# Disease Course and Outcome of Juvenile Rheumatoid Arthritis in a Multicenter Cohort

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***ABSTRACT.*** ***Objective.*** To determine the disease course and outcome in a multicenter cohort of patients with juvenile rheumatoid arthritis (JRA).

***Methods.*** All patients with JRA seen at 3 pediatric rheumatology centers were identified from databases and/or clinic records. Inclusion criteria were a diagnosis of JRA (1977 American College of Rheumatology criteria), a followup period of at least 5 years since onset, and a minimum age of 8 years. Patients were examined and completed a Childhood Health Assessment Questionnaire (CHAQ). Kaplan-Meier curves were constructed to estimate rates of remission, relapse, and arthroplasty. Remission was defined as absence of active arthritis while off treatment for at least 2 years. Outcome measures were active disease duration, CHAQ scores, pain determined by visual analog scales, physician's global assessments, and Steinbrocker functional classifications. Years of education and employment status were ascertained.

***Results.*** We studied 392 patients of 652 (60%) who met the selection criteria. The probabilities of remission at 10 years after onset were 37, 47, 23, and 6% for patients with systemic, pauciarticular, RF– polyarticular, and RF+ polyarticular JRA, respectively. The probability of relapse varied from 30 to 100% at 15 years. The probability of arthroplasty varied from 13 to 57% after 15 years of active disease. We found 2.5% of patients assessed were in Steinbrocker Classes III or IV and 6% were in the highest CHAQ score (> 1.5) group. Compared with national statistics, fewer female patients received post-secondary education and unemployment rates for patients 20 to 24 years of age were higher.

***Conclusion.*** Our results indicate that JRA is a disease that often extends into adulthood. Compared to previous decades, functional outcome has improved; however, the estimated rate of arthroplasty remains very high. Patients with JRA may have difficulty entering the workforce. (J Rheumatol 2002;29:1989–99)

*Key Indexing Terms:*
JUVENILE RHEUMATOID ARTHRITIS OUTCOME REMISSION

Knowledge of the disease course and outcome for patients with juvenile rheumatoid arthritis (JRA) is essential both for providing counseling and for presenting appropriate treatment options for patients and their families. Although the concept that JRA is a condition that is often "outgrown" is now viewed with increasing skepticism[1-3], estimates of remission rates and disease duration for the different subtypes of JRA vary so widely that it is difficult to make consistent conclusions[1-12].

Over the last 40 years a number of studies have assessed functional outcome in cohorts of patients with JRA[1-17]. Nevertheless, continuing evaluation is necessary in order to provide up to date knowledge of the outcome achievable with present treatment strategies. In the last decade, major therapeutic advances in the treatment of JRA have included the widespread use of methotrexate (MTX) and intraarticular corticosteroids[18,19], and the aggressive early introduction of these drugs and/or other disease modifying antirheumatic drugs (DMARD)[1,2,18]. At the same time new methods of assessing disability were introduced. These were based on self or parent-completed questionnaires or observed and timed performance of physical activities rather than on physicians' estimations only[20-22].

Our objective was to determine the prognosis of JRA by an analysis of the disease course and outcome of a large multicenter cohort of patients treated during the past 2 decades. This cohort is at a transitional state. It includes

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patients with more recent disease onset who would have been treated more aggressively, as well as patients with disease onset in earlier decades whose initial treatment reflected standards of that time and in whom more recent treatment may have included newer therapies. Although new classification criteria for arthritis in children and adolescents have recently been proposed, the present cohort of patients was diagnosed and classified according to the 1977 American College of Rheumatology (ACR) criteria[23–25].

Summary statistics for disease course and outcome are presented in this report. Analyses of variables that may predict outcome are the subject of a separate study.

## MATERIALS AND METHODS

*Design*. The design is a retrospective cohort study. Patients were followed at 3 pediatric rheumatology centers and were studied in cross sectional surveys over a 4 year period.

*Patients*. Inclusion criteria were a diagnosis of JRA based on 1977 ACR criteria[25], a period of at least 5 years since the disease onset, and age at study of at least 8 years. Exceptions were 2 patients with intervals of 4.8 and 4.9 years since onset and 2 patients aged 7.82 and 7.95 years. Patients were classified by onset types into systemic, pauciarticular, and polyarticular as defined in the ACR criteria[25]. Patients were excluded if they had juvenile psoriatic arthritis, seronegative enthesitis and arthritis (SEA) syndrome, juvenile ankylosing spondylitis, or arthritis with inflammatory bowel disease[26,27]. The polyarticular onset group was further divided into rheumatoid factor positive (RF+) and rheumatoid factor negative (RF–) groups. For patients with pauciarticular onset, an extended disease course was defined as a cumulative active joint count ≥ 5. A minimum of 5 years since onset was a requirement for study since preliminary analysis of the patient database at one center (Winnipeg) suggested that most remissions occurred within that time. A minimum of 8 years of age and a grade 3 reading level were required so that the Childhood Health Assessment Questionnaire (CHAQ) could be self-administered. Participating pediatric rheumatology centers were the Arthritis Centre, Vancouver, Royal University Hospital, Saskatoon, and the Children's Hospital, Winnipeg.

Patients were identified through existing prospectively collected databases and/or clinic files at the 3 participating pediatric rheumatology centers. Only patients seen since the establishment of dedicated pediatric rheumatology clinics in 1975, 1979, and 1981 at Winnipeg, Vancouver, and Saskatoon, respectively, were included. Patients were recruited at the time of clinic visits, or if no longer attending, through clinic and hospital records, local telephone directories, through their parents if living independently, and through local adult rheumatologists.

To be considered Native North American (North American Indian), a patient was required to have 2 Native North American parents. This information was obtained by clinical history.

*Procedures*. Databases and/or medical charts were reviewed for the following information: date of onset, date of diagnosis at a participating pediatric rheumatology clinic, date active arthritis was last recorded, date of recurrence of arthritis, date medications were discontinued, results of RF and antinuclear antibody (ANA) tests, medications used, and date and type of surgery performed. Date of onset was defined as the date of onset of first symptoms of arthritis, and/or fever in the case of systemic JRA, obtained by history as recorded in medical records or databases.

Between ages 16 and 19, patients with active disease are generally transferred to adult rheumatologists in specialty clinics located in the same health care complexes as the pediatric centers in Winnipeg and Saskatoon or less often to adult rheumatologists in the community. In Vancouver, patients are transferred to a transition clinic where they are seen by participating pediatric rheumatologists until age 23, and are then transferred to the care of adult rheumatologists in the community. Medical records and/or correspondence were thus available for most patients with active disease beyond their followup period in the pediatric clinics.

