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An increasing number of calcium oxalate stone events worsens treatment outcome

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An increasing number of calcium oxalate stone events worsens treatment outcome. Current practice recommends metabolic evaluation of patients who have formed multiple renal stones, but not those with one stone or temporally remote stones. This presumes that recentness and recurrence imply greater risk of new future stones. We hypothesize that number of stones reflects how long patients are permitted to form stones untreated, and that forming more stones, itself, raises risk of future stones despite treatment. Our report is a retrospective analysis of 371 male patients selected from a comprehensive clinical and laboratory data base containing 2,527 patients with nephrolithiasis. Before treatment, number of stone events rises with time of observation, and rate of stone event occurrence is constant or falls. During treatment, relapse is correlated with number of pretreatment stones. Life table analysis showed increasing relapse for patients grouped into those with one, two, and three or more stones. Even though number of stones seems controlled by the interval of observation before treatment, more stones predict higher relapse during treatment. Perhaps by leaving nuclei of crystals as residues, stones appear to promote new stones, and the practice of waiting while patients declare themselves multiple stone formers may not always be the best.

The number of stones a patient has formed, and the recentness of new stones, are widely used to assess need for metabolic evaluation and treatment. For example, the NIH Consensus Conference on Nephrolithiasis recommends metabolic evaluation for adults with two or more stone events, but not for those with only one event [1]. Pak [2] comments that the potential benefit of evaluating single stone formers may not justify the cost. Smith [3] recommends that patients with one stone, and patients whose stones all occurred in the past, be given conservative management, and not studied extensively. The practice of evaluating and treating patients with many and recent stones, and only counselling patients with single or temporally remote stones, to maintain high urine volume and prudent diets, assumes that more and recent stones mean a greater stone forming propensity within the patient. This presumption implies either a higher frequency and severity of stone forming metabolic disorders than would be found among patients with one stone or no recent stones, or a greater risk that such disorders will lead to active stone disease if untreated.

The first of these two implications does not accord with what we have reported; stone number is not related strikingly to the accepted metabolic causes of stone formation. Among patients with only one stone each [4], not divided by sex, we and Pak [5] found the same metabolic disorders as among patients with multiple stones, except for less marked hypercalciuria. Among patients with over 10 stones each, we found no different [6] mixture, or severity, of metabolic disorders than among all other patients, except that [7] women with above 10 stones had higher urine calcium excretion rates than women with less than 10 stones. Timing and number of stones do not seem to predict the outcome of metabolic evaluation.

Our findings do support the second implication, though indirectly. In our appraisal of factors predicting relapse of treated stone disease, we [8] reported that the interval between the last pretreatment stone and the beginning of treatment predicted relapse: the shorter the interval, the higher the risk of relapse. Since nucleation of calcium oxalate monohydrate (COM), the principle stone forming salt [9], requires higher supersaturations than growth and aggregation [10], any preformed nuclei can foster COM stones. Each stone may deposit COM nuclei in kidneys or renal papilla, and leave some behind after passing. Therefore, past stones could foster new stones, and increase the stone forming response to metabolic abnormalities: stone forming, itself, could promote stones.

We hypothesized that the number of stones an untreated patient forms reflects how long that patient is observed. Longer intervals permit more stones, and more stones, even if due simply to longer intervals, increase the likelihood of relapse during treatment. In the present study, of men stone formers, we find that the number of stones is dependent upon the interval of observation, not the stone forming rate. Nevertheless, number of stones predicts relapse during treatment. That the number of events predicts relapse, yet reflects mainly how long the disease is left to progress untreated, supports the idea that increasing numbers of stones can increase the likelihood of more stones, despite treatment.

Methods

Patients

From our complete series of 2,527 patients, we selected all with calcium oxalate stones documented by stone analysis, in whom we could exclude systemic or renal diseases that cause stones including: primary hyperparathyroidism [11], enteric hyperoxaluria, bowel resection or inflammatory bowel disease [12], primary hyperoxaluria [13, 14], renal tubular acidosis [15],

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and sarcoidosis [16]. We also excluded a patient if any stone contained struvite [17], cystine [18], or more than 50% uric acid or calcium phosphate, even if other stones contained only calcium oxalate. This left 807 calcium oxalate stone formers free of apparent stone forming systemic diseases. Of these, 508 had received treatment for at least 2.5 months, and were taken as the group for initial inclusion. In this group, the main accepted causes of stones included idiopathic hypercalciuria, hyperuricosuria, hypocitrituria, dietary hyperoxaluria, and low urine volume [19–21]. The limited number of women (137) did not permit the kind of analysis we wished to perform, and we were unwilling to pool men and women, because we [22–25] have repeatedly described important gender differences in stone disease. Therefore, we have considered only the 371 men.

Laboratory evaluation

We obtained, at entry, three or four 24-hour urines [19], collected from outpatients on open diets, in which measurements were made of: calcium, oxalate, uric acid, pH, citrate, phosphate, sodium, potassium, magnesium, volume, chloride, sulfate, and creatinine. At the conclusion of each collection, between 7:30 and 9:00 a.m., 12 hours after the last meal, blood was measured for calcium, magnesium, phosphate, uric acid, creatinine, sodium, and potassium. At six to eight weeks of medical therapy for metabolic disorders, and yearly thereafter, each of these materials was measured in one urine and blood.

