Urinary tract infections in children and the risk of ESRF

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Abbreviations
CP: chronic pyelonephritis
ERA-EDTA: European Renal Association - European Dialysis and Transplant Association
ESRF: end-stage renal failure
RN: reflux nephropathy
RRT: renal replacement therapy
PMP: per million population
USRDS: United State Renal Data System
UTI: urinary tract infection
VUR: vesicoureteral reflux

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Abstract

Aims

Paediatric guidance on diagnosis and treatment of urinary tract infections (UTIs) has in the past largely focused on identifying children with vesicoureteral reflux, thought to be at greatest risk of renal scarring. This practice has been questioned; specifically the accepted association between UTI and end-stage renal failure (ESRF) through renal scarring. The aim of this paper is to ascertain whether we can predict *with confidence* the true level of risk that a child with a first time UTI will subsequently develop ESRF attributable to UTI.

Methods

Using data available from renal registries an analytical approach based on previous estimates of risk is used to demonstrate the range of plausible estimates of risk that can be generated and levels of uncertainty that surrounds those estimates.

Results

Estimates of the perceived risk of developing ESRF following UTI range from 1/154 to 1/199900 and are heavily dependent on the assumptions made and the source of data.

Conclusion

There is considerable uncertainty in the relationship between childhood UTI and risk of ESRF based on the data currently available. Until further evidence is available clinicians will continue to debate the risk of UTI and ESRF and consensus opinion will continue to guide management.

Summary

Scarring of the kidneys can lead to ESRF. Most scarring is congenital, though some is caused by childhood urinary tract infection. Invasive investigations are undertaken in the belief that infection may lead to ESRF. We show that the risk of childhood urinary tract infection leading to ESRF is highly uncertain. The routine use of invasive investigations may be unwarranted based on the strength of the current evidence.

Background

Urinary tract infection (UTI) is estimated to have been diagnosed in up to 11.3% of girls and 3.6% of boys by the age of 16 years in the UK(1) with recurrence common(2). Studies from Sweden have shown incidence of first diagnoses of UTI to be around 2% of boys and girls by the age of two years and 2% and 7% by the age of six years(3;4).

Of major importance in diagnosing and treating UTI is the perceived risk of renal scarring resulting from febrile UTI, ultimately leading to end-stage renal failure (ESRF) and premature death. How often episodes of febrile UTI in childhood could lead to end-stage renal failure is of major interest as this would strongly influence the need for follow-up and radiological investigations in these children. A widely cited 1997 study, by Stark(5), estimates that the likelihood of UTI leading to ESRF in females was 1 in every 10,000 patients. The arguments used to support this estimate are erroneous in that they use the incidence of new cases of ERSF per year, rather than prevalence. As a result, the study describes the risk of someone with a childhood UTI developing ESRF during one year, rather than the lifetime risk of developing ESRF.

The 1997 study additionally fails to account for uncertainty in the relationship between febrile UTI and renal scarring and the proportion of ESRF cases that can be attributed to UTI. Any estimates of the risk of UTI leading to ESRF should take account of this uncertain relationship.

Using the method of analysis employed in the Stark study as a starting point, this study examines the lifetime risk of developing ESRF following a childhood UTI as well as considering the uncertainty inherent in any such estimate to determine whether we can predict *with confidence* the true level of risk.

Methods

Working from the information provided in the Stark study, described below are the methods used to derive the original estimates of the risk of UTI leading to ESRF of 1/10,000. The same analytic approach is then used to demonstrate, based on currently available data, the wide range of plausible estimates of risk that can be generated and therefore the significant levels

of uncertainty that surrounds any estimate of risk. Estimates of risk based on the data collected across a range of countries are also calculated.

Data was collected from a range of renal registries(6-10). It was found that there is wide variation in the diagnosis reported as the cause of ESRF resulting from acquired renal scarring and congenitally dysplastic kidneys. In The United Kingdom the renal register reports do not distinguish between congenital and acquired cases and attribute all cases to the diagnosis of pyelonephritis. The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) register also reports cases as pyelenophritis, again without distinction in the reported figure between congenital and acquired cases. In Australia and New Zealand these cases are attributed to reflux nephropathy, again without distinction between acquired and congenital cases. In data from the United States Renal Data System (USRDS) a more detailed breakdown of the causes of ESRF is provided and a distinction is made between those causes related to acquired or congenital scarring (including six different diagnoses for various forms of obstructive or non-obstructive congenital malformations). They do however use the headings of interstitial nephritis/pyelonephritis, chronic pyelonephritis and reflux nephropathy which encompasses both congenital and acquired cases.