Participating subjects were asked to attend one of the centers for a physical examination. Participating investigators (DC, PM, KO, RP, AR) assessed active joint counts and assigned Steinbrocker classifications[28] and global assessment of disease activity (0 = inactive, 1 = mild, 2 = moderate, 3 = severe). An active joint was defined as one with swelling or limitation of movement with heat, pain, or tenderness[25]. All patients were asked to complete a CHAQ and a pain visual analog scale (VAS) independently. The CHAQ was chosen as it allowed for age appropriate activities ranging from childhood to adulthood[20]. CHAQ scores were calculated as the mean score for the 8 categories of activities. Scores were divided into 4 categories: 0 = no disability, $> 0 \leq 0.5$ = mild, $> 0.5 \leq 1.5$ = moderate, and $> 1.5$ = severe[14]. The CHAQ as originally published was used except that the language was simplified somewhat to a grade 3 reading level.

Additional information requested on questionnaires included: current medications, whether subjects considered their arthritis to be presently active or not, place of residence at onset and during disease course, present grade in school or years of education completed, and occupation. Residence was classified as urban, suburban, rural, or reservation. If arthritis had recurred after the patient was discharged from clinic, she/he was asked for the best estimate of the date and duration of recurrence. Patients unable to attend for examination were included in the study if they returned a completed CHAQ by mail. The presence or absence of active disease in these individuals was determined by questionnaire.

In preliminary studies 13 healthy Native North American school children without JRA aged 10.8 ± 0.5 years [mean ± standard deviation (SD)] completed a CHAQ in English. The language of instruction for Native children is English. The children were seen in general pediatric clinics at the Children's Hospital, Winnipeg, for upper respiratory tract infections, minor trauma, or annual physical examinations. The mean score obtained by the children was 0.02 ± 0.02. It was concluded from this that the CHAQ can be used for Native children.

The study was approved by institutional ethics boards at the Universities of Manitoba, Saskatchewan, and British Columbia. Informed consent was obtained from patients and/or their parents.

*Outcome measures*. Outcome measures were CHAQ score, active joint count, and active disease duration. Remission was defined as absence of active arthritis while off all medications for at least 2 years. The date of entry into remission was defined as the last date active arthritis was recorded prior to finding inactive disease. Active disease duration was defined as the interval from date of onset to the date active arthritis was last recorded, if inactive at the time of study, or the date of study if still active. Disease relapse was defined as a recurrence of active arthritis following a remission period as defined above. For patients with recurrent arthritis (periods of arthritis separated by periods of remission), disease duration was the sum of periods of active arthritis. A patient with a reactivation of arthritis after a quiescent period of less than 2 years was deemed to have a persistent disease course.

*Analysis*. All data were collected on prepared forms and entered into a database program (Visual DBase, Borland). Analyses were performed using SAS (SAS Institute, Cary, NC, USA) and SPSS (SPSS, Chicago, IL, USA). For continuous variables differences between 2 groups were assessed by Mann-Whitney test and among more than 2 groups by Kruskal-Wallis test. Chi-square tests were used for categorical measures. Kaplan-Meier survival curves were utilized to calculate the probability of remission over time after disease onset. For patients with recurrent disease who were in remission, the time to last remission was entered. Patients who did not meet the above criteria for remission were censored at an interval extending from the date of onset to the date of study. Similar curves were constructed for duration of remission before relapse, active disease duration before arthroplasty, and age at remission for patients with active disease beyond the 16th birthday.

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Comparisons of the survival curves were made by log-rank tests. Comparisons for years of education and unemployment rates were made with national statistics[29-33] by 2 tailed exact binomial tests. The level of significance was set at $\alpha = 0.05$.

## RESULTS

*Patient retrieval*. A total of 392 patients were studied. This number represented 60% of eligible patients. The remaining 40% could not be located or refused participation. Significant differences between participants and nonparticipants included an older age at onset, an older age at the end of the study period, and a longer interval since onset of disease to the end of the study period in nonparticipants (Table 1). However, the differences were small (Table 1). There was also a higher proportion of males among the nonparticipants. There were no differences in onset subtypes, race, or location of residence (Table 1). Of those studied, 307 (78.3%) patients completed a questionnaire and were examined, while 85 (21.7%) mailed in a questionnaire only.

Patients were studied at a median age of 16.3 years and at a median interval of 10.5 years since disease onset (Table 1). Seven percent of patients were diagnosed between 1974 and 1979; 27% between 1980 and 1984; 36% between 1985 and 1989; and 29% between 1990 and 1994.

Patients studied were first seen at a participating center at a median of 3.1 months (range < 1 mo to 11.6 yrs) after onset and were followed for a median of 6.7 years (range 0.3 to 20.8 yrs) after onset. Among 150 patients in remission at the time of study, 125 had continued to be followed for a median of 2.1 years (range < 1 mo to 14.4 yrs) after active arthritis had last been documented. In 10, active disease had last been documented at the last visit at a participating center; and in 14, entry into remission had occurred after their last visit (data were missing for one case). For patients with recurrent disease, disease reactivation occurred during the followup period in 27 and after discharge in the remaining 44.

*Remissions*. At the time of study, 39% of patients were in remission and an additional 17% had inactive disease but did not meet criteria for remission; 41% still had active disease. The status was unknown in 3%. Overall, 76% of the 150 remissions began 5 years or less after onset, 15% in the next 5 years, and the remaining 9% began after 10 years. Dates of remission were missing for 2 cases.

By Kaplan-Meier analysis, the probability of remission increased during the first 5 years after onset (Figure 1A). However, the differences between the projected remission rates at 5 and 10 years were small, except for patients with pauciarticular JRA. For patients with other subtypes, the chance of remission at 10 years remained well below 50%, and for patients with RF+ polyarticular JRA, below 10% (Figure 1A).

Ninety-one percent of the remissions occurred before the age of 16 years. These included 97% of 18 remissions in patients with systemic, 94% of 111 in those with pauciarticular, and 79% of 19 in those with RF– polyarticular onset disease.

