 studies. [6, 9, 13, 14] In 2 the majority were female, 80% and 93%, respectively. [9, 13, 14] In the one study from Japan wherein the 79% of the subjects were male, 91% of recurrent infections were in boys. [6] Scarring at the end of the study was not specified in 5 studies. Radionuclide renal scans were performed 8 studies and scarring ranged from .5 to 17%. IVP's were used to assess scarring in 4 older studies and rates were higher—ranging from 4.5 to35%. Resolution of reflux at the end of the study period was not specified in 8 series. The rate of reflux resolution of specific grades was shown 3 studies and ranged widely from 10 to 94%. Overall resolution rates were provided in 7 studies, without specifying grade, and they ranged from 13 to 51%.

Discussion

This detailed examination of the populations in these studies demonstrates that there are relevant differences, which may account for disparate outcomes. Studies with patients from the United States or in whom patients from the United States were included tended to have a majority of girls—ranging from approximately 80 to 100%. Conversely, studies from Europe, Japan and Australia had much higher percentages of boys—ranging from around 40 to 80%. While it is impossible to be certain, this may account for the relatively high recurrent UTI rate in these studies, since routine neonatal circumcision is not practiced in those countries and boys with intact foreskins and VUR are at a higher risk of urinary infection. [26] Unfortunately, the gender of those with recurrent UTI was not always revealed. However, the few males in the RIVUR study who had UTI's on medication were all uncircumcised. 91% of the recurrent UTI's in the Kaneko series from Japan were in boys and, again, routine neonatal circumcision is not practiced in Japan. An exception was the earlier experience of Govan, wherein all the subjects were female and a large percentage (50%) developed infection on prophylaxis. [5] Looking at all the rates of recurrent UTI and gender, it is a mixed picture, but gender and circumcision status may play a significant role in presentation and in overall success of long term prophylaxis. This remains a speculation, however, until and unless proven by properly performed trials with well identified subgroups of circumcised and uncircumcised boys.

By design, the grades included in these studies varied widely. The IRSC and Swedish trials limited themselves to higher grade (III, IV) VUR at the outset. The Birmingham and Smellie series also had a majority with "dilating" VUR. For the remainder, most of the reflux ranged from grades I to III. The highest outcome scarring rates, determined either by renal scan or IVP, were in those studies with higher grades—ranging from 13 to 35%. [16, 23, 24] Lower outcome scarring rates were seen in studies predominated by the lower grades—ranging from 3.5 to 12%. [9, 12, 18] Ages included varied widely, and many studies included children older than 10 years. Given the differing genders and VUR grades included, there

were no clear outcome discrepancies when comparing studies that were confined to younger children to those with older children.

The definition of UTI, either at entry or during the period of observation also varied significantly. Two studies included children without a history of infection, but who presented with hydronephrosis or voiding dysfunction. [13, 14, 15] The majority of the infections at presentation and follow up were febrile. Minimal colony counts were not specified in seven series. In eleven, urinalysis results were not reported and the presence of pyuria was not required in order to diagnose UTI. The method of urine collection was not specified in 9 series. In 3 studies, only catheterized specimens were allowed from non-toilet trained infants and recurrent UTI rates ranged from 9 to 20%. [7, 9, 17] Bagged specimens from non-toilet trained infants were permitted in 6 series and recurrent UTI's ranged from 7 to 36%. [8, 13, 14, 18, 19, 24, 25] The inclusion of bagged specimens renders the data suspect, since such specimens can be contaminated—falsely increasing the reported infection incidence. Again, VUR grade and gender distribution varied, perhaps also accounting for some differences in UTI occurrence while on medication.

Renal scarring at presentation was not specified in 3 series. [6, 7, 8] IVP's were the radiographic tool used to assess scarring in 4 older studies, while the remaining 11 studies employed radionuclide scanning. 4 studies had initial scarring rates 10% or less, while in the remainder initial scarring rates ranged from 25 to 100%. Of those 4 with the lowest initial scar rates, reported outcome scarring ranged from 0.5 to 35% and reported recurrent UTI rates were 13%. [4, 9, 15, 16] The remainder with higher initial scarring rates reported recurrent UTI rates ranging from 14 to 50% and scarring at outcome ranging from 3.5 to 35%.

Bowel and bladder dysfunction (BBD) was not noted in the majority. In 3 series it was assessed and children with BBD were excluded. [10, 12, 20, 21, 22] In 2 series BBD was prospectively assessed in the studied cohort and only in the RIVUR study was BBD correlated with outcome. [9] Subjects in the RIVUR trial with BBD had a much higher incidence of infection while on prophylaxis. The purposeful exclusion of children with BBD or the failure to assess for BBD, therefore, might significantly alter the outcome of long term prophylaxis in a cohort of children with VUR. In six series, attempts at compliance enforcement and monitoring occurred. In particular, the Roussey-Kesler series, wherein compliance was not monitored, reported that 25% of children on TMP/SMZ had infections sensitive to the antibiotic, suggesting that the subjects were not taking the medication. [8] The efficacy of prophylaxis might not be accurately evaluated, therefore, unless some effort at compliance is present. Follow up ranged from 1 to 5 years. No correlation between outcomes and follow up length was evident.

