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TOPIC PAPER

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Development of kidney scars after acute uncomplicated pyelonephritis: relationship with clinical, laboratory and imaging data at diagnosis

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Abstract *Background*: Acute pyelonephritis is a potential cause of kidney scars. *Aim*: To evaluate the relationship between clinical, laboratory and imaging data and the development of kidney scars in acute pyelonephritis. *Methods*: All consecutive patients hospitalized for acute uncomplicated pyelonephritis in our nephrology unit from June 1996 to June 2004 were considered: 58 females, median age 25.6 years (16–52). Diagnosis of pyelonephritis required parenchymal lesions shown by CT or NMR scan. *Results*: The lesions were bilateral in 17.2% (10/58) patients, unilateral, but multifocal in 81.0% (47/58); at CT or NMR, 65.5% of the lesions were classified as simple, 19% with tendency to colliquation and 15.5% abscessual. The median interval between first symptoms and diagnosis was 5 days (1–25); at referral, only 20.7% had a positive urine culture and 94.8% (55/58) had undergone previous antibiotic treatment. The therapeutic protocol required intravenous therapy for ≥2 weeks, followed by 2–4 weeks of oral therapy. At 6–8 months, the prevalence of kidney scars was 29.3%. Their development was highly correlated with the type of lesions at diagnosis (highest risk with abscessual lesions; uni- and multivariate analysis). No other clinical or laboratory marker (age, fever, positive cultures, levels of acute phase reactants, interval between onset and diagnosis) was correlated with the outcome (scars). *Conclusions*: The type of lesion at diagnosis of acute uncomplicated pyelonephritis is highly correlated with the development of kidney scars. Further studies are needed to test the therapeutic schedules tailored according to the imaging data.

Keywords Acute pyelonephritis · Kidney scars · Antibiotic therapy · Computerized tomography · Nuclear magnetic resonance

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Introduction

Acute kidney infections, with segmental destruction of the renal parenchyma, have been known since ancient times, as Egyptian and Greek medicine give clear descriptions of this potentially lethal disease. In 1910, Thiemich defined the profile of this disease in a paediatric setting [1]. According to the classic interpretation, the term "pyelonephritis" defines a non-tubercular, bacterial infection of the upper urinary tract, involving calyces, pelvis, and kidney parenchyma [1–3].

According to the presence or absence of anatomical or clinical factors, pyelonephritis is usually defined as "complicated" (presence of predisposing factors) versus "uncomplicated" (absence) or, alternatively, as "secondary" versus "primary" [4–6].

Almost a century after Thiemich's pivotal paper, there are still several reasons to critically reconsider the diagnosis, therapy and long-term sequelae of acute pyelonephritis.

Acute uncomplicated pyelonephritis is a relatively common disease affecting mainly children and young women; the symptoms are wide-ranging, from a cystitis-like illness with mild flank pain to a life-threatening sepsis [1–6].

In children, the diagnostic work-up usually includes an initial evaluation of the kidney parenchymal lesions and a subsequent control for the detection of scars, 3 months to 1 year after the initial episode; the risk of scars ranges from about 35% to almost 100% in various series [7–12].

The development of scars has been related to several factors, including patient age, the presence of parenchymal lesions at presentation and the diagnostic delay [13–18].

The natural history of kidney scars in adults is less well known, due to widespread diagnostic minimalism which limits the work-up to a general clinical evaluation (fever, flank pain, lower urinary symptoms) and a few laboratory tests (urine culture, urinary sediment analysis, blood-cell count, acute-phase reactants) [19–23].

This attitude, mainly supported by healthcare-cost constraints, should be reconsidered in the light of recent classification criteria for chronic kidney disease, defined as any persistent abnormality at imaging, in addition to reduced renal function [24–25]. Therefore, the presence of kidney scars (independently of renal function) indicates chronic kidney disease, a condition that should be controlled over time.

Furthermore, while many recent trials have investigated the best approach in ''naïve'' patients with full-blown presentation and without previous antibiotic therapy, the approaches in the cases previously treated with various antibiotics or in patients with severe disease are not standardized; however, a history of failure of previous therapy is almost the rule (at least in some settings) in patients referred to specialists, and the disease may be more severe in such cases due to a negative selection bias [19–23].