To determine the proportions of patients who remit by the 16th birthday, patients age 16 years or older at the time of study were considered separately. In this group of 205 patients, 36% of 25 patients with systemic, 52% of 99 with pauciarticular, 24% of 46 with polyarticular RF–, and none of 35 with RF+ polyarticular onset JRA were in remission by the age of 16 years. The status was unknown in 4. Among the remaining patients, the probability of active disease persisting into the 3rd and 4th decades of life was high,

*Table 1*. Patients meeting selection criteria.

| | Patients Studied | Patients Not Studied | p |
|---|---|---|---|
| N (%) | 392 (60) | 259 (40) | |
| Age at onset, median (range), yrs | 4.7 (0.3–16.3) | 6.5 (0.1–16.9) | 0.010 |
| Age at end of study*, median (range), yrs | 18.8 (8.6–35.8) | 21.8 (9.2–38.0) | < 0.0001 |
| Time from onset to end of study*, median (range), yrs | 13.5 (5.6–25.8) | 15.0 (6.8–30.8) | < 0.0001 |
| Age at time of study, median (range), yrs | 16.3 (7.8–32.1) | NA | |
| Time from onset to date of study, median (range), yrs | 10.5 (4.8–23.1) | NA | |
| Male/female | 88/304 | 80/179 | 0.016 |
| Residence | | | |
| City: suburb: rural: reservation, n | 190: 39: 140: 21 | 119: 17: 101: 9 | NS |
| (%) | (49: 10: 36: 5) | (48: 6: 7: 41: 4) | |
| Onset subtype | | | |
| Systemic: pauciarticular: RF– poly: RF+ poly, n | 48: 224: 80: 40 | 35: 154: 53: 17 | NS |
| (%) | (12: 57: 20: 10) | (14: 59: 20: 7) | |
| Race | | | |
| Caucasian: Native American: mixed Native American: Asian: other, n | 326: 38: 11: 11: 6 | 202: 27: 4: 11: 8 | NS |
| (%) | (83: 10: 3: 3: 2) | (80: 11: 2: 4: 3) | |

* Date data collection for this study was completed. NA: not applicable, NS: not significant.

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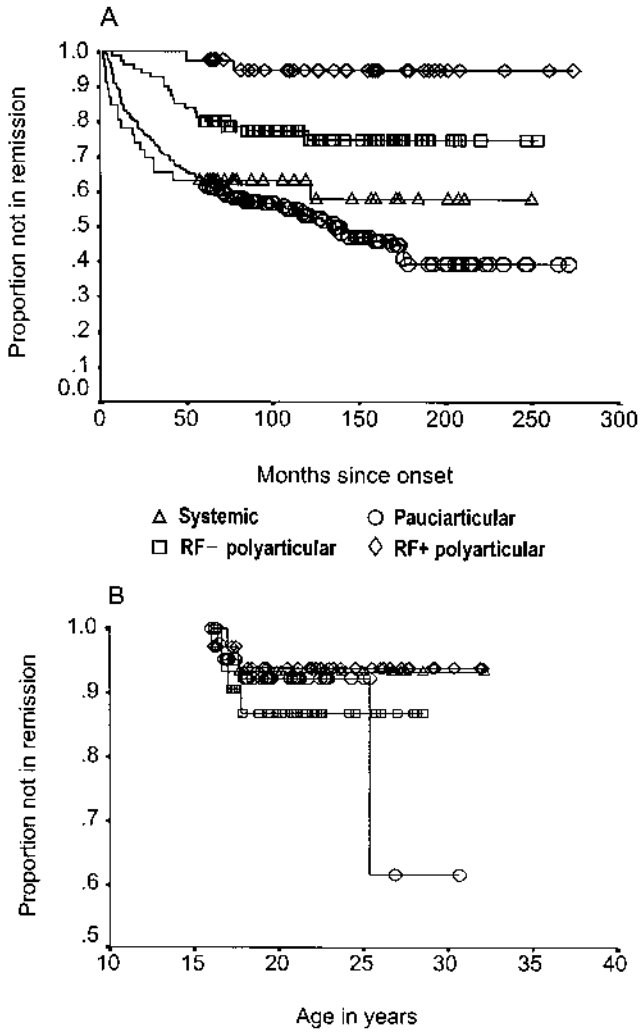


*Figure 1.* Kaplan-Meier curves for remissions. Censored patients with systemic, pauciarticular, RF–, and RF+ polyarticular onset JRA. Panel A. Remissions. The time to remission was defined as the interval from onset to the date active arthritis was last recorded. For patients with recurrent disease the time of last remission was entered as an event. Patients with either persistent or recurrent disease who were not in remission were censored at an interval from disease onset to time of study. Data for this analysis were available for 47 patients with systemic, 220 with pauciarticular, 80 with RF– polyarticular, and 40 with RF+ polyarticular JRA. The probability of remission was 37, 37, 19, and 3% at 5 years and 37, 47, 23, and 6% at 10 years, respectively, for patients with systemic, pauciarticular, RF– polyarticular, and RF+ polyarticular onset. The projected rates of remission were significantly different for the 4 subtypes ($p < 0.0001$). Panel B. Remissions at or after the age of 16 years: Remissions occurring after the 16th birthday were calculated for patients who were 16 years or older at the time of study and who were not in remission at 16 years of age. For patients with recurrent disease the age at last remission was entered. The analysis was based on 130 patients. The probability of active disease was 93% up to age 32 for patients with systemic (n = 15), 62% up to age 30 for patients with pauciarticular (n = 45), 87% up to age 28 for patients with RF– polyarticular (n = 35), and 94% up to age 32 for patients with RF+ polyarticular JRA (n = 35). The probabilities of continued active disease were similar for the 4 subtypes ($p = 0.738$).

varying from 62% for patients with pauciarticular disease to over 90% for patients with systemic and RF+ polyarticular onset (Figure 1B).

*Disease relapse*. Among patients with recurrent disease, the median interval between the end of the first episode of arthritis to disease recurrence was 6.2 (range 2.5–10.0), 5.2 (2.1–13.4), and 3.1 (2.3–12.9) years in patients with systemic, pauciarticular, and polyarticular RF– onset, respectively. Relapses occurred at a median age of 19.5 (17.7–24.2), 11.7 (5.2–22.8), and 16.6 (8.0–27.9) years, respectively. At the time of study 18 of the 71 patients were once again in remission: 34 had active disease, 16 were inactive but did not meet criteria for remission, and status was unknown in 3.

By Kaplan-Meier analysis, the probability of relapse for patients with pauciarticular and RF– polyarticular JRA continued to increase even after 10 years of remission; however, for patients with systemic JRA, the chance of relapse appeared to stabilize after this time (Figure 2A).

*Extended pauciarticular disease course*. Twenty percent of patients with pauciarticular onset developed extended arthritis (Figure 2B). Most patients who extended did so within 7 years of disease onset, but occasional patients continued to accumulate 5 or more affected joints for many years after disease onset. The median time to extension was 3.9 years (range 0.7–15.7) after onset.

*Active disease duration*. Active disease duration varied from < 1 year to > 20 years within each onset subtype (Figure 2C). Median values were lowest for patients with systemic and pauciarticular JRA (Figure 2C).

