Rheumatoid Arthritis: Diagnostic Workup and Treatment

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Staff Rheumatologist
VA Pittsburgh Healthcare System
Learning Objectives

upon completion of this session, participants will be able to

• Describe common clinical features of Rheumatoid Arthritis
• Screen patients to improve early diagnosis of RA
• Be familiar with methods of outcome assessment in RA
• Grasp the treat to target approach consistent with current guidelines for RA management
Rheumatoid Arthritis

Normal Joint

Capsule
Synovial membrane
Synoviocytes
Cartilage

Early

Angiogenesis
Neutrophils
Synoviocyte accumulation
Dendritic cell
T cells
B cells

RA

Established

Plasma cell
Bone erosion
Neutrophils
Pannus

RA = rheumatoid arthritis.
Adapted with permission from Choy and Panayi. *N Engl J Med.* 2001;344:907. Copyright © 2001 Massachusetts Medical Society. All rights reserved.
Bone Damage in RA

Normal Joint

Periarticular osteoporosis

Erosion

Generalized skeletal osteoporosis

Patient Case: Lillian presents to PCP

• 57 year-old woman who presents to her PCP with a 2 month history of morning pain and prolonged morning stiffness > 60 minutes in both hands.

• This has interfered with her ability to perform her work as a teacher.

• The hand pain has progressively increased and now her wrists and ankles are also painful. She now has difficulty standing for long periods at work or at home due to foot and ankle pain.

• In addition, she began to feel extremely tired. No energy to do her usual activities.
Patient Case: Lillian

• She is 5’6” 232# BMI 37.5 (class II obesity defined as BMI 35-39)

• Her sister has OA and their mother did as well. She dismissed her symptoms to getting older. Tried warm water soaks and OTC Aleve with little improvement.

• In addition to obesity, Lillian has hyperlipidemia for which she has been on a statin for the last several years.

• Upon examination, Lillian has tenderness in response to a squeeze test across her MCP joints. PCP agreed with her that her hand pain may likely be OA. PCP prescribed one month of Naproxen 500mg twice daily.
### The 2010 ACR/EULAR Classification Criteria for RA

<table>
<thead>
<tr>
<th>1. Joint involvement (swollen or tender joint on exam or synovitis on ultrasound) (0 to 5 points max)</th>
<th>2. Serology (0 to 3 points max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• One medium to large joint (shoulders, elbows, hips, knees, ankles)</td>
<td>• Negative RF and negative ACPA 0</td>
</tr>
<tr>
<td>• 2-10 med to large joints</td>
<td>• Low +RF or low +ACPA (&lt;3 times the nml upper limit) 2</td>
</tr>
<tr>
<td>• 1-3 small joints (MCP, PIP, 2-5 MTP or wrist with or without large joint involvement)</td>
<td>• High +RF or high +ACPA (&gt;3 times the nml upper limits) 3</td>
</tr>
<tr>
<td>• 4-10 small joints (with or without large joint involvement)</td>
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<tr>
<td>• &gt;10 joints (at least one small joint involved)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Acute phase reactants (0 to 1 points max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normal CRP and ESR 0</td>
</tr>
<tr>
<td>• Abnormal CRP or ESR 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Duration of symptoms (0 to 1 points max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt;6 weeks 0</td>
</tr>
<tr>
<td>• ≥6 weeks 1</td>
</tr>
</tbody>
</table>

ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PIP = proximal interphalangeal; RF = rheumatoid factor
Question #1

According to the 2010 ACR/EULAR classification criteria for RA, which of the following should be considered in the initial work-up of a patient with joint pain?

A. Presence of rheumatoid nodules
B. Synovitis in at least one joint
C. Radiographic erosive changes
D. Symmetric arthritis
Answer #1

According to the 2010 ACR/EULAR classification criteria for RA, which of the following should be considered in the initial work-up of a patient with joint pain?