The aim of this paper was to analyze the relationship between the clinical, laboratory and imaging data at diagnosis of acute ''primary'' pyelonephritis and the development of kidney scars in 58 consecutive patients followed in a Nephrology setting (hospital ward and day hospital) and treated with prolonged antibiotic therapy. None of the patients would have fulfilled the enrolment criteria of recent trials dealing with acute primary pyelonephritis because of the recent antibiotic therapy or negative urine cultures.

Patients and methods

Patients and study setting

All consecutive patients hospitalized in the Nephrology ward or Day Hospital of the Chair of Nephrology, University of Turin, from June 1996 to June 2004 with a diagnosis of acute ''uncomplicated'' or primary pyelonephritis were selected: the entire cohort consisted of 58 patients. Only patients who were hospitalized because of acute pyelonephritis were considered (hospital-acquired cases were excluded).

The patients' charts were prospectively gathered since June 1996. The follow-up included the hospitalization and post-hospitalization periods, during which all the cases were directly followed by the nephrologists working in the hospital ward. As a rule, patients were followed until stabilization or healing of the lesions.

Diagnostic criteria

The diagnosis of acute pyelonephritis was based on involvement of the kidney parenchyma, as shown by Computerized Tomography (CT) or Nuclear Magnetic Resonance Imaging (MRI).

At presentation, the priority was an immediate imaging test, and the most readily available was chosen (more often CT). Subsequent controls were usually performed by MRI to minimize X-ray exposure. All the patients also underwent at least one ultrasound control; however, due to the low sensitivity of the test, a positive ultrasound was not considered as an inclusion criterion.

Clinical suspicion arose in the presence of various combinations of the ''classic'' clinical signs and symptoms of acute pyelonephritis, including fever, flank pain, urinary syndrome or history of recent urinary tract infection. Nevertheless, the choice of a morphological criterion meant that none of the symptoms nor the presence of a positive urine culture were required for diagnosis.

Therapeutic and control protocol

Since all the patients had kidney parenchymal lesions, long-term therapy was performed on the hypothesis that the lesions harbored an active infection and the pathogens would be present until radiological resolution occurred. The original idea was to combine at least 2–3 weeks of intravenous therapy with at least 2 weeks of oral therapy. The therapy was tailored according to the evolution of the lesions at CT or NMR scan and the anti-biogram, when available. The present therapeutic protocol consists of three phases. Phase 1: due to the usual pattern of antibiotic resistance of *E. coli* in our setting (Table 1), the therapy starts with i.v. meropenem (3 g t.i.d.) and amikacin (doses adjusted according to the

Table 1 *Escherichia coli* sensitivity to different antibiotics in the period January–June 2003 (Microbiology—S. Giovanni Battista Hospital, overall data)

Antibiotic	Hospitalized patients	Outpatients
Amikacin	100%	100%
Amoxicillin/Clavulanate	85.1%	95.8%
Ceftriaxone	96.3%	99.7%
Ciprofloxacin	71.2%	84.3%
Cotrimoxazole	61.3%	79.8%
Meropenem	100%	100%
Imipenem	100%	100%

plasma levels); the use of quinolones was not indicated as first line, as the resistance rates were already relatively high and are still growing, up to over 30% (San Giovanni Battista Hospital, Torino, Italy, Table 1). This first phase usually takes place in the hospital and lasts for 14 days. A MRI control is scheduled after 10–14 days of therapy. In the case of poor response, meropenem is continued, in association with a different, individually chosen drug. Upon improvement or resolution of the lesion, the therapy passes to Phase 2. Phase 2 consists of 7 days of once daily intravenous ceftriaxone (2 g q.i.d.), on an out-patient basis. In the meantime, the oral therapy starts and continues in Phase 3. Phase 3 consists of the oral therapy alone and lasts for a further 2–4 weeks. The oral drug is chosen on the basis of the initial anti-biogram, when available, and, in some cases, of the side effects of the previous drugs. The most widely used drugs are amoxicillin/clavulanic acid, trimethoprim sulphamethoxazole or a quinolone agent.

