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CLINICAL NEPHROLOGY

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Do kidneys outgrow the risk of reflux nephropathy?

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Abstract Three-quarters of human kidneys have segments that will allow intrarenal reflux if the person is one of the 1% that is also born with vesicoureteric reflux (VUR). It is likely that entry of infected urine into these segments produces permanent damage within just a few days, as it does in piglets and adult pigs. This very rapid course leaves no time for delay in diagnosing and treating urine infections in infants, the group that present the greatest clinical difficulties. It is proposed that the reason why the risk of scarring starts off high and falls to virtually nil by 4 years is not due to maturation that leads to an increased resistance to scarring, but because most vulnerable subjects have already scarred their kidneys in infancy. This proposed model has important implications for clinical management. First, it suggests that current practice identifies scars in children due to urine infection, but prevents few. Second, babies known to have VUR from birth, and protected from scarring with prophylactic antibiotics, will not outgrow their scarring risk by any particular age, but will remain at risk until they outgrow their reflux. This suggests their kidneys need to be protected from scarring until then, perhaps by antibiotic prophylaxis. Third, transplant recipients of any age with refluxing ureteric anastamoses or stents will carry a risk of developing a focal scar if they acquire a urine infection, and may need protection.

Keywords Urinary tract infection · Renal scarring · Reflux nephropathy · Vesicoureteric reflux · Maturation

Background to reflux nephropathy, and the concept of "maturing out of the risk"

Up to the age of 4 years [1, 2] children are known to be at risk of developing focal scars in renal segments (reflux nephropathy [3]) after a bacterial urine infection in the presence of vesicoureteric reflux (VUR) [4]. This is an important condition [5]. A small minority will lose so much parenchyme that they reach end-stage renal failure during childhood, but many more will require dialysis or transplantation years later [6, 7], when reflux nephropathy is usually labelled as pyelonephritis. Others will develop hypertension [7]. Although the association between VUR and scarring has been appreciated since the 1960s [4], the lack of complete concordance and the mechanism of scarring was not understood, although the link with intrarenal reflux (IRR) had been suggested [8]. The absence of VUR in some scarred kidneys was easy to explain, since children tend to outgrow VUR [9], but the mechanism leading to the destruction of some segments, with complete preservation of others, remained unclear until Ransley and Risdon [10] developed their piglet model. Their studies have greatly increased the understanding of reflux nephropathy in man.

They used a piglet model because the risk of scarring is greatest in young children [4, 11], and the pig has similar renal maturation and multipapillate anatomy to man, and a long intramural vesical course to the ureter that prevents spontaneous VUR, thereby precluding preexisting reflux nephropathy. Unilateral non-obstructed VUR was created by deroofing the intramural course of one ureter, and after recovery, infection was introduced and sustained in half the piglets by intravesical injection of an *Escherichia coli* broth and wax to provide a floating foreign body. Neither VUR alone, nor cystitis without VUR led to scarring, but scars developed in one or more complete segments of every kidney with both VUR and infection, leaving adjacent segments unaffected. All the spared segments had simple nipple-shaped papillae, whereas the scarred ones had flat or concave compound papillae, and typically occurred at the poles [12], as in man. The compound papillae allowed IRR of urine into the tubules of their segments during VUR [12]. Bacteria introduced into the parenchyme in this way caused permanent damage in days [13], histologically identical to reflux nephropathy in man. Simple papillae do not allow

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IRR [12]; the 27% of human kidneys with only simple papillae [14] may account for children who do not develop scars despite a urine infection and VUR.

The chance of developing reflux nephropathy is much higher in younger children, with babies at greatest risk [4, 11]. A study that considered children remained vulnerable up to the age of 10 years [15] relied on intravenous urography, which may take several years to demonstrate scars, unlike dimercaptosuccinic acid (DMSA) scanning, which reveals scars immediately [16, 17, 18]. A study using DMSA has since shown a negligible risk after the 4th birthday [2]. However, this age-related vulnerability has never been explained. It cannot be due to resolution of VUR because this disappears more slowly [9]. Several other factors may influence the risk of developing scarring in any particular child, such as changes in dysfunctional voiding [19, 20], the pattern of cytokine release [21, 22], and bacterial adherence molecules [23]. Similarly, the mechanism is also unknown whereby children may develop focal defects on DMSA scans soon after a urine infection, which resolve without scarring [21, 24, 25]. One possible explanation for the markedly reduced vulnerability for older children to develop a first scar is that the kidney somehow "matures out of the risk" as it gets older.

Why maturation cannot occur

The two studies we publish simultaneously with this paper show that the concept of renal maturation cannot be correct. In one, we demonstrate that adult pigs are as vulnerable to scarring as piglets [26], and in the other we report typical reflux nephropathy lesions appearing in transplanted mature human kidneys, both histologically and on DMSA scanning [27]. I propose an alternative explanation for the age-related risk of scarring, and the propensity of transplanted kidneys to scar. I suggest that kidneys exposed to reflux of bacteria into their tubules are likely to scar very readily at any age, but that the risk is so high in vulnerable individuals that they will virtually all acquire a scar in infancy. The first few months of life are a period of particularly high risk of urine infections for both sexes. Thus, children (especially girls whose increased risk of urine infections extends well beyond infancy) born with VUR and IRR are all likely to have scarred their kidneys by 4 years. Hence, children reaching 4 years without a scar are likely to have been born with a low or zero risk of scarring from birth; i.e., they have never had VUR, or they have VUR but no compound papillae, or they have VUR and IRR but have the relative protection from ascending infection (e.g., by having a long urethra, that is by being boys). They are therefore at minimal risk of scarring in the future.