A. Presence of rheumatoid nodules
B. Synovitis in at least one joint
C. Radiographic erosive changes
D. Symmetric arthritis
The 2010 ACR/EULAR Classification Criteria for RA

1. Confirmed presence of synovitis in at least 1 joint
2. Absence of an alternative diagnosis that better explains the synovitis
3. Total score of at least 6-10 from individual scores in the 4 domains (joint involvement, serology, acute phase reactants and duration of symptoms)

These criteria do not include the presence of rheumatoid nodules or radiographic erosive changes, both of which are less likely in early RA. Symmetric arthritis is also not recognized in the 2010 criteria, allowing for early asymmetric presentation.
Question #2

Which statement about RA manifestations in early disease is true?

A. Symptoms in small joints of the hand almost always precede symptoms in the toes

B. Involvement of large synovial joints (for example, elbows, shoulders, ankles) is rarely seen in early disease

C. Joints affected in early disease can be unilateral

D. Extensive erosions are commonly seen on imaging
Answer #2

Which statement about RA manifestations in early disease is true?

A. Symptoms in small joints of the hand almost always precede symptoms in the toe joints

B. Involvement of large synovial joints (for example, elbows, shoulders, ankles) is rarely seen in early disease

C. Joints affected in early disease can be unilateral

D. Extensive erosions are commonly seen on imaging
Differential diagnoses to consider

- Limited duration (eg, in viral arthropathy)
- The presence of other diseases (eg, in psoriatic arthritis or arthritis of inflammatory bowel disease [IBD])
- The pattern of joint involvement and other symptoms (eg, in psoriatic arthritis, spondyloarthropathy, or polymyalgia rheumatica [PMR])
- The presence of systemic features (eg, in systemic lupus erythematosus [SLE] or dermatomyositis [DM])
- Diagnostic laboratory tests associated with other conditions (eg, specific autoantibodies in SLE, synovial fluid crystals in gout or calcium pyrophosphate disease)
- Relatively high specificity of ACPAs (anti-CCP) for RA
Autoantibody Markers in RA

- RF (IgM, IgG, IgA)
- Anti-CCP (anti-cyclic citrullinated peptide) Ab
- ANA (up to 30%)
- Antiheterogeneous ribonuclear protein A2/RA33
- Anticollagen antibodies (Type II)
- Anti-glucose-6-phosphate isomerase (anti-GPI) antibodies
- Anti-Sa antibodies
- Anti-heat shock protein antibodies
- Antibodies against advanced glycosylation end products (AGE-IgG)
Diagnostic and Prognostic Significance of Autoantibodies in Very Early RA

- Purpose: to determine the sensitivity, specificity and positive predictive value of RF, anti-CCP, and anti-A2/RA33 in differentiating RA from other arthropathies in very early arthritis

<table>
<thead>
<tr>
<th></th>
<th>RA (n=100)</th>
<th>non-RA (n=80)</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF ≥20</td>
<td>54</td>
<td>9</td>
<td>54</td>
<td>89.0</td>
<td>85.7</td>
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<tr>
<td>RF ≥50</td>
<td>46</td>
<td>2</td>
<td>46</td>
<td>97.4</td>
<td>95.8</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>38</td>
<td>1</td>
<td>38</td>
<td>98.7</td>
<td>97.4</td>
</tr>
<tr>
<td>Anti-A2/RA33</td>
<td>26</td>
<td>8</td>
<td>26</td>
<td>90.0</td>
<td>76.4</td>
</tr>
<tr>
<td>RF ≥20 pos + anti-CCP pos</td>
<td>30</td>
<td>0</td>
<td>30</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>RF ≥20 pos + RA33 pos</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>RF ≥20 neg + anti-CCP pos</td>
<td>8</td>
<td>1</td>
<td>8</td>
<td>98.7</td>
<td>88.9</td>
</tr>
</tbody>
</table>

Nell VPK, et al. ACR 2003, #167

Anti-CCP and RF ≥50 have a PPV of 78% and 88% for developing erosive disease
Patient Case: Lillian phone call

• Lillian calls her PCP in 3 weeks.
• Symptoms were minimally improved.
• Morning stiffness in her joints - now lasting all day. Her hands and wrists are becoming more swollen. She can no longer make a fist.
• She is very frustrated.
Question #3

At this point, what is your next best step?

