PHASE I (Inpatient): Diagnosis

**Inclusion Criteria**
- Child admitted with suspicion for new rheumatologic disease

**Exclusion Criteria**
- Confirmed other diagnosis that explains symptoms

**Admit Criteria**
- To facilitate timeliness of diagnostic workup (e.g., non-ambulatory, fever of unknown origin)
- Aspiration risk/Feeding intolerance
- Symptomatic hypertension
- Respiratory distress

**Screening Labs**
- Evaluate for infection
- Evaluate for malignancy
- Rheumatologic Disease Associated Tests
- Organ Survey

**Exclude Malignancy**
- **Clinical red flags**: Night pain, weight loss, bulky lymphadenopathy, hepatosplenomegaly
- **Abnormal labs**: Elevated LDH/uric acid, multiple cytopenias, inappropriately low platelets/WBC

**Exclude Infection**
- Acute onset of symptoms, Fever of unknown origin, High risk travel/TB exposures
- Consider infectious mimics of rheumatic disease
- Consider ID Consult

**Assess For Major Organ Involvement/Severe Disease**
- Nephritis
- Pulmonary hemorrhage/pulmonary hypertension.
- CNS involvement
- Severe myositis (JDMS)
- Macrophage activation syndrome

**Treat Infection**

**Phase Change**

**Evidence of Underlying Rheumatologic Disease?**
- Yes
- No, treat infection

**Off Pathway**

**Executive Summary**

**Test Your Knowledge**

**Citation Information**

**Explanation of Evidence Ratings**

**Summary of Version Changes**
Treatment

Induction immunosuppression
- Methylprednisolone 30mg/kg IV q 18-24 hours x 1-3 doses
- Steroid sparing medications
- Add immunosuppressive agents based on diagnosis
- Oral Steroid Taper

Non-Pharmacologic Therapy
- Physical Therapy/Occupational Therapy (PT/OT) consult
- Nutrition consult
- Social Work consult

Begin Discharge Planning

Evidence of Major Organ Involvement/Severe Disease?

- Yes
  - Manage Severe Disease
    - Additional evaluations/procedures per consult services (e.g., kidney biopsy)
    - Additional induction immunosuppressive agents (e.g., cyclophosphamide)

- No, plan for discharge

Discharge Criteria

- Adequate ambulation
- Able to swallow (nutrition plan in place)
- Prescriptions ordered and ready
  - Oral Steroid taper 1-2mg/kg/day divided into 2 doses/day
  - Disease specific steroid sparing agents
  - Calcium/vitamin D supplements
  - Consider gastroprotective agent (H2 blocker or PPI)
- Medication teaching (e.g., subcutaneous injections)
- Follow-up appointments: rheumatology clinic, primary MD, PT/OT, infusions, next cyclophosphamide admission

Discharge criteria met

Discharge Instructions

- Rheumatology toolkit (for SCH only)
- Medic alert bracelet
- Medication teaching

Steroid safety: alert provider for high blood pressure or decreased urine output
Learning Objectives

Upon completion of this module, when evaluating a child with suspected rheumatologic disease, participants will be better able to:

1. Describe reasons for a thorough evaluation for infectious entities as part of the initial diagnostic approach
2. Identify symptoms and laboratory findings concerning for possible malignancy in these patients
3. Recognize the appropriate use and limitations of rheumatologic disease associated tests in the initial evaluation
4. Apply the Rheumatology New Diagnosis Pathway to develop an initial management plan when admitting these patients
5. Discuss the general approach to the initial evaluation with patient families

Background

- Approximately 1 in 1000 children suffer from juvenile arthritis or other childhood rheumatologic diseases.
- There is a shortage of trained pediatric rheumatologists.
- Many children with rheumatologic conditions will present to primary care providers for initial evaluation and management.
- Current evidence suggests graduating pediatric residents feel ill equipped to recognize and treat children with rheumatologic disorders.

(Henrickson, M. 2011)
Background: Pathway Goals

- To facilitate timely evaluation, treatment, and discharge of patients admitted for suspected new rheumatologic diagnoses
- To improve non-Rheumatology care providers familiarity and competency with appropriate initial evaluation of children with rheumatologic disorders

Rheumatology New Diagnosis Pathway Overview

**PHASE 1: Diagnosis**
- Exclude alternative diagnoses
- Assess disease extent

**PHASE 2: Treatment**
- Induction immunosuppressive regimen
- Non-pharmacologic therapies
- Discharge planning
Patients who meet the following criteria should be placed on the Rheumatology New Diagnosis Pathway:

**Inclusion Criteria**
- Child admitted with suspicion for new rheumatologic disease

**Exclusion Criteria**
- Confirmed other diagnosis that explains symptoms

[Back to Diagnosis]
Admission Criteria

Admission reserved for children where ambulatory setting is unsafe or insufficient for initial evaluation:

- To facilitate timeliness of diagnostic workup (e.g. non-ambulatory, fever of unknown origin)
- Aspiration risk/Feeding intolerance
- Symptomatic hypertension
- Respiratory distress