Three patient populations are included in the analysis: those with UTI (both febrile and non-febrile), those with renal damage associated with vesicoureteral reflux (VUR) and those with ESRF.

Within Figure 1 the population of interest is the proportion of patients who develop ESRF given that they have had a UTI in childhood; this population is represented by area (B+D). In calculating the risk for this population:

i. Lifetime risk of UTI = (B+D+E+G)

ii. Prevalence of ESRF = (A+B+C+D)

iii. ESRF attributable to renal damage associated with VUR = (B+C)

iv. Proportion of ESRF attributable to renal damage associated with VUR = (B+C)/(A+B+C+D)

v. Risk of UTI leading to ESRF = (B+D) / (B+D+E+G)

The initial, base case analysis, based on that of Stark(5), assumes for all cases of ESRF attributed to renal damage the patient has had a UTI (C=0) and secondly, that renal damage associated with VUR is the only mechanism by which UTI can lead to ESRF (D=0). These assumptions, while useful in the development of the base-case model, do not necessarily reflect the true clinical situation but are retained to allow comparison with the analysis by Stark(5).

Re-analysis using this method is conducted to demonstrate the wide range of plausible alternative estimates, drawing on data available from renal registries and the published literature. Stark bases his analysis on the annual incidence of ESRF, whereas the cumulative lifetime risk of developing ESRF may be more appropriate for estimating the risk of childhood UTI leading to ESRF over the course of lifetime. We show how the choice of annual incidence or cumulative incidence impacts on the estimate of risk. Estimates of risk are for females and are applied to the proportion of the cohort at risk (those who were alive and who had not already developed ESRF). Data for females is used in the first analysis to allow comparison with the estimate made by Stark(5;11).

The five different models tested and the source of data for each are presented in Table 1. The analysis by Stark is based on a mix of data from the USRDS and EDTA registries. Table 2 presents the cumulative incidence of ESRF calculated from EDTA figures. Table 3 demonstrates the risk of childhood UTI leading to ESRF based on estimates of cumulative incidence of ESRF taken from Table 2. We start by presenting the analysis made by Stark and then proceed to change the inputs into the model to show how different assumptions about the parameter values in the model used to calculate risk impact on the model results.

We also present an international comparison of the risk of UTI as the cause of current cases of ESRF to demonstrate how the definition of ESRF and its causes impacts on how risk may be perceived on a country by country basis. Data for this analysis is used for the total population and is based on prevalence of ESRF in the total population, as it was not possible

to make like-for-like comparisons using incidence data between countries using the available published evidence (Table 4).

Results

Table 2 shows the estimated lifetime risk for females of developing ESRF to be 5777 PMP as calculated from estimates of incidence reported by the EDTA(7). The age group of interest is likely to be represented by those patients under 60, as according to Stark, ESRF that occurs after this age is unlikely to be attributable to a childhood UTI. Although no data is presented by Stark(5)[5] to support this assertion, it is plausible that as age increases, the role of childhood UTI in the development of ERSF is more difficult to establish; 60 is used as a cut-off in Models Two and Four to allow direct comparison of risk with Stark. In this particular age group, the risk of developing ESRF during one's lifetime is 2525 PMP.

The result of the Stark model is presented in Table 3 and represents the base-case scenario. By substituting the whole life-time estimate based on the data from the EDTA in place of the estimate of incidence from the USRDS as used by Stark, life-time risk for females developing ESRF as a result of having had a childhood UTI is estimated at about 1/154 (Model 1). But Model 1 does not arrive at a realistic estimate of the true risk, suggesting further deviation from Stark's previous estimate is required.

Stark chose an age cut-off of 60 years. While this is largely arbitrary, it is kept for sake of comparison, as there is no evidence to suggest what an appropriate age cut-off would be. For the group of patients under 60, the risk of UTI leading to ESRF is about 1/352 (Model 2). When using the original estimate of risk of developing ESRF used by Stark and substituting a revised estimate of renal scarring leading to ESRF from the USRDS data[10], the risk is much higher, at about 1/115,000 (Model 3). Using the USRDS figure of ESRF caused by renal scarring and the risk of developing ESRF before the age of 60 from the EDTA data, the estimate of risk is approximately 1/3960 (Model 4).

