Pattern of Joint Involvement and Other Disease Characteristics in 634 Patients with Arthritis of Less Than 16 Weeks' Duration

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ABSTRACT. ***Objective.*** To investigate the distribution of joint involvement in a cohort of patients with very recent onset arthritis and describe the disease characteristics in these patients.

Methods. A very early arthritis clinic (NOR-VEAC) was established as a multicenter study. General practitioners were asked to refer patients presenting with at least 1 swollen joint of maximum 16 weeks' duration. Clinical and laboratory markers were examined.

Results. We included 634 patients during the first 3 years, with mean (25th-75th percentile) arthritis duration of 30 (11–63) days. Monoarthritis was present in 243 (38.3%) patients, 216 (34.1%) had oligoarthritis, and 175 (27.6%) polyarthritis. Patients with polyarthritis were older, had longer duration of arthritis, and were more frequently anti-cyclic citrullinated peptide antibody and rheumatoid factor-positive. Patients in all 3 joint pattern groups (mono-/oligo-/polyarthritis) reported substantial effect on physical function, pain, and fatigue and had elevated levels of acute-phase reactants. Knee or ankle arthritis was most frequent in patients with mono- and oligoarthritis, whereas small joint involvement was most frequent in patients with polyarthritis.

Conclusion. Patients with recent-onset arthritis report a substantial influence on health status. Mono- and oligoarthritis are at least as frequent as polyarthritis. Polyarthritic patients more frequently exhibit features associated with a worse outcome. (First Release June 1 2009; J Rheumatol 2009; 36:1401–6; doi:10.3899/jrheum.081217)

Key Indexing Terms:

ARTHRITIS EPIDEMIOLOGY SYNOVITIS
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The first early arthritis studies were performed in the 1950s and 1960s. Some findings in these studies might have contributed to an underestimation of the prevalence, persistence, and severity of rheumatoid arthritis (RA) and other inflammatory polyarthritides, by indicating that a considerable proportion of patients with early arthritis went into remission[1,2]. Later, it became clear that RA is a severe and disabling disease[3]. From the 1980s, early arthritis clinics (EAC) have been established to improve the knowledge of the disease course of the whole spectrum of inflammatory joint disorders. Early intervention with disease modifying antirheumatic agents (DMARD) is effective not only in early RA[4] but also in patients with undifferentiated arthritis (UA)[5]. Studies from Sweden[6] and Finland[7] have provided additional understanding about the heterogeneity of arthritic disorders in the early stages. Early arthritis has significant effect on sick leave and work disability, regardless of diagnosis[8]. Many early arthritis studies have focused mainly on patients presenting with extensive joint involvement[9-12]. Less is known about the characteristics and prognosis of early arthritis patients presenting with mono- or oligoarthritis, although a few studies regarding presentation and improved outcome with early treatment have been published[13-16].

The Norwegian healthcare system provides opportunities for a close collaboration between primary care and specialized medicine. We established a Norwegian Very Early Arthritis Clinic (NOR-VEAC) focusing on arthritis of less than 16 weeks' duration. The objective of our study was to

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describe the characteristics of individuals with very recent onset arthritis with emphasis on clinical and laboratory findings in the subgroups of patients presenting with mono-, oligo-, and polyarthritis.

MATERIALS AND METHODS

Early arthritis clinic. The NOR-VEAC study was started in 2004 as a multicenter observational study in the south-eastern part of Norway. The 5 participating hospitals serve a region with approximately 1.7 million inhabitants. The initial purpose was to investigate patient characteristics and disease outcomes after 2 years in patients (age 18–75 yrs) presenting with at least 1 clinically swollen joint of ≤ 16 weeks' duration. Primary care physicians in the area received a letter with a request and an opportunity to refer such patients. Referral could be performed by telephone or letter, and patients were guaranteed a consultation with a rheumatologist within 14 days. In order to increase awareness of inflammatory arthritis, the general practitioners were invited to attend evening courses that focused on the importance of early diagnosis and practical training in joint examinations.