Clinical evaluation

All patients were evaluated clinically by one of us (FLC). From medical records and history, and reading of all available radiographs, the time course of new stone formation and passage was constructed, in which a new stone means the appearance by radiograph, or the passage or removal, of a stone not present on a prior radiograph [19, 26]. Each new stone carried the best available date, which was rounded here to the nearest day. Each date of a medical record, x-ray, or procedure, whether associated or not with a new stone, was entered as a data acquisition date, also rounded to the nearest day.

Many stones may occur in one event; especially among patients who have many stones, clusters of stones may pass within a day or even hours and may appear on radiographs separated by only months. Therefore, a data acquisition date may contain more than one stone, and all new stones within a given acquisition date carry that one date. Our analysis uses both events and stone counts. A new stone event means a dated documentation of one or more stones; a new stone means one of the component stones within an event, which may vary from at least one to as many as are counted.

Family history and medication history were taken initially using a formatted patient questionnaire. The questions included stones in first and second degree relatives, names and durations of all medications prescribed for stone prevention, and dates and types of procedures and hospitalizations for stone passage events. Clinical history was taken directly for each point, using the question responses as a prompt. New stones in family members after the initial visit were entered when patients reported them.

Many patients had treatments offered before they came here, including medications, high fluid intake, and diet modifications. Despite an interest in these, we have found patient recollections and past medical records were fragmentary, at best. In particular, treatments were vaguely dated, and usually of very brief duration. We took the long-term strategy of studying patients on the diets and fluid intakes most consistent with their usual habits over the preceding years, so that important effects of either, that could alter urine chemistries, would be detected.

Subsequent to entry, all patients were followed to the degree possible, treating their metabolic disorders in the usual manner [8, 19, 20, 27–30]. Using thiazide, potassium alkali salts, allopurinol, reduced diet oxalate, purine and sodium, and increased water, the urine calcium, oxalate and uric acid were reduced and urine citrate increased to or as close as possible to the normal range, and raise urine volume to >1.5 liter/day. Data acquisition dates after entry included all visits, x-rays, stone passage, changes in medications, and telephone contact with patients, or their doctors. Data acquisition dates could be positive or negative for a stone event; positive dates were coded as relapse.

Compliance during treatment was assessed mainly from laboratory evaluation, supplemented by visits and telephone calls. Most patients told us they were compliant, but when confronted by evident disparities, such as low urine volume, high urine oxalate, urine citrate and pH that did not rise with supposed citrate treatment, urine calcium that did not fall with thiazide, would then admit to a certain lack of consistency. For this reason, urine chemistries were rechecked after one to three months of treatment and yearly thereafter. The full range of treatment data is shown, as what we believe is the most reliable and objective measure of compliance and effectiveness of treatment.

Laboratory methods

Calcium and magnesium were measured by atomic absorption, uric acid by the uricase method [31], citrate using citrate lyase [32], sodium and potassium by flame photometry, creatinine by the acid picrate method, phosphate by the autoanalyzer method, oxalate by zinc reduction (until 1990) [33], and oxalate oxidase (after 1990), pH by electrode.

Statistical methods

All data were kept in a specialized data base using a DataPerfect (WordPerfect Corporation, Ogen, Utah, USA) engine. Patients were selected as noted above, and their data arrays analyzed using the SYSTAT system (SYSTAT, Inc, Evanston, Illinois, USA). Life table analysis used the Survival module of Systat; time in the post-treatment period was taken from onset of treatment to date of last data acquisition; censoring was at first relapse stone event.

We observed that frequency of events and stones was linear when plotted as logarithms on half normal plots [34]. Therefore for all analyses of correlation between either one and metabolic measurement, for *t*-tests, and for entering either into proportional hazard models, both the logarithmic and non-transformed counts of events and stones were used. Our correlation studies employed corrections for multiple testing, as did our *t*-testing. The rate of pretreatment stone forming was calculated as the number of stones formed, divided by the time in years from the first stone to entry into our program. Event rates were similarly calculated.