The working protocol presently includes two further MRI controls (at 3 and 6 months), plus renal scintiscan or ultrasound when necessary.

Radiological definitions

All the imaging data were acquired in the same settings. The radiological lesions were scored by the same skilled operator (MJ). Definition of the type of lesion was based on an integrated analysis of images taken in different phases of the tests (Fig. 1).

"Simple" lesions take up the dye in a late phase and with a homogeneous pattern. At CT and NMR scans, the lesions appear wedge-shaped, radiating from the papilla in the medulla to the cortical space, with or without swelling and with poor enhancement. "Abscessual" lesions are target-shaped: the central core does not show contrast uptake. The peripheral ring takes up the contrast media in a late phase. The lesions showing a "colliquative tendency" have an intermediate appearance: they are non-homogeneous and the target aspect is less pronounced (with different degrees). They represent the switch phase between the two previous lesions. Scarring is visible as renal parenchymal atrophy.

The diagnostic performance of MRI is strongly influenced by the technique employed. Native scans give only elementary information about renal size and the presence of scar or odema. Therefore, gadolinium-enhanced sequences were employed and dynamic studies, including the early cortical and parenchymal nephrographic phases, were performed. In these phases, acute pyelonephritis appears as a hypovascular area. Scars are easily distinguished in the later phases, and are generally hypointense in T2-weighted sequences. The resolution of MRI is similar to that of the CT scan with the contrast media (considered the gold standard), the standard resolution being about 4 mm for both. High-quality MRI studies may allow the detection of lesions up to 3 mm.

Because of the immediate availability of the CT scan, 47/58 cases were diagnosed by this technique and 11/58 by MRI; the latter was the technique of choice to control the outcome (Fig. 2).

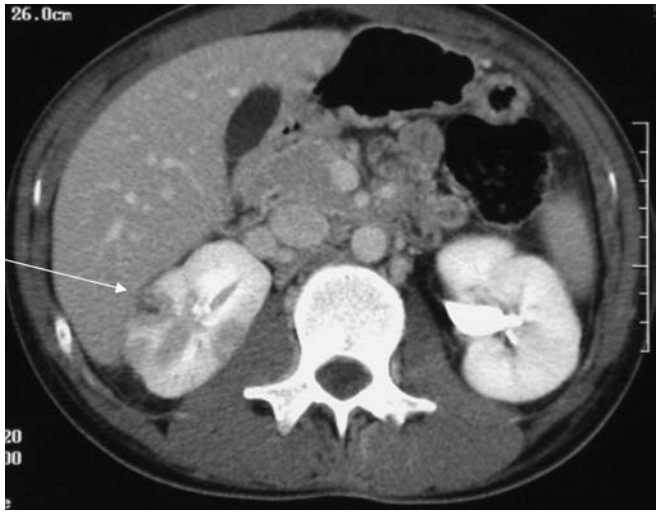

Fig. 1 Large multiple pyelonephritic lesions, including (*white arrow*) and abscessual lesion

