Incidence of Post-Pyelonephritic Renal Scarring: A Meta-Analysis of the Dimercapto-Succinic Acid Literature

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Abbreviations and Acronyms

APN = acute pyelonephritis

DMSA = 99mtechnetium dimercapto-succinic acid

UTI = urinary tract infection

VUR = vesicoureteral reflux

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Purpose: We investigated ethnic differences in the risk of post-pyelonephritic renal scarring in infants and children for possible genetic determinants.

Materials and Methods: We searched all peer reviewed articles published from 1980 through 2006 in the PubMed®, MEDLINE® (Ovid), Cochrane Central Register of Controlled Trials and EMBASE® databases for the keywords, "renal scarring and pyelonephritis," "renal fibrosis" and "kidney scarring." References were included only when they specified acute pyelonephritis defined by a fever, positive urine culture and areas of photopenia in the renal cortex on 99mtechnetium dimercapto-succinic acid renal scans, repeat dimercapto-succinic acid scans obtained at least 3 months after acute pyelonephritis to assess for renal cortical scar formation and absence of recurrent urinary tract infection during followup. When possible data were analyzed according to patients and renal units.

Results: Among 23 references the overall rates of renal scarring in terms of patients and renal units were 41.6% and 37.0%, respectively. In terms of patients the incidence of renal scarring following acute pyelonephritis varied by region, from 26.5% (Australia) to 49.0% (Asia). In terms of renal units the incidence of acquired renal cortical scarring varied by region, from 16.7% (Middle East) to 58.4% (Asia). When combined by vesicoureteral reflux status children and renal units with refluxing ureters exhibited an increased risk of renal scarring (odds ratios 2.8 and 3.7, respectively).

Conclusions: Although scarring was different across some regions, only scarring in Asian studies comparing patients displayed a statistically significant difference. A regional effect explained the heterogeneity observed in the overall estimate for patients and partly for renal units. The greatest risk of renal scarring may be imparted by the presence of vesicoureteral reflux.

Key Words: child, cicatrix, kidney diseases, pyelonephritis, technetium Tc 99m dimercaptosuccinic acid

URINARY tract infection is the most common serious bacterial illness in infants and children with fever. Population estimates of the cumulative incidence of urinary tract infection are affected by whether the diagnosis is based on symptoms, positive urine culture or both, accuracy of specimen collection, age and gender of the cohort being studied, whether fever is a presenting symptom and rate of circumcision in the population.

It has been reported that the cumulative incidence of UTI in children younger than 6 years is 3% to 7% for girls and 1% to 2% for boys.[1–3] Approximately two-thirds of children with febrile UTI will have APN, as defined by new abnormal-

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ities of the renal cortex on DMSA renal scans.[4,A5,A15,A28] Among patients with APN diagnosed by DMSA scan 15% to 52% will exhibit permanent renal cortical abnormalities (renal scarring), one of the most serious complications of APN.[5,A15,A28,A33] Significant scarring may lead to hypertension in 17% to 30% of affected children, and cause renal insufficiency and failure.

While some risk factors of renal scarring, such as young age, treatment delay, infection with P-fimbriated Escherichia coli and high grade VUR, are known, the influence of innate immunity and bacterial virulence factors on the risk of renal scarring remains unclear. Various studies using animal and clinical models have begun to elucidate the relationship between bacterial virulence and host defense factors that may lead to increased profibrotic response. However, the data regarding genetic influences on renal scarring remain sparse. Moreover, the wide range of reported estimates for renal scarring (15% to 52%) raises concern that these estimates are based on patient populations that differ widely from each other in terms of age, gender, reflux status or presence of other urological abnormalities, socioeconomic status and perhaps genetic background.

In an effort to clarify these issues we compared the available literature on renal scarring to determine the incidence of new renal scarring based on strict criteria. In addition, using country where the study was conducted, we investigated whether geographic differences exist in estimates of renal scarring as a possible proxy for genetic and/or socioeconomic variables deserving further study.