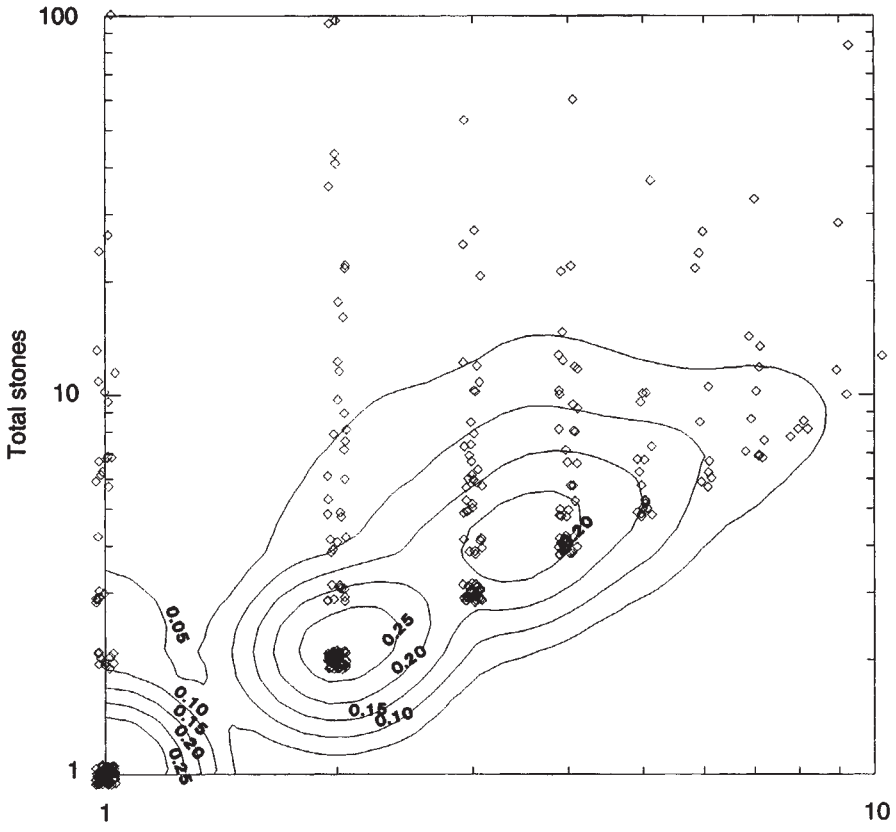

Fig. 1. *Numbers of stones and of stone events among patients with calcium oxalate nephrolithiasis.* Number of stones (y axis) and stone events (x axis) prior to entering treatment in men with calcium oxalate nephrolithiasis. Each point represents one patient. The contour lines connect regions of equal density of points. Clusters are apparent at 1 and 2 events, and a region bounded by 3 and 4 events.

Results

The majority of men had one to four events (Fig. 1) as shown by the thickness of data clusters at those regions. Stones and events are presented as logarithms, because both were log normally distributed (not shown). The overlying plot depicts the density of points on the plane of the graph as contour lines, representing five density levels from 0.05 to 0.25 [34] using a weighting algorithm. Each could, if so drawn, represent an increasing height above the page. Many patients had one event with one stone (left lower corner), a subgroup had one event with two or three stones (along left axis of figure). Another large group of patients had two events with two to four stones (second vertical line of points from left side of figure). A third distinct cluster appears to the right of the cluster at two events, comprised of patients with three and four events, and up to five stones. About the three centers, points spread upwards because events had more than one stone each; below the line of identity, contour plots circle about each other, by convention, but no points could be present.

Increasing time of observation, not event rate, correlates with an increasing number of events (Fig. 2). Mean value of observation time (open circles, Y axis) rises in proportion to an increasing number of events, whereas the mean event rate (star symbols, Y axis) falls or stays constant between two and six events. The number of events reflects mainly the time of observation between first stone and the start of treatment, and is therefore an artifact of how long patients or their doctors waited before making use of our program. Single stone formers entered our program shortly after their stones, as shown by the short interval. Note that the figure presents mean stone event

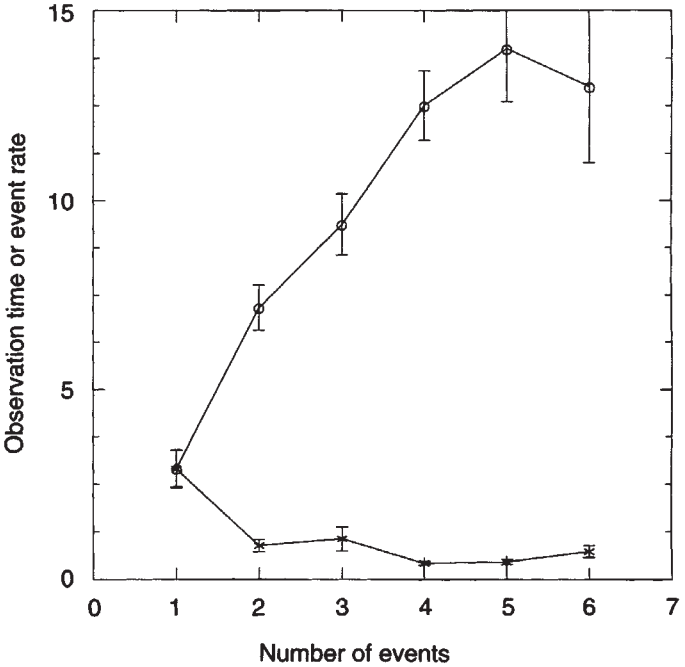

Fig. 2. *Event rate and observation time vs. number of stone events.* Values are Means ± SEM. Event rate (stars) fell between 1 to 2 events, then remained constant; number of events (x axis) increased. Years of observation (open circle) increased in proportion to increasing events.

rates, which are formed for each patient as the ratio of events to time of observation. Because the ratio of a mean is usually unequal to the mean of the ratio, one cannot calculate the

Table 1. Selected clinical and laboratory measurements in relapse and non-relapse patients