*Medications used*. Twenty-nine percent of patients received intraarticular triamcinolone hexacetonide. Virtually all patients with RF+ polyarticular JRA and more than half of those with RF– polyarticular JRA had used DMARD (Table 2). Patients were divided into 5 year blocks according to their dates of diagnosis in order to detect any changes in DMARD use over time. There was a progressive decrease in the use of gold between patients diagnosed in the 1970s and those diagnosed in the 1990s, while the use of MTX more than quadrupled (Figure 3). No patient received biologic agents.

*Surgery*. The requirement for arthroplasty was highest in patients with systemic and RF+ polyarticular JRA, 17 and 23% of whom underwent this type of surgery, respectively. Joints replaced included 33 hips, 16 knees, and 2 shoulders. Among patients requiring surgery, median active disease duration before arthroplasty was 8.0 (range 3–10), 11.5 (8.3–17), 9.3 (1.7–13.0), and 7.9 (5.6–18.3) years, respectively, for patients with systemic, pauciarticular, RF– polyarticular, and RF+ polyarticular JRA. The probability of joint replacement for patients with systemic JRA was greatest within the first 10 years when it exceeded 50%, but did not change after that (Figure 4). In contrast, for patients

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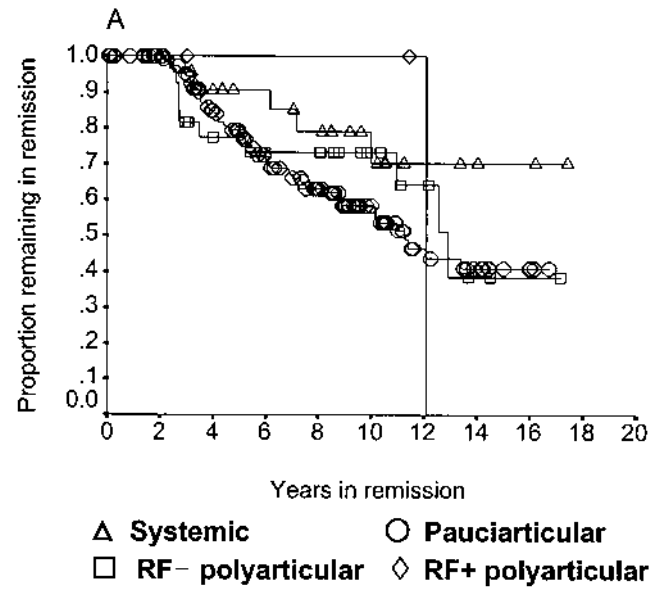


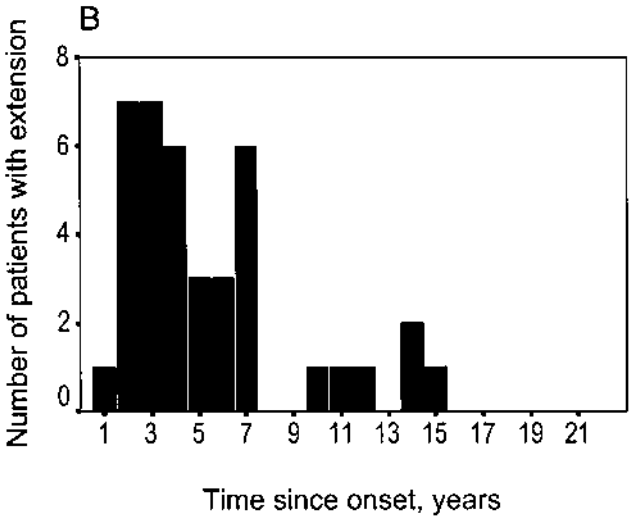


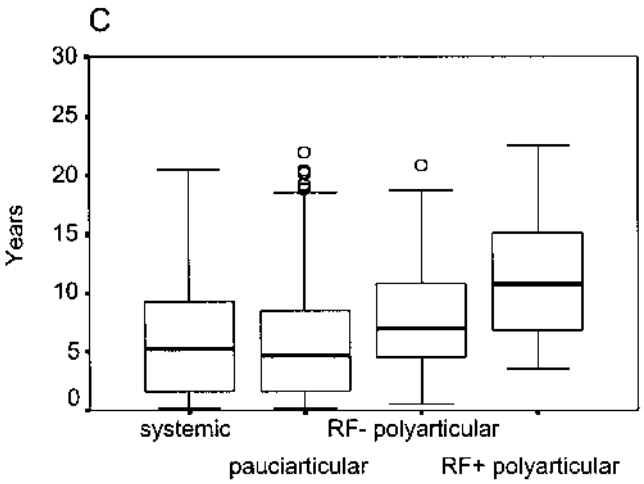


*Figure 2.* Disease course variables. Panel A. Kaplan-Meier curve for disease relapse: the time to relapse was defined as the interval from the start of the first remission to the time of disease recurrence. Analysis was based on data for 204 patients who had remissions including 71 with recurrences. Recurrent disease was observed in 5 (10%) of all patients with systemic, 55 (25%) with pauciarticular, and 11 (12%) with polyarticular JRA. Only one patient with RF+ polyarticular onset had recurrent disease. The probabilities of relapse after 5, 10, and 15 years of disease remission were 9, 30, and 30%, respectively, for patients with systemic JRA; 19, 40, and 58%, respectively, for patients with pauciarticular JRA; 23, 27, and 62%, respectively, for patients with polyarticular RF– JRA; and 0, 0, and 100%, respectively, for patients with RF+ polyarticular JRA. However, only 3 patients with RF+ polyarticular JRA had remissions. There was no significant difference in the projected rates of relapse among the 4 subgroups ($p = 0.470$). Panel B. Time to extension: for patients with pauciarticular JRA, the interval from onset to time that cumulative number of affected joints reached 5 was defined as the time to extension. Y-axis denotes the number of patients with pauciarticular JRA who developed an extended disease course during each year since onset. X-axis denotes the number of years since onset. Analysis was based on 198 patients (data were not available for 26 patients). Thirty-nine patients had an extended disease course; extension occurred within 2 years after onset in 21% of the 39. Panel C. Active disease duration: whiskers represent minimum and maximum values excluding outliers and extreme values. Box lengths represent interquartile range, which includes 50% of the values. ○: Outliers 1.5 to 3 box lengths away from the upper or lower edge of the box. Active disease duration was calculated as the interval from disease onset to entry into remission or time of study if disease was still active. For patients with an intermittent disease course the sum of active disease periods was calculated. Data for this analysis were available for 46 patients with systemic, 222 with pauciarticular, 80 with RF– and 40 with RF+ polyarticular JRA. Median values for active disease duration were 5.3, 4.7, 7.0, and 10.8 years, respectively. Differences among subtypes were significant ($p < 0.0001$).

with RF+ polyarticular JRA, the chance of arthroplasty continued to increase after 10 years (Figure 4).