If this is true, then a transplanted kidney that was unscarred when harvested from a donor over 4 years old is almost certain to have come from an individual who either never had VUR (about 99% of the population) or who had VUR, but no compound papillae (about 0.3%). There is, therefore, about a 73% chance [14] that a transplanted kidney will have at least one compound papilla that has not been scarred because it was protected by its first "owner." If the recipient's ureteroneocystotomy refluxes, and he or she develops a urine infection, each vulnerable segment may therefore be damaged within days, and ultimately scar, like a newborn with VUR and IRR.

If this hypothesis is correct, most infants born at risk would be expected to acquire a renal scar. This can be tested by comparing the incidence of scarring with the chance of being born with both VUR and IRR. The precise incidence of VUR at birth is uncertain, because the invasive nature of cystography precludes examining normal babies, although it has been estimated at 2% [28]. However, six studies in infants (and some older children), from a time when such research was considered ethical, showed reflux in only 4 of 456 (0.9%) normal subjects, of which 3 were unilateral [29, 30, 31, 32, 33, 34]. It seems reasonable to round the estimate up to 1% because the few older subjects may have had reflux and outgrown it. Since each kidney has a 73% chance of having compound papillae [14], the overall maximum calculated scarring risk is 0.73%. Urine infections occur commonly in children with VUR [4, 11, 35], probably because it causes incomplete bladder drainage, which promotes urinary stasis, and girls are at greater risk [5, 11, 36], presumably because of their short urethra. Therefore, a maximum of 0.73% of girls might be expected to develop a scar. We reported that 11.3% of girls in Newcastle were referred because of a urine infection by the age of 16 years, of whom 4.8% had scars [36]. This means that 0.54% of young women in Newcastle have been shown to have kidney scars, about two-thirds of the number predicted. We believe that the true incidence will be even closer to the theoretical maximum, because we know the diagnosis of urinary tract infection is commonly missed [11, 37, 38], and that some general practitioners do not refer all their cases [38]. Not surprisingly, boys have a lower incidence of scarring at 0.16% [36].

The implications of non-maturation

This hypothesis has several implications. First, if most girls born at risk do acquire scars, it indicates that the main result of our present clinical management is to identify rather than to prevent them. Preventing scarring is a difficult challenge. However, there is evidence from Sweden that this can be achieved if a higher priority is given to identifying and treating urine infections in children under 2 years [39]. The very young, with the most risk, present the biggest problems; their signs and symptoms are non-specific [5], and collecting urine requires greater ingenuity [40, 41]. Primary care doctors would need to collect a diagnostic urine sample from every infant with unexplained pyrexia [5, 42], and either use a reliable near-patient diagnostic test to exclude an infection [43] (which does not include a urine dip-test alone [42]), or start antibiotics immediately while the laborato-

ry culture is awaited. If scars form as quickly in human infants as in piglets [13], by the time the laboratory report has reached the doctor's desk, it may be too late.

A second implication concerns the management of neonates known to have VUR. This clinical situation has become increasingly common since VUR was recognised to be familial [44], and later shown to be dominantly inherited [45]. Many newborns have cystograms because their siblings [46] or other relatives [47, 48] have reflux, or because it was predicted by detection of antenatal dilatation, or because they have a contralateral multicystic dysplastic kidney [49]. Such infants are typically offered prophylactic antibiotics or urinary screening until they reach an age when they are considered risk free, presumably because their kidneys are considered to have matured by then [48]. According to the model I propose, this is illogical. If a girl is born with VUR and IRR, but is kept free of urine infections with prophylactic antibiotics up to 4 years of age, she will have been prevented from scarring if she also outgrows her VUR by 4 years. If, however, she still has VUR when she stops her prophylaxis, she will become as vulnerable to scarring at 4 years as she was as a newborn with VUR. The risk period will merely have been postponed. Unfortunately, an implication of this is that such children should be regarded as being at risk until they outgrow their reflux, which can only be determined reliably at present by cystography; a robust but less-invasive test is urgently needed. We also need to determine the best way to protect such children. Antibiotic prophylaxis is used widely, but it is not known whether this is more or less effective than careful urinary surveillance with immediate treatment of diagnosed infections.

Similar considerations apply to transplant recipients. If they reflux into the transplant ureter (either because the anastamosis allows it or because it is stented) and suffer a urine infection (both are common [50, 51]), there is a high probability that the kidney may scar, regardless of the donor age. Since reimplanting a transplant ureter is not without complications [50, 51], such patients require prophylactic antibiotics, or monitoring and prompt treatment for urine infections long term if they are to avoid scarring their graft.

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