All referred patients were managed and followed according to clinical judgment. The patients were considered with regard to the inclusion criteria (arthritis of ≤ 16 wks' duration) and exclusion criteria (joint swelling due to trauma, osteoarthritis, and septic arthritis) of the research part of the project, and eligible patients were then asked to sign an informed consent form. Data from consenting patients were entered into a research database. The study was approved by the regional Ethics Board and the Data Inspectorate.

Data collection. Data collection was performed by rheumatologists and designated study nurses in the different centers. Registration included age, sex, duration of symptoms, comorbidities, extraarticular symptoms, level of education, occupational status, smoking and coffee drinking habits, height, and weight. Sixty-eight swollen joint counts (SJC) and 28 tender joint counts (TJC) were performed by a rheumatologist or by experienced study nurses. Patient-reported outcomes included joint pain, fatigue, and global health status on visual analog scales (VAS), the Norwegian versions of the Health Assessment Questionnaire (HAQ)[17], Medical Outcomes Study Short Form-36 (SF-36)[18,19], and RA Disease Activity Index (RADAI)[19,20]. The assessor reported patient global health on a VAS, as well as treatment (intraarticular steroid injections, DMARD use, and other medication). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were determined at the local laboratories. Serum was frozen and stored at –70°C and used to analyze anti-citrullinated cyclic peptide (anti-CCP) antibodies (Inova Diagnostics, San Diego, CA, USA) and IgM rheumatoid factor (RF). IgM RF was analyzed by an "in house" ELISA as described[21]. The cutoff levels employed for positivity of serologic markers were as follows: IgM RF ≥ 25 IU/ml, anti-CCP2 ≥ 25 units/ml.

Prediction rule. Van der Helm-van Mil, *et al* recently published a prediction rule for development of RA in patients with UA based on the Leiden early arthritis cohort[22]. This prediction rule is calculated based on a questionnaire with 9 variables: sex, age, localization of symptoms, morning stiffness, tender and swollen joint counts, CRP, RF positivity, and anti-CCP positivity, and yields a score between 0 and 14. The prediction rule has shown good discriminatory capacity in several cohorts[23,24]. When cutoff values of 6.0 and 8.0 are used, the prediction rule has shown the highest combination of negative and positive predictive values, respectively. The alternative scoring system with morning stiffness duration instead of severity was applied to the NOR-VEAC patients in our analysis, giving a maximum value of 13.

Statistical analysis. For continuous measures, mean and standard deviations were calculated for variables that were approximately normally distributed; otherwise, median values and percentiles were calculated. Proportions/percentages were calculated for categorical variables. Comparisons across subgroups were performed using chi-squared and analysis of variance/Kruskal-Wallis tests. All analyses were conducted in SPSS 14.0.

RESULTS

By December 31, 2007, 658 patients had been included in the study. Twenty-four patients were excluded from further analyses due to the following reasons (n): no definite arthritis (3), no registration of swollen joints (7), duration of arthritis > 16 weeks (6), age < 18 years or > 75 years (8). Thus, 634 patients with arthritis of maximum 16 weeks' duration were eligible for the analyses. Demographics, disease characteristics, and health status are shown in Table 1. Mean age was 46 years, and 56% of the patients were women. Fifty percent of the patients had arthritis of less than 30 days' duration, and 25% less than 11 days. Serological markers (RF and anti-CCP) were present in 11%–15%. Knee joints were most frequently affected (40.2%), followed by the ankles (31.4%) and the wrists (30.3%). Finger or toe joints were exclusively involved in 114 patients (18.0%). Only 2 patients had hip joint arthritis.

The proportion of patients with monoarthritis was 38.3%, 34.1% had oligoarthritis (2–4 swollen joints), and 27.6% had arthritis of 5 joints or more (polyarthritis). The distribution of swollen joints was different in patients with mono-, oligo-, and polyarthritis (Figure 1). Knees and ankles were the most frequently involved joints in patients with mono- and oligoarthritis, whereas small joints in hands and feet were most frequently affected in the polyarticular patients (Figure 1).