Conclusion

This review demonstrates that the sub-populations of children with VUR have differed in previously published studies of antibiotic prophylaxis and VUR. In addition, the definition of UTI and means of assessing renal involvement was also variable. Their reported clinical outcomes differ as a result. It may, therefore, be inappropriate to combine outcome data

from these series in a meta-analysis, since this serves to blur distinctions between these sub-populations. The results of such a meta-analysis will not help the clinician to properly customize treatment or to understand the benefits and limitations of long term antibiotic prophylaxis in a given individual. Unfortunately, there are no clear recommendations when looking at these studies one at a time either, since within each study sub-populations are combined. It is probable that expectations for the efficacy of antibiotic prophylaxis for an uncircumcised male infant with grade IV VUR will not be the same as for a 5 year old girl with BBD and grade II VUR. Subpopulations, categorized by grade, gender, age, circumcision status and toilet habits, would have to be observed individually while on and off prophylaxis. Given that prospective studies that are randomized, controlled, blinded and with statistical significance for each subpopulation may not be forthcoming, the clinician is left with the need to make individual judgments and follow these children carefully. Explicit guidance from the literature is not available for each sub-group or clinical scenario. Broad recommendations or guidelines based upon meta-analyses, therefore, should be viewed with caution.

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TABLE 1

Presenting Demographics

	Origin	# Enrolled	% Female	Uncirc %	Age Range
RIVUR[9]	US	607	92	63	2–71 mo
SRT[13, 14]	EUR	69	62	97	12–24 mo
Craig[17]	AUST	576	64	85	0–18 yr
Pennesi[18]	EUR	100	52	NS	0–30 mo
Montini[19]	EUR	132	69	NS	1–101 mo
Roussey-Kesler[8]	EUR	225	69	NS	1–36 mo
Garin[7]	SA/US	218	82	NS	3–204 mo
Kaneko[6]	Japan	39	21	NS	.5–111 m0
Smellie[23]	EUR	52	52	NS	1–12 yrs
IRSC (EUR)[20, 21, 22]	EUR	287	76	NS	0 to 10 yrs
Greenfield[15]	US	481	72	NS	1–10 yr
Scholtmeijer[16]	EUR	77	67	NS	.25–14 yr
IRSC (EUR/US)[10]	EUR/US	158	83	87	0–11 yr
Goldraich[12]	SA	202	79	NS	Avg: 31 mo
Skoog[4]	US	468	85 (%)	NS (%)	3–16 yrs
Birm: 2 yrs[24]	EUR	87	55	NS	0–15 yr
Birm: 5 yrs[25]	EUR	53	NS	NS	0–15 yr
Govan[5]	US	73	100	NS	NS

(US: United States, SA: South America, EUR: Europe, AUST: Australia, SRT:Swedish Reflux Trial, IRSC: International Reflux Study in Children, Birm: Birmingham Reflux Study)

Table 2

Presenting VUR grade

	I (%)	II (%)	III (%)	IV (%)	V (%)
RIVUR[9]	11	42	38	8	0
SRT[13, 14]	0	0	59	41	0
Craig[17]		20		22	
Pennesi[18]	0	31	46	33	0
Montini[19]	23	45	32	0	0
Roussey-Kesler[8]	10	65	24	0	0
Garin[7]	17	50	33	0	0
Kaneko[6]	7	8	42	38	1
Smellie[23]	0	2	22	46	29
IRSC (EUR)[20, 2122]	0	0	15	85	0
Greenfield[15]	20	46	22	9	3
Scholtmeijer[16]	12	31	34	17	2
IRSC (EUR/US)[10]	0	0	20	80	0
Goldraich[12]	0	52		48	
Skoog[4]	4	57	53	3	.4
Birm: 2 yrs[24]			2	98	
Birm: 5 yrs[25]			2	98	
Govan[5]		40	53	7	0

(SRT: Swedish Reflux Trial, IRSC: International Reflux Study in Children, Birm: Birmingham Reflux Study)

Table 3

Presenting Clinical Characteristics

	UTI (f, nf, sym, ns)	Col. Ct.	U/A	Infant Coll.	BBD
RIVUR[9]	86%f,14%nf	>100K void, 50K cath	yes	cath	yes
SRT[13, 14]	96% UTI	>100K void		bagged,cath	yes
	4% hydro	anything cath	no		
Craig[17]	79%f,21%nf	>100K void	yes	cath	ns
		>10K cath			
Pennesi[18]	100%f	>1000K void	yes	bagged,cath	ns
Montini[19]	100%f	>100K	yes	bagged	ns
Roussey-Kesler[8]	100%f	>100K	yes	bagged	ns
Garin[7]	ns	>100K	yes	cath	ns
Kaneko[6]	100%f	>100K	yes	ns	ns
Smellie[23]	ns	ns	no	ns	ns
IRSC (EUR)[20, 21, 22]	ns	ns	no	ns	yes(ex)
Greenfield[15]	54% UTI	ns	no	ns	ns
	15%VD, 4% hydro				
Scholtmeijer[16]	ns	ns	no	ns	yes
IRSC (EUR/US)[10]	89%f,11%nf	ns	no	ns	yes(ex)
Goldraich[12]	ns	ns	no	ns	yes (ex)
Skoog[4]	ns	ns	no	ns	ns
Birm: 2 yrs[24]	100%sym	>10K	no	bagged	ns
Birm: 5 yrs[25]	100%sym	>10K	no	bagged	ns
Govan[5]	2/3f,1/3nf	500/cc	no	ns	ns