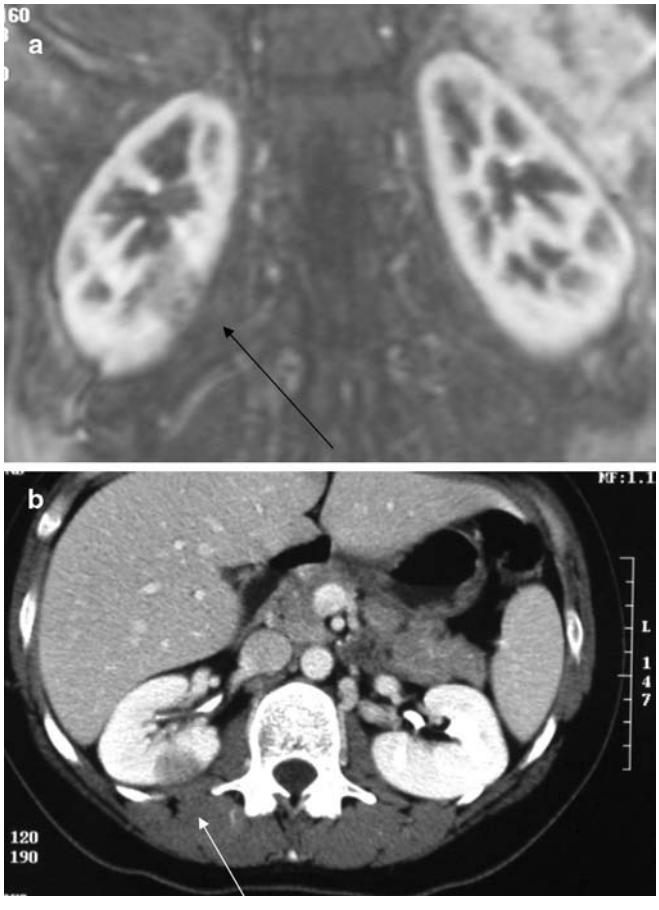

Fig. 2 **a** Another case with large pyelonephritic focus at the MRI. **b** Same case as Fig. 2. Lesions as detected at the CT scan

Table 2 Baseline data of the sample

Patient features	All cases	Responders	Non-responders	*p*
N	58	41	17	
Females	100%	100%	100%	
Age	Median 25.6 Range 16–52	Median 26.8 Range 16–52	Median 24.7 Range 16–47	0.293*
Previous APN (symptoms or scars)	5/58 (8.6%)	5/41 (12.2%)	0/17 (0%)	0.132**
Stone disease	10/58 (17.2%)	9/41 (22%)	1/17 (5.9%)	0.140**
Birth-control pills	44/58 (75.9)	30/41 (73.2%)	14/17 (82.4%)	0.457**
History of urinary tract infections	34/58 (58.6%)	25/41 (61%)	9/17 (52.9%)	0.572**

*Mann–Whitney test
**p chi square Pearson

Clinical definitions

Data were taken from the clinical charts by the same operator (MB) and reviewed in duplicate by the nephrologist in charge of the Nephrology ward (LC) and by the nephrologist dealing with the analysis (GBP).

The presence of predisposing factors was defined according to the usual clinical and imaging criteria. All the patients with predisposing anatomical or clinical factors (including diabetes, collagen disease, any serious concomitant illness, pregnancy) were excluded. The presence of previous kidney scars was not considered as a predisposing factor.

Standard laboratory data were obtained in the same two settings: the Nephrology laboratory of the Chair of Nephrology (renal clearances, proteinuria, microscopic urinalysis) and the General laboratory (ESR, CRP, blood-cell counts, cultural data).

The clinical presentation was prospectively classified as: ''progressive pattern'': increase of malaise, fever and flank pain, reaching a peak in a few days; ''biphasic pattern'': initial presentation with low fever, dull flank pain, rapidly responsive to oral antibiotic or anti-inflammatory therapy; a few days of well-being; abrupt onset of severe symptoms, with flank pain and high fever; or ''acute abdomen pattern'' as the presenting picture or within a few hours.

Study design and statistical methods

The study design was prospective historical, non-randomized.

The analysis was performed with SPSS (Version 11.0).

The descriptive analysis was performed as appropriate (mean and standard deviation for parametric data; median and range for non-parametric data).

According to the imaging data, the patients were divided into ''responders'' (no residual scar from the study episode) and ''non-responders'' (development of new kidney scars). When several lesions were present, the severest one was scored.

The univariate analysis compared the responders and non-responders with regard to the main clinical and demographic determinants: demographic data, clinical and laboratory data, potential risk factors, type of lesion (simple, colliquative tendency, abscessual).

Logistic regression was planned considering the therapeutic response as a dependent variable, and testing and the covariates resulting significant at the previous univariate analysis or, in their absence, those considered as clinically relevant.