A. Labs
B. Refer to Ortho
C. Refer to OT
D. Refer to Rheum
E. Switch NSAIDs
Answer #3

• At this point, what is your next best step?
  A. Labs
  B. Refer to Ortho
  C. Refer to OT
  **D. Refer to Rheum**
  E. Switch NSAIDs

• At this point, Lillain’s PCP refers her to Rheumatology.
"I wish you'd come to me sooner."
RA vs OA

• At initial visit, did Lillian’s exam indicate swelling at the MCPs and wrists?
• Check labs: ESR, CRP, RF, CCP
• How long does the stiffness last?
  • OA < 30 minutes
  • RA 1-2 hours+
• Fatigue?
  • Not typically associated with OA
  • Definitely associated with RA
What would a Rheumatologist do?
“Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests.”
When you suspect inflammatory origin

• “Basic”
  • CBC, CMP, TSH, U/A
  • CXR PA/lateral (e.g. smoker, reports dyspnea)

• “Fancy”
  • RF, anti-CCP, serum uric acid, ESR, CRP
  • If personal or FHx of inflammatory back pain or history of iritis: HLAB27

• If applicable:
  • Viral serologies (parvovirus, Hep B/C, HIV)
  • Lyme screen

• If long-term symptoms: x-rays of hands, feet and most affected joints to assess for erosive changes; provide baseline studies
Patient Case: Lillian - RHEUMATOLOGIST EVALUATION

- 10 weeks after the initial evaluation to her PCP
- Physical examination:
  - No nodules or joint deformities
  - 8 swollen joints (MCP 2,3,4 bilaterally and both wrists) and 11 tender joints (MCP 2,3,4 bilaterally, both wrists, both elbows, and right shoulder). Skin over knuckles are red.
- Lillian rated her global assessment of disease activity on a visual analog scale (VAS) as 85/100. She reported severe fatigue.
- Labs:
  - Elevated ESR of 59, CRP at 10 mg/L, RF at 340 u/mL, and ACPA (anti-CCP) at 35 u/mL
  - Hepatic and renal function normal, as well as her differential
    - Hgb; 11 g/dL and MCV; 79 fL/red cell were slightly lower than normal
- Imaging:
  - Normal chest X-ray
  - Xrays of the hands and feet: no erosions
### The 2010 ACR/EULAR Classification Criteria for RA

#### 1. Joint involvement
**Swollen or tender joint on exam or synovitis on ultrasound**
- One medium to large joint (shoulders, elbows, hips, knees, ankles) 0
- 2-10 med to large joints 1
- 1-3 small joints (MCP, PIP, 2-5 MTP or wrist with or without large joint involvement) 2
- 4-10 small joints (with or without large joint involvement) 3
- >10 joints (at least one small joint involved) 5

#### 2. Serology
- Negative RF and negative ACPA 0
- Low +RF or low +ACPA (<3 times the nml upper limit) 2
- High +RF or high +ACPA (>3 times the nml upper limits) 3

#### 3. Acute phase reactants
- Normal CRP and ESR 0
- Abnormal CRP or ESR 1

#### 4. Duration of symptoms
- <6 weeks 0
- ≥6 weeks 1

*ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PIP = proximal interphalangeal; RF = rheumatoid factor*
## Outcomes assessments

- The Treat to Target (TTT) approach requires the use of Validated Disease Activity Tools

- ACR/EULAR Recommended disease activity measures include:
  - CDAI: Clinical Disease Activity Index
  - DAS28: Disease Activity Score with 28 joint counts
  - SDAI: Simplified Disease Activity Index

<table>
<thead>
<tr>
<th>Scale</th>
<th>Remission</th>
<th>Low</th>
<th>Mod</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDAI</td>
<td>0-76</td>
<td>≤ 2.8</td>
<td>&gt; 2.8 – 10</td>
<td>&gt;10 – 22</td>
</tr>
<tr>
<td>DAS28</td>
<td>0-9.4</td>
<td>&lt; 2.6</td>
<td>≥ 2.6 - &lt; 3.2</td>
<td>≥3.2 - ≤ 5.1</td>
</tr>
<tr>
<td>SDAI</td>
<td>0-86</td>
<td>≤ 3.3</td>
<td>&gt; 3.3 - ≤ 11</td>
<td>&gt;11 - ≤ 26</td>
</tr>
</tbody>
</table>
28 Joint Count for Arthritis
# Clinical Disease Activity Index (CDAI)