Comparisons in Table 4 are based on the prevalence of ESRF across the whole population for each country. This table shows the probability that any current case of ESRF may have been associated with a UTI in childhood. Due to the differences in the way that data is reported between countries, this estimate is based on the prevalence of ESRF at all ages. This will most likely overestimate the risk of a childhood UTI leading to ESRF; however, there will still exist differences in risk estimates arising from the way in which the causes of ESRF and those patients with ESRF are defined in different countries and regions and it is the relative differences that are of importance in the comparison made in Table 4.

Discussion

In this study we found that the risk of developing ESRF following a first time UTI in females is uncertain and potentially much greater than that estimated in a previous study. Depending on the assumptions we made in our model, we found estimates of risk to vary between 1/861 to 1/3300, with an outlying value of 1/199,900 when the data from the US register USRDS was used. If the figures are calculated instead for patients with febrile UTI then the risk will be substantially higher. Jodal et al(12) found that the incidence of febrile UTI by the age of seven was 2.7% for girls, roughly one third the estimate of risk of any childhood UTI. If only febrile UTI were considered each estimate of risk given above would between three and four times greater.

It is well known that in particular circumstances UTI is associated with a risk of renal scarring(13). This is estimated to occur in 5-15% of children within the two years of their first presentation with a febrile UTI(2). Young children, especially infants, are assumed to be at greater risk of developing renal scarring than older children or adults. Renal scarring is known to be associated with long-term morbidities such as, pregnancy complications, chronic kidney disease and in some cases, established ESRF. End stage renal failure is irreversible and requires regular dialysis or transplantation if the individual is to survive(14).

A major problem when calculating the risks of a UTI is the difficulty in separating congenital renal dysplasia from acquired scarring due to acute pyelonephritis. This is in many cases both clinically and scientifically a very complex differential diagnosis. It was previously

believed that acquired renal scarring was very common. With the advent of prenatal ultrasound it has however become evident that much of this scarring was present at birth.

It is clear from this analysis that there are marked differences in attribution of causes of ESRF across different countries. This is related to the diagnostic difficulties mentioned above and makes it difficult to estimate the real likelihood that a childhood UTI will go on to cause ESRF. It can be reasonably assumed that although the rates of UTI leading to ESRF differ across countries, much of this difference may be attributable to the way that the causes of ESRF are defined. To avoid this ambiguity, the analyses presented here includes an international comparison to show where these differences arise and how they impact on the results. For example, in Australia and New Zealand, 3% of ESRF cases are attributed to reflux nephropathy, while in the UK, 12% of cases are attributed to pyelonephritis.

Within the analyses presented here, estimation of life-time risk of developing ESRF as a result of having had a childhood UTI is highly variable; results are highly dependent on which registry data is included in the analysis. The USRDS registry (as used in Model 3) provides the greatest detail in defining the causes of ESRF. As a result, the model based on figures from this registry provides arguably the most reliable estimate.

Stark argues that the number of patients who have a single UTI in childhood who then go on to have ESRF is very small, and that the risk of developing ESRF as a result of a childhood UTI is low[5]. This would suggest that the investigations often undertaken to diagnose VUR and renal scarring in children with first-time UTI are unwarranted and significant changes in clinical practice may be required, though such investigations may be warranted for reasons unrelated to concerns about developing long-term complications such as ESRF. If risk cannot be estimated reliably, the implications for the management of children who present with symptoms suggestive of UTI become unclear.

The confusion about the risk of a UTI highlighted in the present analyses can significantly explain the wide differences in opinion about how to manage children who have had this infection. Over the past decade there has been a strong debate that has focussed on the relationship between UTI, VUR and scarring. Venhola and Uhari(15) e.g. argue that ‘the overall importance of VUR is confounded because of the natural tendency of VUR to resolve

spontaneously, its dynamic nature, and its different grades in children'. In line with the recently published UK guidelines from NICE(16) which outline a less invasive programme of management, they recommend 'less unpleasant and possibly unnecessary imaging tests for VUR'(15). This is refuted by some professionals who argue for more rather than less *assiduous management* given evidence and clinical anecdotes 'which indicate that scars may develop in infant kidneys quicker than urine culture can confirm the diagnosis, and that reflux nephropathy has no age limit'(17).

Conclusion

Re-analysis of a previously published model shows that there is considerable uncertainty in the relationship between childhood UTI and risk of ESRF based on the data currently available. Until further evidence is available clinicians will continue to debate the risk of UTI and ESRF and consensus opinion will continue to guide management. Registers that try to separate acquired from congenital renal scarring are needed in order to establish the true risk of childhood UTI leading to ESRF and to guide appropriate clinical management.