Rheumatology New Diagnosis Pathway: Ordersets

PHASE 1: Diagnosis
- Rheum New (Unknown) Diagnosis Admit Orderset
- Rheum Lupus and MCTD Screening Labs Orderset

PHASE 2: Treatment
- Rheum High Dose IV Steroid Orderset
- Rheum Immune Globulin Infusion Orderset
- Rheum Maintenance Medication Orderset
- Cyclophosphamide Infusion Orderset

Back to Diagnosis
When to Suspect a Rheumatologic Disorder

- Sub-acute to chronic time course
- Multi-system involvement, especially:
  - joints, muscles, skin, kidneys
- Persistent fevers or systemic inflammation not responding to first line therapies
- After thorough evaluation for alternative diagnoses

Inclusion and Exclusion Criteria (Cont'd)

- Includes children admitted with suspicion for:
  - Juvenile Idiopathic Arthritis (JIA)
  - Juvenile Dermatomyositis (JDMS)
  - Primary Vasculitis
  - Macrophage Activation Syndrome (MAS)
  - Mixed Connective Tissue Disease (MCTD)
  - Systemic Lupus Erythematosus (SLE)
  - Systemic Sclerosis
Phase 1 Diagnosis:

Initial laboratory evaluation:

- Exclude alternative diagnoses
- Assess disease extent

Screening Labs

- Evaluate for infection
- Evaluate for malignancy
- Rheumatologic Disease Associated Tests
- Organ survey
Phase 1 Diagnosis:
Exclude Alternative Diagnoses - Infection

Symptoms of occult infections may overlap symptoms of rheumatologic diseases:

- Arthritis may be a feature of certain infections or post-infectious processes
- Abnormal serologic tests have been reported in certain infections (i.e. Positive ANAs in setting of EBV infection; rheumatoid factor positivity in subacute bacterial endocarditis)
- Infectious etiologies are identified in 23-51% of patients in fever of unknown origin case series

(Chow, 2011; Breda, 2010; Kasai, 2011; Lima, 2010).

**Rule Out Infection**
- Acute onset of symptoms, Fever of unknown origin
- High risk travel/TB exposures
- Consider infectious mimics of rheumatic disease
- Consider ID Consult

**CLINICAL PEARLS:**

- Treatment of rheumatologic conditions involves immunosuppressive medications

**NOTE:** It is important to rule out infection prior to treatment to avoid masking or worsening an underlying infection
### Phase 1 Diagnosis:  
**Exclude Alternative Diagnoses – Infection (Cont'd)**

#### Selected Infectious Mimics of Rheumatic Disease:

<table>
<thead>
<tr>
<th>Prominent joint findings:</th>
<th>Joint findings, systemic rash:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Septic arthritis</td>
<td>• Lyme disease (endemic areas)</td>
</tr>
<tr>
<td>• Osteomyelitis/reactive effusion</td>
<td>• Parvovirus B19</td>
</tr>
<tr>
<td>• Toxic synovitis/ post-infectious arthritis</td>
<td>• Neisseria (gonorrhoeae, or meningitidis)</td>
</tr>
<tr>
<td>• Reactive arthritis with enteric/ genitourinary infections (Salmonella, Shigella, Chlamydia)</td>
<td>• Acute Rheumatic Fever</td>
</tr>
<tr>
<td></td>
<td>• Rickettsial diseases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prominent fevers, +/- CBC changes:</th>
<th>Fever of unknown origin + lymphadenopathy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adenovirus</td>
<td>• Bartonella</td>
</tr>
<tr>
<td>• EBV/CMV</td>
<td>• Tuberculosis</td>
</tr>
<tr>
<td>• HIV</td>
<td></td>
</tr>
<tr>
<td>• HHV-6</td>
<td></td>
</tr>
<tr>
<td>• Parvovirus B19</td>
<td></td>
</tr>
<tr>
<td>• Rickettsial diseases</td>
<td></td>
</tr>
</tbody>
</table>


Slide Courtesy of M. Kronman, 2012

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[Back to Diagnosis]
Inflammatory Markers:

- Standard inflammatory markers (ESR, CRP, WBC count) cannot accurately differentiate between systemic infections and rheumatologic diagnoses.
- Normal inflammatory markers do not exclude a rheumatologic diagnosis.
- Trends in inflammatory markers over time are most useful as markers of disease activity and to assess for response to therapy.