Measurement	Relapse	No relapse
Number of subjects	71	300
Age at entry *years*	40 ± 1	44 ± 1[c]
Age at first stone	31 ± 1	35.8 ± 0.6[d]
Stones in family *(%)*	30 (42%)	121 (41%)
Follow-up interval *years*	5.2 ± 0.54	6.8 ± 0.28[c]
Total stones/pt	5 ± 1	3 ± 1[c]
Number of events/pt	3.75 ± 0.40	2.68 ± 0.15[c]
Event rate *#/year*	1.79 ± 0.68	1.38 ± 0.14
Duration of stones *years*	9.26 ± 0.91	7.7 ± 0.41
Urine volume (liter/24 hr)	1.50 ± 0.07	1.72 ± 0.05[b]
Urine [calcium] *mg/liter*	185 ± 9	162 ± 4[b]
Urine [oxalate] *mg/liter*	28 ± 1	24 ± 0.5[d]

Laboratory measurements are before treatment; during treatment, no laboratory measurements differed. Stones and events are all pretreatment.

[a] Interval (years) from onset of treatment to last dated new clinical information Differs from relapse, [b] $P < 0.05$, [c] <0.02, [d] <0.001

expected mean event rate by simply dividing the number of events by the mean observation time, nor calculate the correct mean observation time by multiplying the event number by the mean event rate.

Since our question concerned relapse, we divided our patients into those who did and did not relapse (Table 1). Men with relapse were younger, followed up for a shorter interval after treatment, had more pretreatment stones and stone events, and lower pretreatment urine volume (Fig. 3A and Table 1), and correspondingly higher pretreatment calcium and oxalate concentrations (Table 1) than men who did not relapse. Calcium and oxalate excretion rates were the same in relapse and no relapse patients before treatment (Fig. 3A). The fraction of patients with a family history of stones in first degree relatives was the same for relapse and non-relapse patients (Table 1).

No other laboratory measurement during the pretreatment (Fig. 3A), or treatment periods (Fig. 3B), nor change in any measurement between pretreatment and treatment intervals (Fig. 3C) differed between patients who did and did not relapse. As expected, treatment raised urine pH, urine volume, and urine citrate, and greatly reduced urine calcium as can be seen from the graph of changes for their values (Fig. 3C). Changes for the two groups were not different, and values overlap (Fig. 3C). No correlation coefficient between either stone number or event number and any of these laboratory measurements was significant (not shown). Given the overlap of all relevant urine measurements, classifications of patients into such categories as hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitrituria were equivalent, by definition, and are not further shown. Although our figures (Fig. 3A-C) omit normal ranges, for clarity, the degree of restoration of all chemistries into the normal range by treatment was equivalent, as the final values (Fig. 3B) overlap.

To determine the independent covariates of relapse, we calculated the Cox proportional hazards model [35, 36] using all of the variables that differed between those with and those without relapse (Table 2). Age, pretreatment urine volume, and the logarithm of total stone events contributed. From the regression coefficients, we calculated the relative risk (RR, Table 2) when each of the three prognostic variables was displaced 1 SD above or below its mean value; this relative risk is the ratio of the hazard function at the displaced value of the prognostic variable to the hazard function at the mean value. When the number of events changes between 0.24 and 4.4 events, for example, a swing of 2 SD, risk rises by 2.85; in contrast, increasing age or increasing urine volume before treatment reduces risk.

Given the important predictive value of pretreatment event number for relapse, and that the numbers of events in our population were clustered into one, two, and three or more (Fig. 1), we divided our patients into those having one, two, or three or more events to determine if this division accurately predicted relapse. Non-parametric survival curves (Fig. 4) for the three groups separate clearly, and differ by log rank testing ($P < 0.001$ for Mantel-Haenszel, Breslow-Gehan, and Tarone-Ware chi square statistics).

As expected (Table 3), the three groups differ in number of pretreatment stones, and the fraction of patients who relapsed was highest in Group 3, lowest in Group 1 ($\chi^2 = 10.2$, $P < 0.01$). Age no longer varied smoothly with relapse. As in the pooled analysis of Figure 1, time of observation increased with number of stone events in each group, and rate decreased between one and two events. Urine pH during treatment was highest in Group 3. A proportional hazard analysis of the seven observations (excluding relapse fraction) that differed among the three groups (Table 3), revealed total stones formed [0.02 regression coefficient (0.005 to 0.034 95% CI), $P = 0.008$] and age [−0.026, (−0.053 to −0.003 95% CI), $P = 0.026$] as significant. In other words, even after grouping by event number, number of stones itself offered an additional prediction of relapse, as did younger age.

Discussion

The majority of male stone patients studied had had between one and five episodes of new stones between the beginning of their disease and the time their treatment began, and within this interval the number of events correlated mainly with the time between onset of disease and treatment, not differences in stone forming rate. Even though the number of events reflected time of observation, and the latter depended upon when patients and their doctors chose to use our program, the number of events predicted outcome of treatment, whereas accepted urinary stone risk factors [30] such as urine calcium, oxalate, and citrate did not, and left as remaining independent predictors only age and pretreatment urine volume.