MATERIALS AND METHODS

Following a search methodology used by the American Urological Association Pediatric Vesicoureteral Reflux Clinical Guidelines Panel (1997), we identified all peer reviewed articles published from 1980 through 2006 on the rates of new renal scarring after pyelonephritis using the PubMed, Medline (Ovid), Cochrane Central Register of Controlled Trials and EMBASE search engines. Key words included "renal scarring and pyelonephritis," "renal fibrosis" and "kidney scarring." Additional articles were selected from the list of references of retrieved publications.

A total of 35 references were identified with the first episode of APN defined by a fever and/or positive urine culture and areas of photopenia in the renal cortex on DMSA renal scans consistent with acute inflammation, and when repeat DMSA scans obtained at least 3 months after APN to assess for persistent cortical abnormalities suggested acquired renal scarring (see Appendix). Thus, references were excluded when it could not be determined that the initial lesions observed on DMSA renal scan were consistent with APN and not congenital cortical abnormalities or acquired defects from prior UTIs. Among those references satisfying the 2 inclusion criteria references were excluded when patients had recurrent UTIs during followup and, therefore, renal cortical abnormalities could not be ascribed to the first lesion identified on DMSA renal scan. In cases where DMSA scans were labeled as "equivocal" or "without change" it was inferred that these findings represented areas of scar formation. Scar formation was calculated by analyzing the number of patients or renal units with persistent DMSA positive scans after 3 months compared to patients who initially presented with DMSA positive lesions.

Major characteristics, such as geographic location, average age, gender distribution, percentage of patients initially presenting with renal cortical involvement on DSMA scan (percentage with true APN) and percentage with renal lesions seen on followup DMSA scan, were collected. Other imaging studies, including renal ultrasound and voiding cystourethrogram, were noted, and relationship to and grade of VUR were compiled as well. Results were charted according to major geographic location to establish major trends regarding scar incidence.

A total of 187 references were retrieved from online searches, of which 28 satisfied inclusion and exclusion criteria and were reviewed further. Among the 28 references there were 3 pairs of references (Ditchfield et al,[A9,A10] Hitzel et al,[A13,A14] and Tepmongokol[A31] and Vilaichone[A32] et al) and a set of 3 references (Chiou,[A7] Lin[A22] and Wang[A34] et al) that corresponded to the same cohort of patients, which were combined to generate 4 independent patient cohorts. Thus, there were 23 patient cohorts available for analysis.

Of the 23 studies analyzed 13 discussed outcomes in terms of patients and 7 in terms of renal units. Three studies discussed outcomes in both terms. Among the 23 cohorts 2,106 children were enrolled, of whom at least 1,408 with findings consistent with APN were actually followed with a second DMSA scan. Renal outcome was assessed explicitly in 758 renal units. A total of 17 cohorts (74%) were prospective in nature. All series were published between 1992 and 2006. In terms of geographic location 5 cohorts (22%) were reported from Asia, 11 (48%) from Europe, 2 from Latin America, 2 from the Middle East, 1 from the United States and 1 from Oceania, and 1 was a multicenter, multiregion study (including sites in Latin America, Asia and Europe).

A total of 17 cohorts provided the mean age of the sample (38 months) at presentation. Another set of 4 cohorts provided the median age at presentation (maximum 9 months). A total of 21 cohorts provided gender distribution (males 12% to 73%). Among 19 cohorts the first DMSA scan was performed within the first 15 days of symptoms, while the followup scan was performed at a median of 6 months (mean 9.7, range 3 to 29) after the first scan. Four cohorts underwent second scans performed as early as 3 months.

Estimates were ideally reported as occurring per child, since these data reflect more clinically useful information. However, when the incidence of scarring was reported per renal unit involved that estimate is also provided. In some circumstances estimates are only available per renal unit and not per child.