Results

Baseline data

The main clinical and demographic features of the acute pyelonephritis patients are reported in Table 2. All the patients were females, mostly young, with a median age of 25.6 years (range 16–52). About half of them reported a history of lower urinary tract infections; a history of kidney stones was also common, and the use of birth-control pills was almost the rule (Table 2).

Clinical and imaging data

By definition, the diagnosis was based on NMR or CT scans in all the patients.

Bilateral lesions were found in 17.2% of the cases and unilateral, multifocal lesions in 81%; simple, non-colliquating lesions were present in 65.5% of the patients, a lesion with colliquative tendency in 19% and an abscess in 15.5% (Table 3). Moreover, 4/58 patients (6.9%) were diagnosed at the initial imaging work-up as already having one or more kidney scars unrelated to the study episode.

The overall prevalence of positive conventional ultrasounds was low (31/58: 53.4%) (Table 3). Ultrasound positivity was significantly correlated with the presence of severe lesions (the prevalence of positive ultrasound was 8/11 in lesions with colliquative tendency, 8/9 in abscessual lesions and 15/38 in simple lesions; $p = 0.01$). Positive ultrasounds were also significantly correlated with the outcome (kidney scars) (Table 2).

At least, two of the ''paradigmatic'' clinical signs (malaise, high fever, costo-vertebral pain and tender-

ness, urinary syndrome) were present in all the cases; however, one patient had no flank pain, only about half had lower urinary symptoms and two patients were non-febrile at the time of diagnosis (Table 3).

The median interval between the first symptoms and diagnosis was 5 days (1–25 days); 39 cases were referred from the emergency room, six from the outpatient unit and 13 from other hospital wards. At referral, serum creatinine was within the normal range in most patients (86%), but >1.2 mg/dl in eight patients; acute inflammatory signs at diagnosis were the rule (Table 3).

Urine culture was negative in most cases (positive in only 12/58 patients), presumably due to the previous antibiotic therapy (reported by 55/58 patients in the last 2 days). The pathogens cultivated in the positive cases were: *E. coli* in eight cases; *Staphylococcus epidermidis*, *S. aureus*, *Torulopsis glabrata*, and *Enterococcus faecalis* in one patient each. Precise data on the previous antibiotic therapy are lacking, due to frequent recall bias; in the recent years, however, low-dose quinolones (e.g. Ciprofloxacin 250 mg twice daily) were relatively frequent (recorded in eight cases).

Interestingly, a negative urine culture was compatible with severe, abscessual lesions (Table 3).

The most frequent clinical presentation pattern was the ''progressive pattern'', i.e., increase of malaise, fever and flank pain, reaching a peak in a few days (81%), followed by the ''biphasic pattern'' (present at diagnosis