As expected, patients with polyarthritis had longer arthritis duration, and higher DAS28 and HAQ levels, and were more frequently anti-CCP and RF-positive than those with monoarthritis and oligoarthritis (Table 1). Although polyarthritic patients were most affected by their disease, even patients with mono- and oligoarthritis had moderate to high scores on patient global, pain, and fatigue VAS, as well as elevated acute-phase reactants and prolonged duration of morning stiffness. Mono- and oligoarthritic patients also reported substantial effect on health status, depicted by mean HAQ scores of 0.62 and 0.82, respectively, as well as decreased SF-36 scores.

The results of the Dutch prediction rule in the NOR-VEAC patients are shown in Table 2. The proportion of patients fulfilling the individual criteria was, not surprisingly, highest among the polyarticular patients, but for some aspects, like morning stiffness and CRP, some patients in the oligo- and even in the monoarticular group fulfilled the criteria.

DISCUSSION

The concept of "early arthritis" is changing. Whereas most early studies focused on patients with a confirmed RA diagnosis, the emphasis has shifted towards patients in a very early stage of disease. In our study median arthritis duration was 30 days, and 70% of the patients had either mono- or oligoarthritis. The age and sex distributions differed from a typical early RA study, with lower age and proportion of women. In the NOR-VEAC study, patients are seen extreme-

Table 1. Demographics, disease characteristics, and health status in 634 patients with very early arthritis, with comparisons between subgroups according to number of swollen joints [mean (standard deviation) or median (25th–75th percentile) values for continuous variables, n (%) for counts].

	All Patients, N = 634	Monoarticular, N = 243	Oligoarticular, N = 216	Polyarticular, N = 175	p*
Female sex	353 (55.5)	128 (52.7)	123 (56.9)	101 (57.7)	0.49
Age, yrs	46 (15)	45 (14)	43 (15)	51 (15)	< 0.001
Daily smoker	137 (21.6)	56 (23.0)	45 (20.8)	36 (20.6)	0.78
≥ 4 cups coffee/day	150 (23.7)	62 (25.5)	42 (19.4)	46 (26.3)	0.20
Arthritis duration, days	30 (11–63)	22 (7–52)	28 (13–61)	47 (19–75)	< 0.001
SJC, 0–68	2 (1–5)	1 (1–1)	2 (2–3)	9 (6–14)	NA
TJC, 0–28	1 (0–4)	1 (0–1)	1 (0–2)	6 (3–11)	NA
ESR, mm/h	24 (11–47)	17 (10–33)	26 (13–49)	32 (15–60)	< 0.001
CRP, mg/l	13.5 (3.6–35.4)	9.0 (2.9–25.0)	15.5 (3.5–43.0)	18.3 (6.0–45.6)	< 0.001
IgM RF-positive†	54/484 (11.2)	8/188 (4.3)	8/169 (4.7)	38/127 (29.9)	< 0.001
Anti-CCP2-positive†	70/492 (14.2)	9/190 (4.7)	13/173 (7.5)	49/129 (37.2)	< 0.001
Assessor's global VAS, mm	36 (21)	26 (16)	35 (19)	50 (20)	< 0.001
Patient's global VAS, mm	53 (24)	48 (26)	53 (23)	58 (23)	< 0.001
Joint pain VAS, mm	52 (26)	49 (28)	53 (24)	55 (24)	0.045
Fatigue VAS, mm	40 (29)	34 (29)	42 (30)	46 (27)	< 0.001
Morning stiffness > 1 h	325 (51.3)	94 (38.7)	116 (53.7)	115 (65.7)	0.006
DAS28	4.0 (1.3)	3.3 (0.9)	3.8 (1.0)	5.2 (1.3)	NA
HAQ (0–3)	0.82 (0.65)	0.62 (0.55)	0.82 (0.63)	1.09 (0.69)	< 0.001
SF-36					
PCS	33.5 (10.6)	36.3 (11.3)	31.9 (9.8)	31.8 (9.7)	< 0.001
MCS	48.3 (11.4)	49.9 (10.8)	48.5 (11.2)	46.0 (12.0)	0.002