(f: febrile, nf: non-febrile, sym: symptomatic, ns: not shown, SRT: Swedish Reflux Trial, IRSC: International Reflux Study in Children, Birm: Birmingham Reflux Study, ex: patients with BBD were excluded from that series.)

Table 4

Presenting Upper Tract Radiographic Findings

	RS/IVP	Renal USG	% Renal Scar
RIVUR[9]	RS	yes	4
SRT[13, 14]	RS	no	62
Craig[17]	RS	yes	25
Pennesi[18]	RS	no	40
Montini[19]	RS	no	94
Roussey-Kesler[8]	none	yes	ns
Garin[7]	RS	yes	ns
Kaneko[6]	none	no	ns
Smellie[23]	RS	no	100
IRSC (EUR)[20, 21, 22]	RS	yes	82
Greenfield[15]	RS	no	10
Scholtmeijer[16]	RS/IVP	no	6
IRSC (EUR/US)[10]	IVP	no	66
Goldraich[12]	RS	no	44
Skoog[4]	RS	no	8.2 %
Birm: 2 yrs[24]	IVP	no	59
Birm: 5 yrs[25]	IVP	no	59
Govan[5]	IVP	no	56

(RS: radionuclide renal scan, IVP: intravenous pyelogram, USG: renal ultrasound, SRT: Swedish Reflux Trial, IRSC: International Reflux Study in Children, Birm: Birmingham Reflux Study)

Table 5

Clinical Protocol

	Follow up	Medication	Compliance Measured
RIVUR[9]	2 yr	TMP/SMZ	yes
SRT[13, 14]	2 yr	TMP,cefadox, nitro	yes
Craig[17]	12 mo	ns	yes
Pennesi[18]	2 yr	TMP/SMZ	no
Montini[19]	12 mo	co-TMP, Amox/Clav	yes
Roussey-Kesler[8]	18 mo	TMP/SMZ	no
Garin[7]	1 yr	TMP/SMZ, Nitro	yes
Kaneko[6]	16 mo	cefaclor	no
Smellie[23]	4–10 yr	TMP, TMP/SMZ, Nitro	no
IRSC (EUR)[20, 21, 22]	5 yr	ns	no
Greenfield[15]	ns	TMP/SMZ, nitro	no
Scholtmeijer[16]	ns	ns	no
IRSC (EUR/US)[10]	5 yr	ns	no
Goldraich[12]	69 mo	Nitro	yes
Skoog[4]	5 yr	ns	no
Birm: 2 yrs[24]	2 yr	TMP/SMZ, nitro	no
Birm: 5 yrs[25]	5 yr	TMP/SMZ, nitro	no
Govan[5]	1–6 yr	ns	no

(TMP: trimethoprim, TMP/SMZ: trimethoprim sulfamethoxazole, Nitro: nitrofurantoin, Amox/Clav: amoxicillin/clavulinic acid, SRT: Swedish Reflux Trial, IRSC: International Reflux Study in Children, Birm: Birmingham Reflux Study)

Table 6

Clinical Outcomes

	UTI	%Scar (RS)	%Scar (IVP)	VUR res olution
RIVUR[9]	13%, 3/4f	12%	ns	51%
	93% female, 7% male (all uncirc)			
SRT[13, 14]	14% all f	0%	ns	13%
	80% female			
Craig[17]	9% all f	8%	ns	ns
Pennesi[18]	36%	10%	ns	I:96%,II:86%,III:74%,IV:94%
Montini[19]	7% all f	ns	1%	ns
Roussey-Kesler[8]	17% 3/4f	ns	ns	ns
Garin[7]	20%	6%	ns	I: 37.5%,II:12.5%,III: 10.3%
Kaneko[6]	28%			
	91% male	ns	ns	ns
Smellie[23]	32%	13%	ns	20%
IRSC (EUR)[20, 21, 22]	28%, 57%f	17%	ns	ns
Greenfield[15]	13%	ns	ns	29%
Scholtmeijer[16]	ns	ns	3%	ns
IRSC (EUR/US)[10]	ns	ns	20%	ns
Goldraich[12]	43.5%	3.5%	ns	40%–90% (low gr-high gr)
Skoog[4]	ns	.5%	ns	41%
Birm: 2 yrs[24]	23%	ns	35%	43%
Birm: 5 yrs[25]	21%	ns	4.5%	49%
Govan[5]	50%	3/4f ns	ns	ns

(UTI/f: febrile, ns: not shown, SRT: Swedish Reflux Trial, IRSC: International Reflux Study in Children, Birm: Birmingham Reflux Study)