We suggest, for men, at least, that increasing numbers of stones somehow promote more stones, despite treatments that reduce urine supersaturation, such as thiazide, citrate and water, or reduce nucleation such as Allopurinol or reduced dietary purine levels. Our past results [8] seem rather prescient, in that a short interval between start of treatment and the last new stone predicted relapse during treatment, as though a recent stone had somehow affected treatment outcome. Possibly, repeated stones deposit nucleation centers within tubules or on urinary surfaces [37]. Crystals may adhere to renal cells, damage them, and set up nucleation sites [38]. Many stones may simply increase risk that tiny new stones will be present at the start of treatment, too small to see on radiographs, yet able to grow or even nucleate new crystals, and appear later as

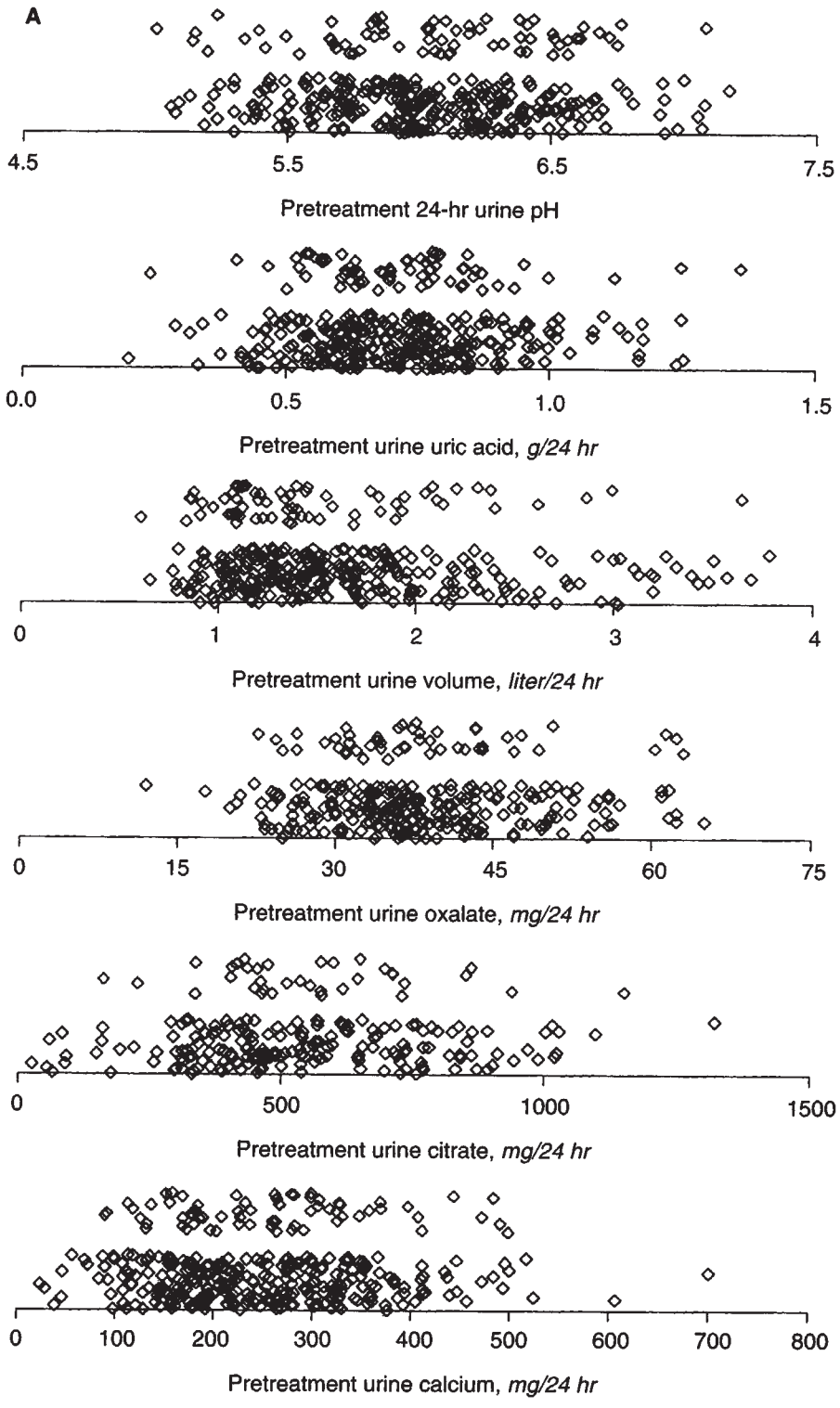

Fig. 3. *Pretreatment* (**A**), *during treatment* (**B**), *and difference between pretreatment and treatment* (**C**) *for 6 major urinary stone risk factors.* Lower portions of each plot represent non-relapsing patients, upper points those with relapse. Mean values for pretreatment urine volume, urine calcium concentration and urine oxalate concentration differed between relapse and non relapse patients, and are in Table 1. No other values differed between groups. All values for changes (Fig. 3c) differed significantly from zero except for fall in urine oxalate, relapse patients. Normal mean values for men 1 ± SD are: calcium 169 ± 146 mg/24 hr; citrate 531 ± 416 mg/24 hr; oxalate 35 ± 17 mg/24 hr; volume 1.27 ± 104 liter/24 hr; uric acid 0.674 ± 0.330 g/24 hr, pH 6.01 ± 0.05.