* Comparing mono, oligo, and polyarticular patients (ANOVA/Kruskal-Wallis test). † Because analysis of frozen sera was performed separately, analyses for IgM rheumatoid factor, and anti-CCP2 were not available in all patients. NA: not applicable (because of stratification according to joint counts); SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; anti-CCP2: antibodies to cyclic citrullinated protein analyzed by second-generation ELISA; VAS: visual analog scale; DAS28: Disease Activity Score 28-joint count; HAQ: Health Assessment Questionnaire without recording the use of aids; SF-36: Short-Form Health Survey; PCS: physical component summary; MCS: mental component summary.

ly early, and this, together with the wide inclusion criteria, makes the patient population different from patients in most other early arthritis clinics. The British NOAR cohort focuses on patients with early inflammatory polyarthritis[25]. This cohort, although community-based, has a selected patient population, as only patients with at least 2 swollen joints and symptom duration more than 4 weeks are included. The Dutch EAC in Leiden[26] includes patients with any arthritis of ≤ 2 years' duration, thus the propensity of identifying patients with a more insidious onset of disease (i.e., patients with RA) is greater in this cohort than in NOR-VEAC.

We designed our VEAC based on experience from the Oslo reactive arthritis study[27], where essential features were collaboration with primary healthcare and the ability to provide specialist care for arthritis patients in acute stages with minimal delay. By encouraging general practitioners to refer all patients with recent onset joint swelling, the chance of overlooking serious inflammatory arthritis is reduced. Wide inclusion criteria enhance the potential to mirror the whole diagnostic spectrum of early arthritides in the population. Further, early arthritis clinics provide opportunities to identify predictors of a severe disease course, like anti-CCP, RF, and other biomarkers[28,29].

Additionally, NOR-VEAC sought to strengthen the cooperation between first- and second-line healthcare and raise the awareness of inflammatory arthritis through education of primary care physicians. We anticipated that guaranteeing a maximum waiting period of 14 days from referral would improve the perception of rheumatology as a specialty that proactively offers early diagnosis and treatment in potentially chronic diseases. To our knowledge no cohort with shorter median disease duration has been reported. VEAC can even be considered a preventive tool, as early treatment with methotrexate in UA has been shown to delay the diagnosis of RA[5]. In fact, partial funding for the NOR-VEAC was received from money assigned to the prevention of health problems. All patients were treated according to the best clinical practice, with about 28% receiving a DMARD over the first year[30].

Few studies have focused on joint distribution in patients with early arthritis. In a study from the 1970s, involvement of large joints (shoulder, wrist, elbow, knee) and metatarsophalangeals I and III was predictive of severe disease[31]. A more recent study from the Leiden EAC also showed that large joint arthritis was associated with a destructive course in patients with early RA[32]. Extensive assessment of joint involvement could therefore yield useful information about the expected disease course in patients with early arthritis. Twenty-eight-joint counts are often used to record joint involvement in patients with RA, but ankles and feet are fre-