<table>
<thead>
<tr>
<th>Joint</th>
<th>Left Tender</th>
<th>Left Swollen</th>
<th>Right Tender</th>
<th>Right Swollen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Elbow</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Wrist</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCP 1</td>
<td></td>
<td></td>
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<tr>
<td>MCP 2</td>
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<tr>
<td>MCP 3</td>
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<tr>
<td>MCP 4</td>
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<tr>
<td>MCP 5</td>
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<tr>
<td>PIP 1</td>
<td></td>
<td></td>
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<tr>
<td>PIP 2</td>
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<td>PIP 3</td>
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<tr>
<td>PIP 4</td>
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<tr>
<td>PIP 5</td>
<td></td>
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<tr>
<td>Knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Tender:</td>
<td>Swollen:</td>
<td></td>
<td></td>
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</tbody>
</table>

## Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

- **Very Well**
- **Well**
- **Poor**

Your Name________________________ Date of Birth ________ Today's Date ________

## Provider Global Assessment of Disease Activity

- **Very Well**
- **Well**
- **Poor**
Our patient Lillian:
TJC: 11
SJC: 8
PGA: 8.5
EGA: 6

CDAI: 33.5 HIGH ACTIVITY
Disease Activity Score 28 (DAS 28)

- Assesses disease activity on a continuous scale
- Calculated using the following variables:
  - Tender joints, of 28 counted
  - Swollen joints, of 28 counted
  - ESR
  - Patient’s general health or patient’s global assessment of disease activity (visual analog scale [VAS])

\[
\text{DAS28-ESR} = 0.56 \times \sqrt{TJC} + 0.28 \times \sqrt{SJC} + 0.70 \times \ln(ESR) + 0.014 \times GH.
\]


Our patient Lillian:
- TJC: 11
- SJC: 8
- ESR: 59
- VAS: 85

DAS: 6.69  HIGH ACTIVITY

Simple Disease Activity Index (SDAI)

Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Very Poor

Your Name_________________________ Date of Birth _________ Today's Date __________

Provider Global Assessment of Disease Activity

Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Very Poor

How to Score the SDAI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Value</th>
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<tbody>
<tr>
<td>Tender joint score</td>
<td>(0-28)</td>
<td></td>
</tr>
<tr>
<td>Swollen joint score</td>
<td>(0-28)</td>
<td></td>
</tr>
<tr>
<td>Patient global score</td>
<td>(0-10)</td>
<td></td>
</tr>
<tr>
<td>Provider global score</td>
<td>(0-10)</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>(0-10)</td>
<td></td>
</tr>
<tr>
<td>Add the above values to calculate the SDAI score</td>
<td>(0-86)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SDAI Score Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 – 3.3</td>
</tr>
<tr>
<td>3.4 – 11.0</td>
</tr>
<tr>
<td>11.1 – 26.0</td>
</tr>
<tr>
<td>26.1 – 86.0</td>
</tr>
</tbody>
</table>

Our patient Lillian:

TJC: 11
SJC: 8
PGA: 8.5
EGA: 6
CRP: 10

SDAI: 43 HIGH ACTIVITY
Question #4

- Rheumatologists use disease activity assessment tools to determine how to continue treating patients. Of the validated composite disease activity measures endorsed by ACR and EULAR, which is the LEAST complicated to use in clinical practice?

A. DAS 28  
B. CDAI  
C. SDAI  
D. BIN 36
Rheumatologists use disease activity assessment tools to determine how to continue treating patients. Of the validated composite disease activity measures endorsed by ACR and EULAR, which is the LEAST complicated to use in clinical practice?