"new" stones. All of these seem reasonable hypotheses for other investigations.

Our finding that time of observation controls the numbers of stone events is consistent with a lack of correlation between number of stone events and metabolic stone risk factor measurements [4, 6, 7]. If the number of stone events reflects mainly time of observation, then no correlation would be expected. Patients can be considered as reasonably homogeneous in stone forming propensity, and merely permitted varying times to express that propensity.

A number of objections to our conclusion must be considered. One might hypothesize that our patients with many stones

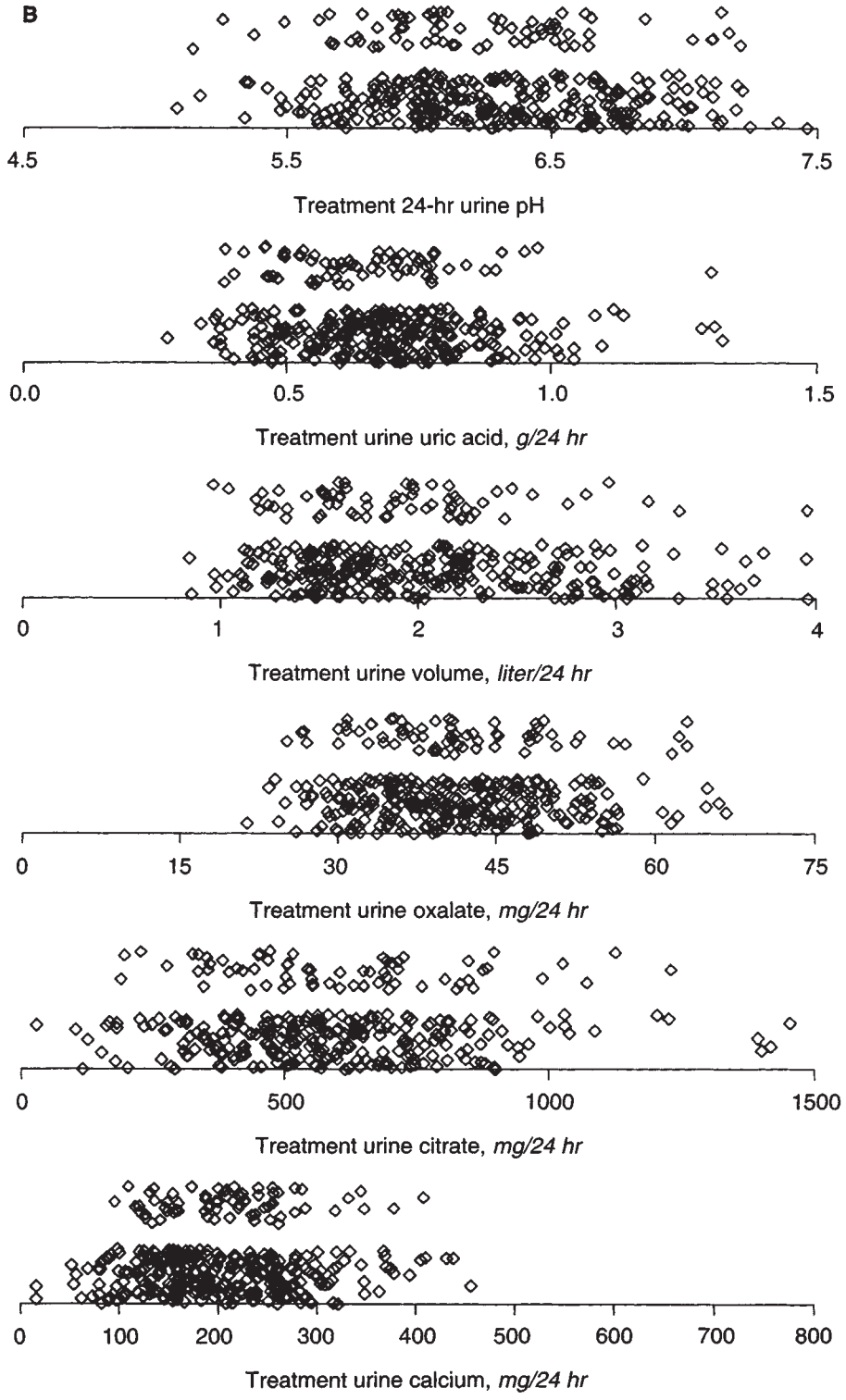

Fig. 3. *Continued*

failed on treatment elsewhere before referral to us, and are therefore selected as treatment resistant. However, we found that treatment efforts before referral were of little significance. Of the 371 patients, only 10 received any treatments apart from diet advice, and of these, only five took sustained treatment for more than three months. One might conjecture that patients with many stones were less vigorously treated here than those with one stone, but recurrent stone formers were always offered the same or more vigorous treatments in our program than those with only one stone. It seems unlikely, therefore, that selective undertreatment of patients with many pretreatment stones could have caused more relapse in this group. Low