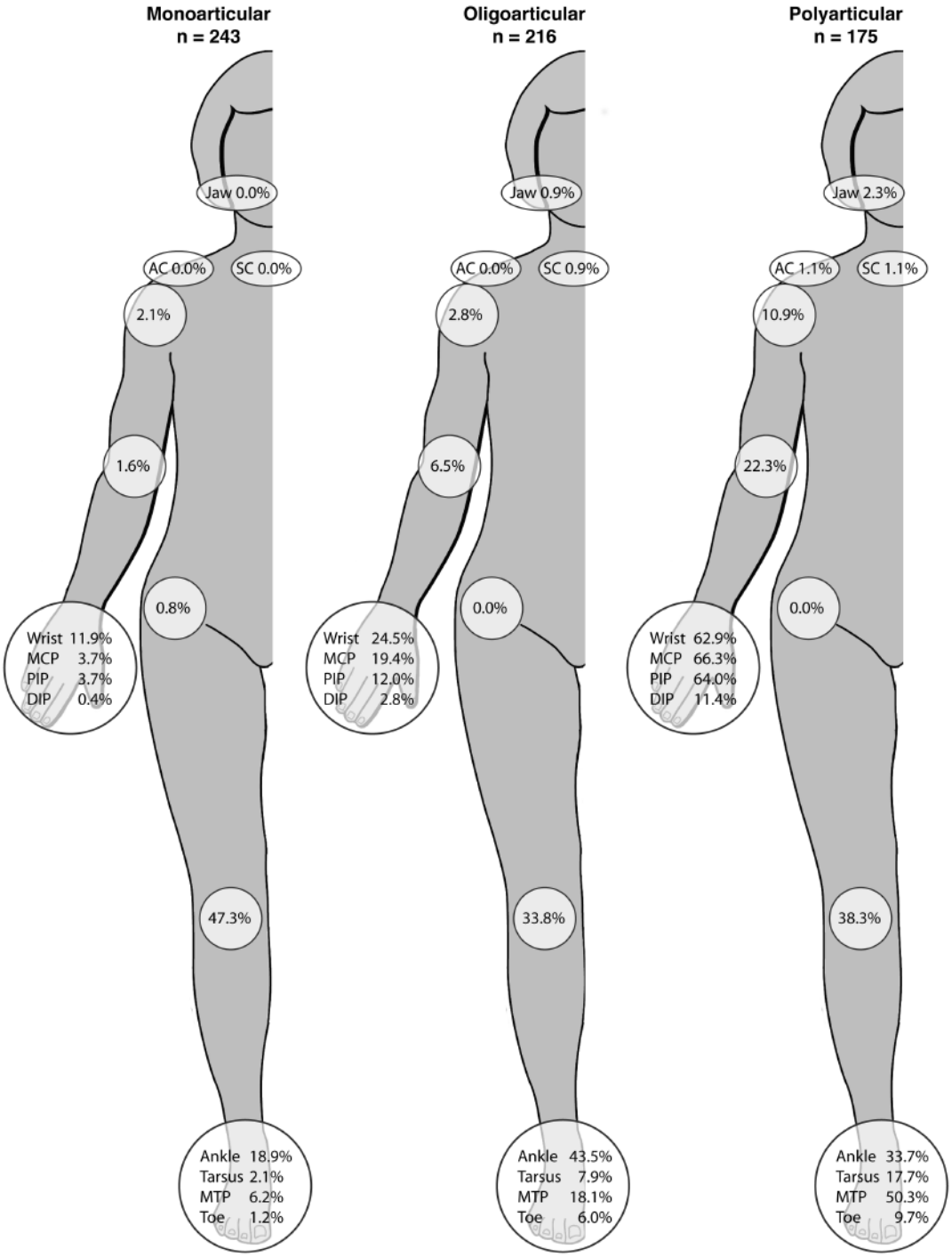

Figure 1. Distribution of swollen joints in patients with mono-, oligo-, and polyarthritis.

quently involved in very early arthritis (Figure 1), including reactive arthritis[27]. Thus, extensive joint counts (e.g., 44- or 68-SJC, which include the feet) should ideally be used to fully assess joint involvement in patients with early arthritis.

When research data are collected within the setting of regular clinical practice, some methodological challenges are encountered. First, when a patient is received in an emergency situation with recent onset joint swelling, inclusion in the research project has to be performed immediately, before joint aspiration and other procedures are performed. The use of study nurses in order to provide patients with immediate information about the project facilitated inclusion. Nevertheless, we must take into account missed inclusion of several patients with early arthritis due to the

Table 2. Proportions of patients in the mono, oligo, and polyarticular groups fulfilling the individual criteria, and score results of the prediction rule for RA development[22].