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Tables

Table 1: Summary of risk models and sources of data for each parameter

	Model				
Parameter	Stark	One	Two	Three	Four
Annual Incidence of ESRF	USRDS(5)	N/A	N/A	USRDS(5)	NA
Cumulative incidence of ESRF	NA	EDTA(7)	EDTA(7)	NA	EDTA(7)
ESRF associated with VUR	Stark(5)	Stark(5)	Stark(5)	USRDS(8)	USRDS(8)

Table 2: Cumulative incidence of ESRF: Females only (calculated from EDTA incidence figures(7))

Age band	Number at start	Mortality rate per million per year	Number at end	Number at risk	Annual incidence of ESRF per million	Number with ESRF (new)	Cumulative ESRF
0 to 1	1000000	4940	995060	997530	8.5	8	8
1 to 4	995051.5	240	994096.3	994573.9	8.5	34	42
5 to 9	994062.5	106	993535.6	993799	8.5	42	85
10 to 14	993493.4	106	992966.8	993230.1	8.5	42	127
15 to 19	992924.6	248	991693.4	992309	8.5	42	169
20 to 24	991651.2	248	990421.6	991036.4	38.2	189	358
25 to 29	990232.3	436	988073.6	989152.9	38.2	189	547
30 to 34	987884.6	436	985731	986807.8	38.2	188	736
35 to 39	985542.6	952	980851.4	983197	38.2	188	923
40 to 44	980663.6	952	975995.6	978329.6	38.2	187	1110
45 to 49	975808.8	2509	963567.3	969688	98.8	479	1589
50 to 54	963088.2	2509	951006.3	957047.3	98.8	473	2062
55 to 59	950533.5	5918	922407.2	936470.4	98.8	463	2525
60 to 64	921944.6	5918	894664.3	908304.4	98.8	449	2973
65 to 69	894215.6	16701	819544.1	856879.8	224.3	961	3934
70 to 74	818583.1	16701	750227.3	784405.2	224.3	880	4814
75 to 79	749347.6	51252	557319.8	653333.7	169.2	553	5367
80 to 84	556767.1	51252	414089.9	485428.5	169.2	411	5777

Table 2 adapted from the NICE guidelines on the management of UTI in children(16)

Table 3: Risk of childhood UTI leading to ESRF(females only)

	Stark	Model 1	Model 2	Model 3	Model 4
Incidence of ESRF (PMP)*	87	5777	2525	87	2525
Prevalence of UTI (%)	8.0	8.0	8.0	8.0	8.0
ESRF associated with VUR (%)	9.0	9.0	9.0	0.49	0.49
Risk of UTI leading to ESRF (as a ratio)	1/10217	1/154	1/352	1/114943	1/3960

Model 1: Incidence of ESRF is all ages; ESRF associated with VUR is based on EDTA data
Model 2: Incidence of ESRF is up to age 60; ESRF associated with VUR is based on EDTA data
Model 3: Incidence of ESRF is based on Stark estimate; ESRF associated with VUR is based on USRDS data
Model 4: Incidence of ESRF is up to age 60; ESRF associated with VUR is based on USRDS data

Table 4: Comparison of international risk estimates based on prevalence (based on all sex and age groups)

	Europe	Australia	New Zealand	USA	UK
Prevalence of ESRF (PMP)	662(9)	822(18)	808(18)	1665(8)	774(6)
Prevalence of UTI (%)	8.0(5)	8.0(5)	8.0(5)	8.0(5)	8.0(5)
ESRF due to renal scarring associated with VUR (%)	9.0(9)	3.0(18)	3.0(18)	0.8(8)	12.0(6)
Risk of UTI leading to ESRF (as a ratio)	1/1429	1/3244	1/3300	1/199900	1/861

Figure Legends

Figure 1: Model of risk of UTI leading to ESRF

The populations represented in the Figure 1 are as follows:

1. Whole population: H
2. Patients that have had a childhood UTI: E+B+D+G
3. Patients with ESRF: A+B+C+D
4. Patients with Renal damage associated with VUR: B+C+E+F
5. Patients with ESRF that had a childhood UTI: B+D
6. Patients with ESRF and renal damage associated with VUR: B+C
7. Patients with ESRF and renal damage associated VUR and have had a childhood UTI : B