*Outcome measures*. Results of physician assessments are shown in Figure 5. Median active joint counts were highest in patients with RF+ JRA (Figure 5A). Global assessments of moderate or severe disease activity occurred in more than one-third of patients with RF+ polyarticular JRA, but were much less frequent among the remaining patients (Figure 5B).

The great majority of patients with pauciarticular JRA and more than half of those with systemic JRA were in Steinbrocker Class I; however, the frequency of patients in Steinbrocker Class III or IV was highest among those with systemic JRA (7%) (Figure 5C).

Among 325 patients who had both assessments, the proportions of patients reporting no disability on the CHAQ were lower than the physician assessed Steinbrocker Class I designations. Frequencies in the worst outcome group were also higher than those assigned to Steinbrocker classes III and IV. For example, altogether, 45% had a CHAQ score of 0 whereas 66.5% were assigned to Steinbrocker Class I. Similarly, 6% had a CHAQ score > 1.5, but only 2.5% were in Steinbrocker Classes III and IV. Patients with RF+ polyarticular JRA were the most symptomatic, as they had

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*Table 2*. Medications used by patients.

| | All Patients | Systemic | Pauciarticular | RF– Polyarticular | RF+ Polyarticular | p |
|---|---|---|---|---|---|---|
| N | 392 | 48 | 224 | 80 | 40 | |
| IATH, n (%) | 113 (29) | 11 (23) | 71 (32) | 20 (25) | 11 (28) | NS |
| NSAID ever, n (%) | 386 (99) | 48 (100) | 219 (98) | 80 (100) | 39 (98) | NS |
| Prednisone ever, n (%) | 107 (27) | 29 (60) | 28 (13) | 7 (34) | 23 (58) | < 0.0001 |
| DMARD ever, n (%) | 138 (35) | 20 (42) | 35 (16) | 44 (55) | 39 (98) | < 0.0001 |
| NSAID at time of study, n (%) | 136 (35) | 21 (44) | 51 (23) | 33 (41) | 31 (78) | < 0.0001 |
| Prednisone at time of study, n (%) | 27 (7) | (13) | 5 (2) | 8 (10) | 8 (20) | < 0.0001 |
| DMARD at time of study, n (%) | 84 (21) | 8 (17) | 27 (12) | 25 (31) | 24 (60) | < 0.0001 |

P values shown are for comparisons of onset subtypes. IATH: intraarticular triamcinolone hexacetonide, NSAID: nonsteroidal antiinflammatory drugs, DMARD: disease modifying antirheumatic drugs, NS: not significant.

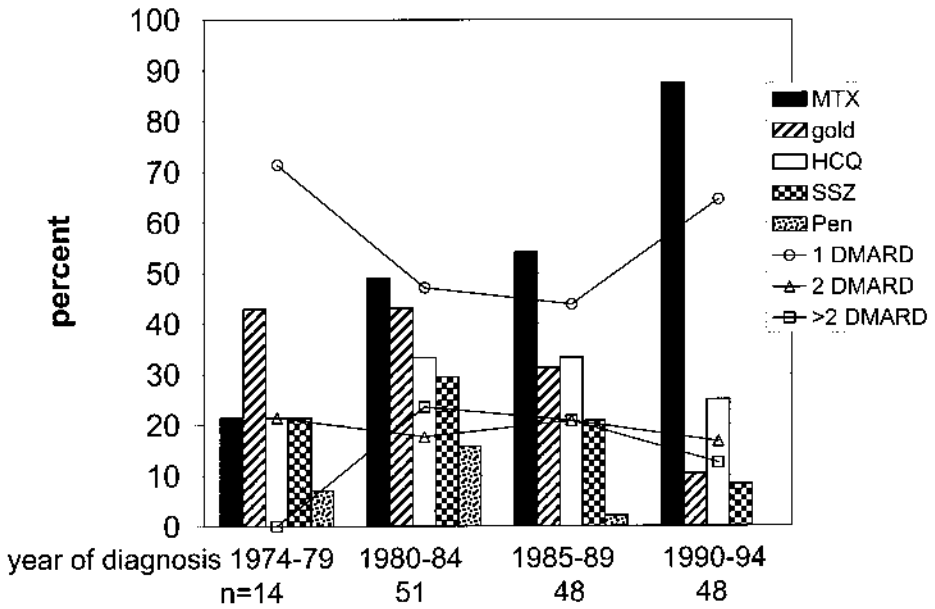


*Figure 3*. Use of DMARD. Years of diagnosis divided into 5 year periods are shown on the X-axis. Y-axis shows percentage of patients taking each DMARD as a proportion of the number (n) of patients taking DMARD for each of the 5 year groups. Use of intramuscular gold at any time during disease decreased from 43% for those diagnosed between 1974 and 1979 to 10% for patients diagnosed between 1990 and 1994; while the use of MTX increased from 21% to 88%. Use of hydroxychloroquine (HCQ) and sulfasalazine (SSZ) was highest in patients diagnosed between 1980 and 1989. Use of multiple DMARD was also most frequent in patients from this period, with 18% to 21% using two and 21% to 24% using more than two agents. The data collection procedure did not differentiate whether these agents were used simultaneously or sequentially. Gold: sodium aurothiomalate or auranofin; Pen: penicillamine; 1, 2, or > 2 DMARD: patients who received 1, 2, or more than 2 DMARD during followup period.

the highest frequency and duration of morning stiffness and the highest VAS scores (Figure 6C).

*Socioeconomic outcome*. Of the 240 patients still attending school, 230 (95.8%) were in age-appropriate grades at school, 6 (3%) were more than a year behind, and 4 (1.5%) were more than a year ahead of expected grades. The mean and median number of years of education for patients ≥ 15 years of age were 12.5 and 12 years, respectively, comparable to the national figures of 12.3 and 12.7 years, respectively, recorded in the 1996 Canadian census[29]. Stratification by age and sex for patients 20 to 29 years of age indicated similar rates of completion of high school, 85% (17 of 20) for male and 89% (79 of 89) for female patients, compared to national rates of 79% and 84% (p = 0.601 and 0.307, respectively)[30]. Similarly the rate of post-secondary education for males, 55% (11 of 20), was comparable to the national rate of 64% (p = 0.487); however, a lower rate 55% (49 of 89) was obtained for female patients compared to a rate of 71% for women of this age group in the general population (p = 0.001)[30].