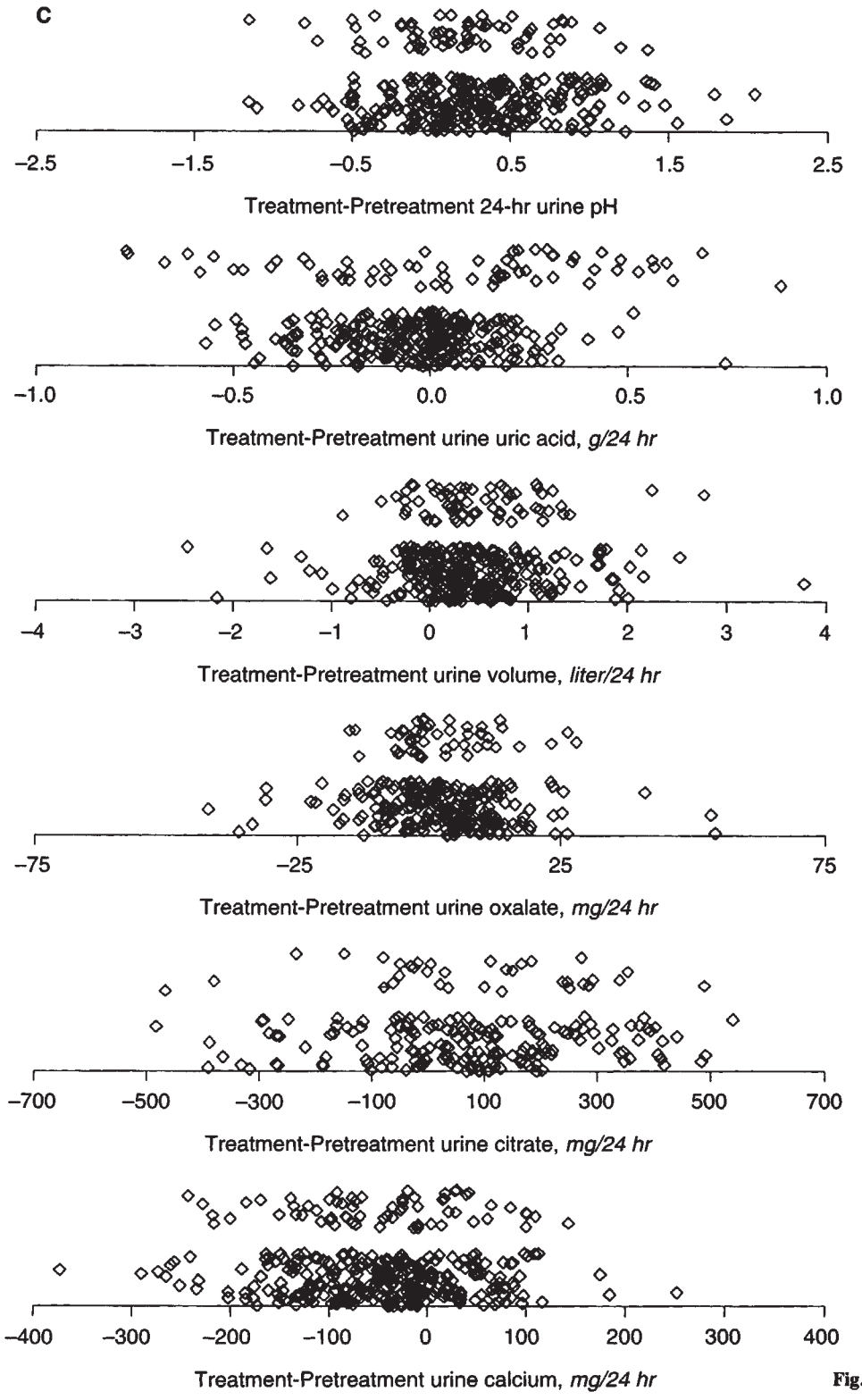

Fig. 3. *Continued*

calcium diet, suspected as a cause of increased stones [39], is not used in our program because of risk of bone disease [40–44]. Our follow-up program is fixed at six weeks and yearly thereafter for all patients, and those with more pretreatment stones did not receive higher follow-up measurement rates; this excludes systematic overcounting of relapse among them from greater surveillance. Our data presented here absolutely exclude differences in all measured urine stone risk factors except

Table 2. Independent covariates of relapse estimated by Cox proportional hazards method

Prognostic Variable	Regression Coefficient	*P*	Max LL	RR Low	RR High	Ratio of Risks
Log # of events	0.776 (.445 to 1.108)	0.000	−345.766	0.592	1.688	2.85
Age years	−0.029 (−.053 to −.005)	0.019	−342.710	0.727	1.374	1.89
Urine volume liter/day	−0.376 (−.805 to .053)	0.086	−340.999	0.752	1.33	1.76

Regression coefficients have units of (1/the variable), and are shown with 95% confidence intervals in parentheses. *P* values are two sided significance levels for coefficients. The *P* value for regression including all variables shown is <0.001; Abbreviations are: Max LL, log likelihood (LL) estimate of regression fit; starting value for LL is 354.3. RR, ratio of hazard function for values of prognostic variable 1 SD below or above mean values to the value of the hazard function at the mean value; RR low is the ratio when the variable is displayed 1 SD in the direction that reduces risk, that is, less events, higher age or volume; RR high is the opposite; ratio of risks is the ratio of RR values, high/low, for example an increase of age from 1 SD unit below to 1 SD unit above the mean increases risk of relapse by 1.89, or 89%; mean values for prognostic variables with SD are: Log # events, 0.81 ± 0.68 (2.24 ± 2 events); age, 42.8 ± 11 years; urine volume before treatment, 1.67 ± .76 liter/day.