A. DAS 28
B. CDAI
C. SDAI
D. BIN 36
Treatment options

- csDMARD (conventional synthetic disease modifying anti-rheumatic drug)
  - Leflunomide (Arava)
  - Hydroxychlorquine (Plaquenil)
  - Methotrexate (Trexall)
  - Sulfsalazine (Azulfidine)

- BRMs (Biologic response modifiers)
  - TNF-inhibitors
    - Etanercept (Enbrel)
    - Infliximab (Remicade)
    - Adalimumab (Humira)
    - Golimumab (Simponi)
    - Certolizumab pegol (Cimzia)
  - IL-1 inhibition
    - Anakinra (Kineret)

- T cell co-stimulatory inhibitor
  - Abatacept (Orencia)
  - B cell depletion
    - Rituximab (Rituxan)

- IL-6 inhibition
  - Tocilizumab (Actemra)

- IL-17 inhibition
  - Secukinumab (Cosentyx)

- IL-12/23 blockade
  - Ustekinumab (Stelara)

- tsDMARD (targeted synthetic disease modifying anti-rheumatic drug)
  - Tofacitinib (Xeljanz)
  - Baricitinib (Olumiant)
  - Upadacitinib (Rinvoq)
Question #5

- After being diagnosed with RA, which treatment option would you recommend as first line treatment
  A. A TNF-inhibitor such as Adalimumab (Humira)
  B. A csDMARD (conventional synthetic disease modifying anti-rheumatic drug), such as Methotrexate
  C. A JAK (janus kinase)-inhibitor tsDMARD (targeted synthetic disease modifying anti-rheumatic drug) such as Tofacitinib (Xeljanz)
  D. A different NSAID such as Meloxicam
Answer #5

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  D. A different NSAID such as Meloxicam
Patient Case: Lillian Rheum Follow-up

• Lillian presents 3 months after diagnosis & initiating treatment with MTX 15MG PO QW
• Improvement has been minimal. c/o pain, prolonged stiffness. Depressed. Fatigued.
• Because of pain and fatigue, she is considering early retirement

Our patient Lillian:
TJC: 10
SJC: 6
PGA: 6
EGA: 6

CDAI: 28 HIGH ACTIVITY
ACR Treatment Algorithm

TNF +/- MTX
OR
NON-TNF +/- MTX
ACR Guidelines Suggest Control of Disease Progression Should Start Early to Limit Joint Damage

“Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease modifying agent. The goal of treatment is to arrest the disease and achieve remission.”

Patient Case: Lillian continued

- Lillian’s initial CDAI 33.5
- After 3+ months of MTX, CDAI 28
- Because she experienced symptoms several months prior to diagnosis, she is at higher risk for long term joint damage than she would have had she been diagnosed earlier
- Her Rheumatologist recommends ADDING another drug to her regimen that would hopefully yield greater efficacy
ACR Algorithm for Treatment of Established RA

Single TNFi failure, switch to second TNFi.

Second TNFi failure, switch class

Do not discontinue all RA treatments**
Treatment Principles and Goals

• Shared decision making
• Frequent monitoring
• Measurement of disease activity
• Adjustment of treatment to achieve clinical remission or LOW DISEASE ACTIVITY

**This is ESSENTIAL to avoid disease progression, joint damage, and long term consequences such as deformity and disability.**
Patient case: Lillian continued

• Having determined MTX monotherapy insufficient to achieve treatment goals, Adalimumab is added to MTX

• Patients with IR (incomplete response) to csDMARDs (such as MTX) have been noted to benefit from intensive treatment with addition of a biologic

• After 3 months of Adalimumab + MTX CDAI is now 6.

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<td></td>
</tr>
<tr>
<td>Patient global score</td>
<td>(0-10)</td>
<td></td>
</tr>
<tr>
<td>Provider global score</td>
<td>(0-10)</td>
<td></td>
</tr>
<tr>
<td>Add the above values to calculate the CDAI score</td>
<td>(0-76)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<td>2.9 - 10.0</td>
</tr>
<tr>
<td>10.1 - 22.0</td>
</tr>
<tr>
<td>22.1 - 76.0</td>
</tr>
</tbody>
</table>

Our patient Lillian:
TJC: 2
SJC: 0
PGA: 2
EGA: 2

CDAI: 6 LOW ACTIVITY
Listen to your patient. He’s telling you the diagnosis.

- William Osler MD

Thank you!
References

• van der Heijde DMFM. Br J Rheumatol. 1995:34(suppl 2):74-78.