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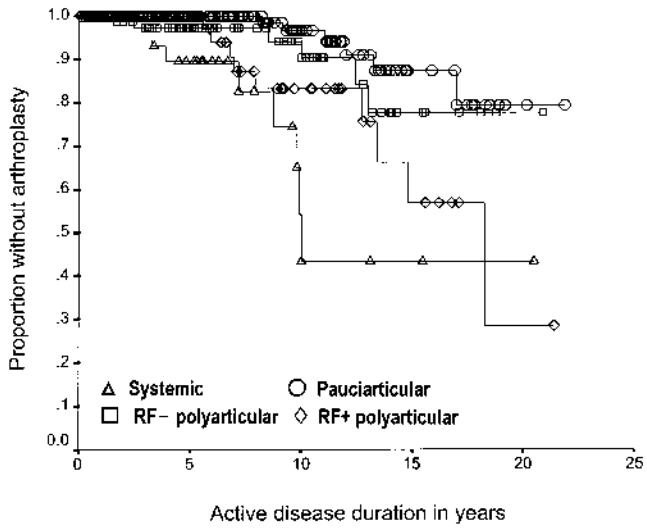


*Figure 4.* Kaplan-Meier curve for active disease duration to time of arthroplasty. Interval from disease onset to time of arthroplasty was calculated. Patients without arthroplasty were censored at an interval extending from disease onset to time of remission or to time of study if still active. For patients with intermittent disease, total disease duration to time of study was calculated as the sum of active disease periods. A total of 29 patients (7%) underwent arthroplasty, 8 (17%) with systemic, 6 (3%) pauciarticular, 6 (8%) polyarticular RF–, and 9 (23%) with RF+ polyarticular JRA. Probability of joint replacement was 57, 3, 10, and 17%, respectively, after 10 years of active disease and 57, 13, 22, and 43% after 15 years for patients with systemic, pauciarticular, RF– and RF+ polyarticular onset. The projected rates of arthroplasty differed among the 4 subgroups ($p < 0.0001$).

Among 146 patients aged 18 years or older, 33 (23%) were students, 81 (55%) were employed, 12 (8%) were homemakers, 13 (9%) were unemployed, 5 patients listed "none" as occupation, and data were missing for one. When students, homemakers, and those listing no occupation were excluded, the unemployment rates for those older than 15 years were 20% (4 of 16) for male and 13.0% (10 of 77) for female patients and were not different from national rates of

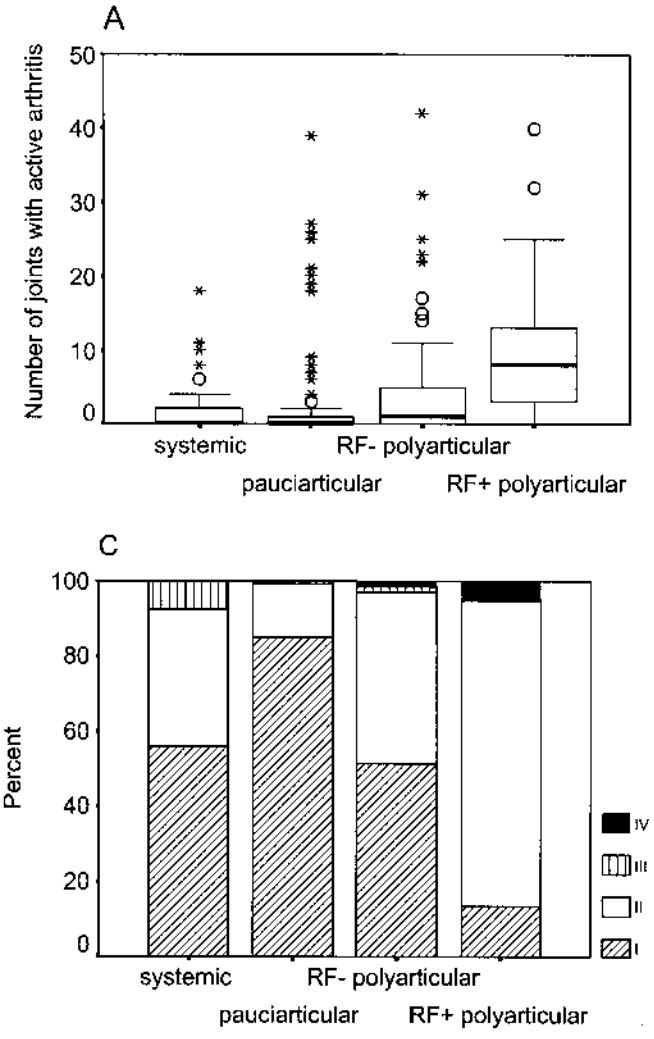


*Figure 5.* Physicians' measures: Patients were examined at the time of study. Panel A. Active joint count (box and whisker plot data as in Figure 2). * Extreme values, > 3 box lengths away from the upper or lower edge of the box. Data were available for 36 patients with systemic, 171 pauciarticular, and 69 RF– and 38 RF+ polyarticular JRA. Median values were 0, 0, 1, and 8, respectively. Differences among groups were significant ($p < 0.0001$). Panel B. Physicians' global assessments of disease activity rated on a scale of 0 to 3: 0 = none, 1 = mild, 2 = moderate, 3 = severe. Analysis was based on 40 patients with systemic, 177 with pauciarticular, 71 with RF– and 37 with RF+ polyarticular JRA. Severe and moderate disease activity was found in 38% of patients with RF+ polyarticular JRA, and 14% to 18% of the remaining patients. Frequencies of patients in each category were significantly different among the groups ($p < 0.0001$). Panel C. Steinbrocker functional classifications. Data were available from 41 patients with systemic, 181 with pauciarticular, 66 with RF– and 37 with RF+ polyarticular JRA. Steinbrocker functional class I was assigned most often for patients with pauciarticular onset, 85%, followed by patients with systemic, 56%, and RF– polyarticular JRA, 52%. Only 14% of those with RF+ polyarticular JRA had no disability. Seven percent of patients with systemic, 0.5% with pauciarticular, 3% with RF– and 5% with polyarticular RF+ onset JRA were in Steinbrocker Classes III or IV. Differences among the groups were significant ($p < 0.0001$).