Table 3 Disease presentation: imaging, laboratory and clinical data

		All cases	Responders	Non-responders	*P*
Imaging data	Positive ultrasounds *N* (%)	31/58 (53.4%)	18/41 (43.9%)	13/17 (76.5%)	0.024**
	Single/multiple lesions *N* (%)	Single 11/58 (19%) Multifocal 47/58 (81%)	Single 8/41 (19.5%) Multifocal 33/41 (80.5%)	Single 3/17 (17.6%) Multifocal 14/17 (82.4%)	0.869**
	Bilateral *N* (%)	10/58 (17.2%)	8/41 (19.5%)	2/17 (11.8%)	0.477**
	Simple lesions *N* (%)	38/58 (65.5%)	33/41 (80.5%)	5/17 (29.4%)	0.000**
	Colliquative tendency *N* (%)	11/58 (19%)	6/41 (14.6%)	5/17 (29.4%)	0.191**
	Abscesses *N* (%)	9/58 (15.5%)	2/41 (4.9%)	7/17 (41.2%)	0.001**
Laboratory data at diagnosis	Positive urine culture *N* (%)	12/58 (20.7%)	10/41 (24.4%)	2/17 (11.8%)	0.280**
	ESR (mm/h) median (range)	53 (13–133)	51 (13–133)	54 (17–103)	0.500*
	CRP (mg/l) median (range)	41 (2–272)	36.5 (2–272)	96 (8–217)	0.094*
	WBC (N/mm^3) median (range)	14,030 (4,230–39,000)	13,000 (4,230–33,000)	16,440 (6,500–39,000)	0.086*
	SCr (mg/dl) median (range)	0.85 (0.5–2.5)	0.8 (0.5–2.5)	0.95 (0.7–2)	0.089*
	Leukocyturia *N*/field	<6: 19/58 (32.8%) 6–12: 18/58 (31%) >12: 21/58 (36.2%)	<6: 11/41 (26.8%) 6–12: 13/41 (31.7%) >12: 17/41 (41.5%)	<6: 8/17 (47.1%) 6–12: 5/17 (29.4%) >12: 4/17 (23.5%)	0.115*
	Microhematuria	41/58 (70.7%)	31/41 (75.6%)	10/17 (58.8%)	0.201**
	Urinary casts	11/58 (19%)	8/41 (19.5%)	3/17 (17.6%)	0.869**
Symptoms and other elements at diagnosis	Fever	56/58 (96.6%)	39/41 (95.9%)	17/17 (100%)	0.354**
	Flank pain	57/58 (98.3%)	40/41 (97.6%)	17/17 (100%)	0.516**
	Lower tract symptoms	33/58 (56.9%)	24/41 (58.5%)	9/17 (52.9%)	0.695**
	Time between symptoms and diagnosis: median (range)	5 (1–25)	6 (1–25)	5 (1–15)	0.621*
	Time between symptoms and diagnosis	1 day 6.9% 2 days 5.2% 3 days 15.5% 4 days 12.1% 5 days 8.6% ≥6 days 46.5% Missing 5.2%	1 day 4.9% 2 days 2.4% 3 days 19.5% 4 days 12.2% 5 days 7.3% ≥6 days 48.8% Missing 4.9%	1 day 11.8% 2 days 11.8% 3 days 5.9% 4 days 11.8% 5 days 11.8% ≥6 days 41% Missing 5.9%	0.396**
	Referral Outpatient Emergency room Other wards	6/58 (10.3%) 39/58 (67.2%) 13/58 (22.4%)	5/41 (12.2%) 28/41 (68.3%) 8/41 (19.5%)	1/17 (5.9%) 11/17 (64.7%) 5/17 (29.4%)	0.603**
	Progressive pattern	47/58 (81%)	34/41 (82.9%)	13/17 (76.5%)	0.568**
	Biphasic pattern	7/58 (12.1%)	3/41 (7.3%)	4/17 (23.5%)	0.084**
	Acute abdomen pattern	4/58 (6.9%)	4/41 (9.8%)	0/17 (0%)	0.182**

*P Mann–Whitney test
**P Pearson's chi square

in 12.1%) and the "acute abdomen pattern" (6.9%) (Table 3).

Prevalence of kidney scars, follow-up and outcome predictors

The overall prevalence of kidney scars was 29.3%.

The time to radiological stabilization-healing of the lesion was long: at 15 days, 12/12 patients who underwent an imaging examination had active lesions; 24/42 patients with a control at 1 month had active lesions. The evolution toward healing or scarring was complete at 6 months in all the patients.

Conversely, the time to normalization of clinical inflammatory signs was relatively short: fever, median of 3 days (1–8 days), ESR 9 days (3–90 days), CRP 9 days (2–66 days).

The clinical tolerance to long-term therapy was good: the most common minor side effects were a slight increase in cytolysis liver enzymes and a moderate and transient leukopenia (in ten cases).

The prevalence of scars was the highest in abscessual lesions (77.8%), followed by lesions with colliquative tendency (45.5%) and "simple" lesions (13.1%; $p < 0.001$).

None of the clinical or laboratory parameters was correlated with the selected outcome, except for the type of initial lesion ($p < 0.001$) and renal ultrasound positivity ($p = 0.024$), the latter correlated with the presence of renal abscesses (Table 3).

The role of the initial lesions was further confirmed by the multivariate analysis (p: 0.016, Table 4).

Discussion

Our main finding was a high correlation between the type of kidney parenchymal lesion at diagnosis and the development of kidney scars; none of the other clinical or biochemical parameters was significantly correlated with kidney scarring (Table. 3, 4).