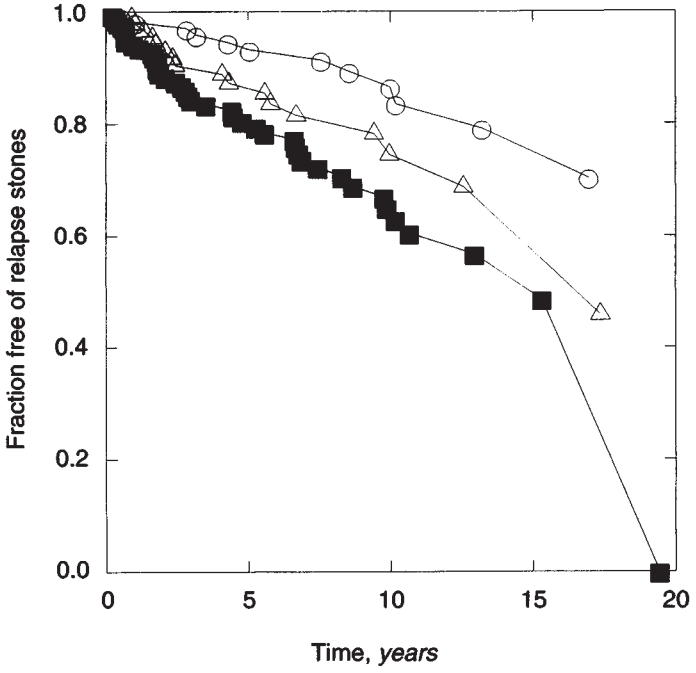

Fig. 4. *Stone relapse among men with treated calcium oxalate nephrolithiasis.* Open circles are men with one stone event, open triangle men with two stone events, and closed squares men with three or more stone events before starting treatment. Empirical Kaplan Meier life table method.

Table 3. Observations that differed among men grouped by number of stone events

Measurement	Group 1	Group 2	Group 3
Number of patients	114	96	161
Number (%) with relapse	12 (10.5)	17 (17.7)	42 (26.1)
Number of pretreatment stones per patient	3.36 ± 0.92	6.9 ± 1.6	10.1 ± 1.4[c]
Age *years*	42 ± 1	41 ± 1	44 ± 1[d]
Time from 1st stone to entry *years*	2.91 ± 0.48	7.13 ± 0.6[c]	12.1 ± 0.5[de]
Rate (stones/year)	4.91 ± 0.81	2.09 ± 0.63[c]	2.25 ± 0.92[a]
Time of follow-up *years*	7.4 ± 0.5	6.4 ± 0.5	5.9 ± 0.4[b]
Age at first stone *years*	39.3 ± 1.1	33.9 ± 1.1[c]	32.2 ± 0.7[c]
Urine pH during treatment	6.19 ± 0.04	6.28 ± 0.05	6.31 ± 0.04[b]

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$ vs. group 1, [d] $P < 0.05$, [e] $P < 0.001$ vs. group 2

Groups are patients with 1, 2 and 3 or more events, respectively. Percent relapse differs among the 3 groups, $\chi^2 = 10.7$, $P < 0.01$).

as noted. We find it curious that urine volume before treatment predicts relapse, yet urine volume during treatment does not. We cannot explain this. Finally, family history of stones is associated with relapse [45]; however, family history of stones occurred to an exactly equal extent in relapse and non-relapse patients in this study.

The clinical implications of our study, if correct, must affect practice. If increasing numbers of events worsen prognosis for men during treatment, and if increasing time from first stone permits an increasing number of events, early intervention after even one stone event may be a better prevention strategy than permitting patients to form more stones, and thereby "prove" themselves chronic stone producers. In a township study [46] most patients with single stones had recurrences. We found the number of events and number of stones were independent correlates of relapse; this supports the natural clinical instinct to view a patient with an event containing 20 stones as "more active" than a patient with only one stone in an event, and supports the practice of evaluating patients with multiple stones and one event. We do not understand what determines number of stones per event.

The idea that stones are autocatalytic also supports the idea that dormant or temporally remote stones may well be best left untreated. Once the process ceases, for whatever reason, it may not reignite. On the other hand, given even one recent stone, efforts at prevention are not unreasonable. These may, indeed, take the form of diet or minimal uses of active medications, as one stone offers a better prognosis than many stones. The actual outcome of prospective studies that segregate single but recent stone formers could be very useful for guiding practice in this difficult area. As well, prospective trials of stone treatments may well benefit from stratified randomization on event number. Finally, the significance of these results for females remains uncertain.

Overall, the dogma that single stones require little or no evaluation or treatment seems potentially wrong. We cannot,

from this study, make universal recommendations about practice, but certainly the issue of outcome for this type of patient requires more study given our results. At very least, single stone formers require careful evaluation for recurrence.

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