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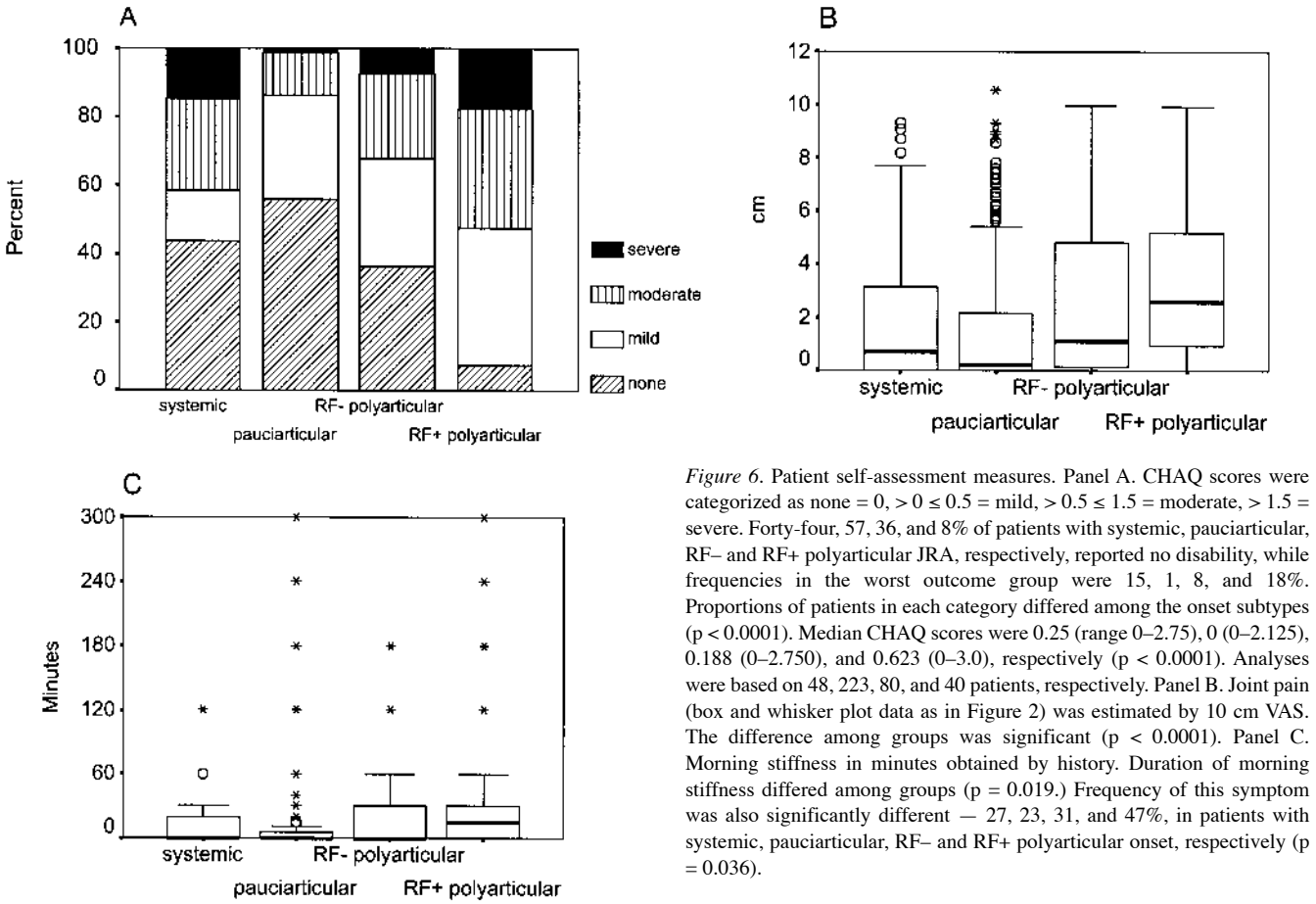


*Figure 6.* Patient self-assessment measures. Panel A. CHAQ scores were categorized as none = 0, > 0 ≤ 0.5 = mild, > 0.5 ≤ 1.5 = moderate, > 1.5 = severe. Forty-four, 57, 36, and 8% of patients with systemic, pauciarticular, RF– and RF+ polyarticular JRA, respectively, reported no disability, while frequencies in the worst outcome group were 15, 1, 8, and 18%. Proportions of patients in each category differed among the onset subtypes ($p < 0.0001$). Median CHAQ scores were 0.25 (range 0–2.75), 0 (0–2.125), 0.188 (0–2.750), and 0.623 (0–3.0), respectively ($p < 0.0001$). Analyses were based on 48, 223, 80, and 40 patients, respectively. Panel B. Joint pain (box and whisker plot data as in Figure 2) was estimated by 10 cm VAS. The difference among groups was significant ($p < 0.0001$). Panel C. Morning stiffness in minutes obtained by history. Duration of morning stiffness differed among groups ($p = 0.019$.) Frequency of this symptom was also significantly different — 27, 23, 31, and 47%, in patients with systemic, pauciarticular, RF– and RF+ polyarticular onset, respectively ($p = 0.036$).

7.8% ($p = 0.066$) and 7.3% ($p = 0.073$), respectively[31,32]. However, the rates for those aged 20 to 24 years were 44.4% for male and 20.5% for female patients, while the rates for the general population in this age group were 12.5% ($p = 0.018$) and 9.8% ($p = 0.033$), respectively[33]. In contrast, for patients aged 25 to 34 years the unemployment rates were no different from those of the general population — 0 for male and 3.3% for female patients, compared with 7.6% ($p = 0.669$) and 6.9% ($p = 0.720$), respectively, in the general population[33]. We found 75% (114 of 152) of patients ≥ 18 years of age were single and 25% (38) were married or had common-law relationships.

## DISCUSSION

The concept that JRA is a disease that often remits before adulthood has been challenged during the past decade[1-3]. Our analysis shows that for patients with RF+ polyarticular JRA, disease is essentially unremitting. Only one-third of patients with systemic, a quarter of patients with RF– polyarticular, and half of those with pauciarticular onset JRA achieved remission by the age of 16 years, while the probability of continued active disease into the late twenties or early thirties was high for patients who were not in remission by this age. Remissions most often occur within the first 5 years after onset and the probability of remission for patients with systemic and RF– polyarticular onset is low after that. For patients with pauciarticular JRA, the chance of later remissions is better, but also progressively decreases after 5 years.

Studies of patients followed for a mean of at least 10 years have documented varying frequencies of remissions — from 29% to 78% for patients with pauciarticular onset, 36% to 75% for patients with systemic onset, and 53% to 65% for those with polyarticular onset disease[1,2,4,7,8,11,12,35,36]. Comparisons between studies may not be relevant for the older studies, when treatment strategies were different. Comparisons are also difficult when patients with juvenile psoriatic arthritis and SEA syndrome have not clearly been excluded from the patient populations, and when, within the polyarticular onset group, patients with or without rheumatoid factor have not been distinguished. Nevertheless, one recent comparable study using Kaplan-Meier survival curves estimated 10 year remission rates of 38% and 54% for systemic and pauciarticular (excluding patients with spondyloarthropathies) juvenile chronic arthritis[34]. These are similar to our rates of 37% and 47%, respectively. The estimated 15% remission rate for the polyarticular group is difficult to compare to our results

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because the relative numbers of RF– and RF+ cases were not stated[34]. Both studies suggest lower remission rates than generally reported previously.