Variable	Points	Mono (n = 243)	Oligo (n = 216)	Poly (n = 175)	p
Female sex	1	52.7	56.9	57.7	0.49
Small joints	0.5	14.8	42.1	93.1	< 0.001
Symmetrical arthritis	0.5	NA	54.6	90.9	NA
Arthritis in upper extremities	1	23.5	46.8	90.9	< 0.001
Arthritis in upper and lower extremities	1.5	NA	25.9	64.6	< 0.001
Morning stiffness 30–59 min	0.5	16.5	18.1	17.7	0.68
Morning stiffness ≥ 60 min	1	38.7	53.7	65.7	0.006
TJC 4–10	0.5	2.1	15.3	42.9	NA
TJC ≥ 11	1	0.4	17.6	63.4	NA
SJC 4–10	0.5	NA	17.6	63.4	NA
SJC ≥ 11	1	NA	NA	100	NA
CRP 5–50	0.5	57.0	53.7	55.2	0.77
CRP ≥ 51	1.5	14.0	23.1	28.7	0.001
Rheumatoid factor positivity	1	4.3	4.7	29.9	< 0.001
Anti-CCP positivity	2	4.7	7.5	37.2	< 0.001
Prediction rule scores					
Total score, mean (range)		2.87 (0.49–6.82)	3.97 (1.00–7.50)	6.85 (2.74–11.19)	
Score ≤ 6 (low)		99.6	91.7	31.4	
Score > 6 and < 8 (intermediate)		0.4	8.3	42.3	
Score ≥ 8 (high)		0.0	0.0	26.3	

Values are percentages if not stated otherwise. NA: not applicable; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; CCP: cyclic citrullinated peptide.

logistical challenges in actual clinical practice. The expected number of inclusions should have been higher than 658 within a population of 1.7 million over a 3-year period if the known incidence of arthritides is taken into account[6,7]. The upper limit of 16 weeks' duration of joint swelling also excludes patients with a more insidious onset of symptoms, as is the case with some RA patients. Second, the definition of recent onset arthritis itself is challenging. We included patients with recurring episodes of undiagnosed arthritis if the previous episode of joint swelling took place more than 6 months prior to enrolment. This eligibility criterion allowed for some patients with crystal arthropathies to be included in the project. Seven patients (6 with monoarthritis, 1 with oligoarthritis) were diagnosed with gout at the initial visit. We believe that these patients, although not prone to develop chronic inflammatory arthritis, are informative as part of the disease spectrum in patients with recent onset joint swelling.

In early stages of disease, specific disease classification and prediction of outcome is difficult, and many patients will have UA. Depending on the study population, 6%–55% of patients with UA progress to RA within 1 year[33], but prognosis is dependent not only on whether a diagnosis of RA can be made. Some patients with UA are at risk of a disease course as serious as patients with RA[11], and these patients need to be recognized early. To further explore the characteristics of our patients, we calculated the individual patient scores in the NOR-VEAC material according to the prediction rule from the Leiden EAC. Many variables in the questionnaire are based on a multitude of involved joints. Subsequently, only 1 patient in the monoarticular group and very few in the oligoarticular group achieved a score higher than 6. No patients with mono- or oligoarthritis achieved a score over 8, which is the cutoff value associated with high probability of RA development. One limitation is that the prediction rule was designed for patients with UA, and may not be valid when applied, as in our case, to all patients with early arthritis.

Our study highlights that oligo- and monoarthritis occur even somewhat more frequently that polyarthritis in patients with recent onset arthritis, and that small joint involvement is less frequent in patients with mono- and oligoarthritis. Our results contribute to the understanding of the heterogeneity of early arthritis. Disease activity increased, as expected, with increasing number of involved joints. Factors commonly associated with a worse outcome, such as anti-CCP, RF, and higher age at disease onset were more frequently found in patients with polyarthritis, and these patients achieved higher scores according to the Dutch prediction rule for RA development. Preliminary comparative analyses have shown similar patient characteristics in an Estonian VEAC using the same protocol as NOR-VEAC[34]. Future followup results will clarify whether predictors of persistent arthritis or RA in NOR-VEAC are different from identified predictors in other early arthritis studies with different inclusion criteria.

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