The context in which the study was performed had several peculiarities that need to be considered before the results can be generalized.

First, the subjects were patients who could not be enrolled in a randomized controlled trial; this was mainly because of the previous empirical antibiotic therapy and negative urine cultures, both are usually considered as the reasons for exclusion in the large trials on which the common guidelines are based [19–23].

The Nephrology setting is the second point distinguishing our study from the recent trials, mostly performed in General Medicine or Urology settings [19–23, 26–28]. This is probably an effect of the logistics of our Hospital (a "tertiary" University hospital): patients are usually referred because previous therapeutic approaches have failed, and acute "uncomplicated" pyelonephritis is traditionally followed in Nephrology.

Moreover, because of our co-operation with infectiologists, the protocol used in our setting includes prolonged anti-microbial therapy. This decision is based on the "classic" assumption of our Nephrology school that active lesions (not yet healed or evolved into kidney scars) still harbor the pathogens and that the scars may have a detrimental effect on kidney function [30].

None of these assumption has been proven. However, the evidence against them is also relatively weak, in particular concerning the long-term effect of kidney scars. Indeed, even the longest studies did not follow the patients for more than 10–20 years, a period that may be too short to reveal a detrimental effect in a population at low risk of chronic kidney disease, such as young women or children [13–18, 24–25].

In our setting, the prevalence of kidney scars (29.3%) was lower than that usually reported in adults (approximately 50%) [13, 15, 30–32].

Discussion of the reasons for our policy and the effect of this non-randomized study design on the development of kidney scars is beyond the scope of the present study, which is mainly focused on the predictors of scar development at the baseline. However, the hypothesis that only long-term antibiotic therapy (allowing a low prevalence of scars) can modulate the results and permit the disclosure of differences (otherwise masked by a higher prevalence of scars) should be kept in mind.

In this context, it is noteworthy that none of the clinical or biochemical parameters was correlated with the severity of the lesions nor with the outcome (kidney scars), with the partial exception of renal ultrasound

Table 4 Multivariate analysis

Covariates	*B*	SE	Wald	*df*	Sig.	Exp(*B*)
Age	0.037	0.043	0.748	1	0.387	1.038
Abscess (versus other)	−2.471	1.022	5.843	1	0.016	0.085
SCr	1.099	0.959	1.311	1	0.252	3.000
WBC count	0.853	1.153	0.548	1	0.459	2.347
CRP	0.008	0.005	2.240	1	0.135	1.008
Constant	−2.659	2.164	1.510	1	0.219	0.070

Probability of being a "responder" according to the different covariates. Age, serum creatinine (*sCr*), white blood-cell count (*WBC*), C reactive protein (*CRP*) are dichotomized at the median value. Abscessual lesions are dichotomized versus the other lesions (simple and with colliquative tendency)

positivity, which reflects the severity of the lesions. The overall prevalence of positive ultrasounds (53.4%) was in line with literature reports (about 50% positivity); however, the finding of higher sensitivity to severe lesions (8/9 in abscessual lesions, 8/11 in lesions with colliquative tendency) suggests that this method can identify up to 80% of severe lesions.

This study, the first to demonstrate a significant relationship between the type of lesion and the development of kidney scars, suggests several further clinical and research topics.

The relationship between the type of lesion and the development of kidney scars should be tested on a larger scale and with different antibiotic therapies; the importance of a longer course of antibiotics in avoiding scars is suggested by our data but cannot be proved without sufficiently large randomized controlled trials or, at least, well-designed prospective observational studies.

To define the optimal antibiotic therapy and duration, further studies are needed in settings with a negative selection bias (such as ours) and where the patients are routinely referred after the failure of the empirical antibiotic therapies. Last but not least, the appealing idea of tailoring the duration of therapy according to the imaging data should be tested in different patient populations.

Acknowledgments Preliminary data on 52 patients were presented in a Nephrology Forum in Milan, Giornate dell'Ospedale san Carlo Borromeo, December 2003.

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