Our results are also more pessimistic than an overall remission rate of 61% in those entering adulthood reported recently by Andersson Gare[3]. That was a population study and thus patients with less severe disease were probably included[3]. In contrast, our study was from 3 referral centers. However, each is the only specialized pediatric rheumatology center in each province, and the 3 centers almost certainly see the great majority of children with JRA in these provinces.

Late relapses after prolonged disease remissions have recently been recognized in other studies of JRA. In an Italian study, 34% of patients with systemic JRA relapsed after a mean remission period of 9 years[36]; 20% of patients in another longterm study from Denmark also had late relapses[12]. In our study, the probability of relapse was estimated to be even higher for most subgroups, varying from 30% to 100%. Moreover, except among patients with pauciarticular JRA, half the relapses occurred after the age of 16 years. Thus the occurrence of both prolonged active disease and late relapses indicates that JRA is a disease that extends into adulthood for many patients.

An extended polyarticular disease course for patients with pauciarticular JRA has been correlated with a worse prognosis in previous studies[11,13]. A recent publication estimates the risk of extension at only 30% within the first 2 years of disease[37]. The present analysis indicates that the median time from disease onset to conversion to extended joint involvement is relatively long — 4 years. Thus although this development describes a worse prognosis, it may not always be used as an early indicator of disease outcome. Nevertheless, it is possible that the duration between onset and extension may influence longterm outcome.

A cross sectional retrospective cohort study such as this is not designed to evaluate specific treatment. Rather, it reflects overall treatment during the followup period. For the present cohort this includes a changing use of DMARD and the introduction of intraarticular triamcinolone hexacetonide but not the use of biologic agents. As shown, patients diagnosed in the 1980s had most often used multiple agents, probably reflecting successive use of DMARD as active disease duration increased and successive DMARD failed. In contrast, those diagnosed later were most often taking a single DMARD, and most often MTX, perhaps indicating satisfaction with this single agent, but also probably a shorter followup period.

Publications over the past 3 decades have shown an improvement in functional outcome for patients with JRA. While disease duration, patient selection, and disease courses have varied, studies reporting series of patients with a mean or minimum of 10 years of disease show a decline in the frequency of patients in Steinbrocker Classes III and IV. For patients with pauciarticular JRA this decline has been from 8% to 14% in the 1970s to 0% since the 1980s, and our results (0.5%) continue this trend[6,7,10,13,15,16]. Exceptions are a report of 0% in 1977[8] and another of 7% in 2000[34]. Similarly, the frequencies of patients with polyarticular onset JRA in these functional classes are 20% to 50% in the 1970s, 11% to 14% in the 1980s, 5% to 12% in the 1990s, and 3% in the present study[6-8,10,13,15-17]. For patients with RF+ polyarticular JRA specifically, the frequencies are 25% in a 1984 study[10], 15% in 1994[17], and 5% in our study.

The extent of improvement in patients with systemic JRA is more uncertain, with frequencies ranging from 15% to 40% in Class III and IV in the 1970s, 13% to 31% in the 1980s, 0% in the 1990s, and higher frequencies of 29% and 19% in recent studies[6-8,10,13,15-17,34-36]. The present study suggests a more moderate outcome of 7% in Class III–IV. These variations likely reflect the heterogeneity in severity among patients with systemic JRA. For example, Lomater, *et al* recently reported a worse functional outcome in those with intermittent or persistent disease, whereas those with a monocyclic disease course had a good prognosis[36].

As noted, the CHAQ detected disability more frequently than was evident by Steinbrocker classifications[13]. In agreement with other studies, we found most patients with pauciarticular onset had no or mild disability[13,14]. At the other extreme more than half of patients with RF+ polyarticular JRA developed significant disability. The greatest variation occurs in patients with RF– polyarticular and systemic onset JRA. While 40% have no disability, one-third or more developed moderate or severe disability.

In our cohort of patients the probability of arthroplasty was surprisingly high for patients with systemic and RF+ polyarticular JRA. Moreover, the analysis estimated a higher requirement for surgery after a shorter duration of arthritis in patients with systemic JRA. As in other studies, hips were most often replaced[17,36]. The rates of arthroplasty estimated in this study were comparable to those reported in 1994 in a selected group of young adults with JRA, in whom 72% required hip arthroplasty after a mean disease duration of 20 years[17]. Altogether, the results suggest serious damage to the hips is a considerable risk for patients with systemic or RF+ polyarticular disease who have prolonged disease of 10 years or longer.

While the educational achievements of our patients were similar to the general population up to secondary school levels, fewer female patients attained post-secondary schooling. In addition, the unemployment rate for young adult patients 20 to 24 years of age was higher than that of their peers in the general population. Peterson, *et al* also noted similar rates of completion of high school between older patients with JRA and age matched controls, but post-secondary education was not reported[38]. Higher unemployment rates among patients were also noted in that study[38].

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Together, these results confirm considerable difficulty adapting to adult life, and the explanations for these observations are likely to include factors other than physical disability[38].

The retrospective cohort design is a disadvantage of the present study as data collection was incomplete for a number of items retrieved from medical records. The relatively low rate of retrieval of eligible patients was also a drawback. While statistically significant, the differences between participants and nonparticipants were numerically small. The principal differences related to an older present age and the longer time lapse since onset of disease among nonparticipants. Nevertheless, the patients who did not participate are a potential source of bias. In particular, the higher proportion of males among nonparticipants may have altered the results, as other studies indicate females may have a worse prognosis[13]. Also, for 22% of patients in this study, current disease status was determined by self-reports, and was not confirmed by physician examination. Other shortcomings are regional or cultural differences in interpretation of the questions posed in the CHAQ. For example the activities required in the CHAQ, particularly those pertaining to self-care, may perhaps require a greater degree of functional competence for patients living in remote underserviced areas.

In summary, this study provides estimations of rates of remission, relapse, and joint replacement surgery, and documents functional outcome in patients with JRA who have attended a specialized clinic. The analyses suggest JRA should be considered a disease of childhood onset that often extends into or relapses during early adulthood. Extrapolation of the data would suggest that with present treatments a significant proportion may continue to have active disease for all their adult life. While functional outcome has improved, disability still develops in significant numbers, and the rate of arthroplasty is depressingly high for patients with systemic and RF+ polyarticular onset. The reasons for lower rates of post-secondary education in females and higher unemployment rates in young adults compared to the general population require further study.

It has been suggested that patients receiving optimal treatment at disease onset today may have a better outcome than their predecessors[4]. However, optimal treatment also means well selected treatment. Our results confirm that all patients with RF+ polyarticular JRA are candidates for aggressive therapy. However, for the other subtypes of JRA, because of the variable outcome, early predictors of outcome are needed to determine which patients would benefit from similar aggressive therapy. Together with the results presented here, the identification of such predictors will provide a basis on which to formulate a prognosis for patients with JRA.

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