[LOE: Expert Opinion/Case-Control Studies] (Choe, 2013; Frosch, 2009; Kocher, 2003; Taekema, 2009; Wittkowski, 2008)
Mycobacterium Tuberculosis Evaluation:

- Recommended for all patients undergoing evaluation of suspected rheumatologic disease
  - Active Tuberculosis may present with joint symptoms:
    - Monoarticular arthritis from direct joint infection with mycobacteria
    - A reactive, polyarticular arthritis may be associated with active tuberculosis
- Latent TB infection should be excluded in all patients prior to initiation of immunosuppressive medications
  - Recommended screening tests:
    - < 5 years: Tuberculin Skin Test (PPD)
    - ≥ 5 years: Quantiferon Gold (Interferon-Gamma Release Assay)

EXAMPLE:

- 16 yo F with 4 weeks of malaise, joint pain, and sore throat; admitted due to difficulty with oral intake, dehydration
- Physical exam reveals tender cervical lymphadenopathy, large tonsils and splenomegaly, muscle tenderness, no obvious arthritis
- Lab evaluation notable for:

  ALT: 200
  BUN, Cr, albumin: normal CRP <0.8; ESR 12
  Mono spot: negative
  ANA positive, 1:80 titer
Phase 1 Diagnosis: 
Exclude Alternative Diagnoses – Infection (Cont’d)

EXAMPLE: (Cont’d)
• 16 yo F with 4 weeks of malaise, joint pain, and sore throat

QUESTION:
• What is on the differential diagnosis?

ANSWER:
• Viral Illness/post-infectious syndrome (CMV, EBV, hepatitis)
• Malignancy: leukemia less likely given no anemia but CBC requires close monitoring for recovery; lymphoma possibility if not resolving
• SLE: less likely without arthritis, rash, nephritis or evidence of other end-organ involvement
• JDMS: elevated AST/ALT may be from muscle or liver but JDMS unlikely without rash or nailfold capillary changes

Back to Diagnosis
EXAMPLE: (Cont'd)
- 16 yo F with 4 weeks of malaise, joint pain, and sore throat

QUESTION:
- What additional lab tests would you request?

ANSWER:
- Repeat CBC – improving
- Repeat AST/ALT – improving
- GGT, CK, LDH, uric acid
- EBV IgG, IgM, Early Antigen Antibody: **POSITIVE**
What if:

- Identified infectious disease is failing to resolve or adequately respond to appropriate treatment measures?

Consider: Concomitant Infection and Rheumatologic Disease

- Infections may trigger a flare or the initial presentation of an underlying rheumatologic condition
- Rheumatologic disorders such as SLE lead to impaired immune function, and result in increased susceptibility to infections

[Diagram showing decision pathways]

Back to Diagnosis
Phase 1 Diagnosis:
Exclude Alternative Diagnoses – Infection (Cont'd)

Summary/ Recommendations:

- Cultures (Blood, other body fluid as indicated by symptoms)
- CBC, ESR, CRP
  - Do not reliably discriminate between occult infection and rheumatologic conditions
  - Useful to follow response to interventions overtime
- TB evaluation
- ASO/Streptozyme if suspicion for antecedent Strep infection
- ID consult for guidance with specific serologies, additional evaluation

[LOE: Expert Opinion/Case-Control Studies] (Abdulaziz, 2012; Ansell, 2000; Behrens, 2007; Binstad, 2005; Choe, 2013; Chow, 2011; Daikh, 2013; Frick, 2006; Frosch, 2009; Gaeta, 2006; Gedalia, 2002; Hazelton, 2013; Junnila, 2006; Kang, 2009; Kasai, 2011; Jasper, 2010; Lima, 2010; Mourad, 2003; Ringold, 2013; Southwood, 2008; Wittowski, 2008; local expert opinion)
Phase 1 Diagnosis: Exclude Alternative Diagnoses – Malignancy

Signs and symptoms of certain malignancies may overlap those of rheumatologic diagnoses:

- 25% of acute lymphocytic leukemia (ALL) patients present with musculoskeletal symptoms
- Positive ANA’s and swollen joints may occur in ALL patients
- Fatigue, fever, lymphadenopathy or organomegaly may be prominent in rheumatologic diseases such as SLE or Systemic onset JIA but are also features of malignancies such as leukemia or lymphoma

(Jones, 2006; Redaelli, 2005; Riccio, 2013)

CLINICAL PEARL:

- Initial treatment for rheumatologic diagnoses often involves corticosteroids which may partially treat or mask an underlying malignancy.

NOTE: It is important to conduct a thorough oncologic evaluation prior to initiation of treatment for rheumatologic disease
Phase 1 Diagnosis:
Exclude Alternative Diagnoses – Malignancy (Cont'd)

EXAMPLE:
• A 4 yo F was referred to rheumatology clinic for joint pains and fatigue for 3-4 months. The pain involved both lower extremities and caused intermittent limping and night wakening. She began having spiking fevers 3 days a week 1 month prior to presentation and a 2-3 lb weight loss.
• Physical exam revealed marked tenderness of her right distal thigh and an antalgic gait.
• Initial laboratory evaluation at PMD:

  6.8
  32
  288
  ESR 86
  LDH, Uric Acid  WNL

Phase 1 Diagnosis:
Exclude Alternative Diagnoses – Malignancy (Cont'd)

What are the ‘RED FLAGS’ in this story?

STOP

and write down your answers.
EXAMPLE: RED FLAGS

- A 4 yo F was referred to rheumatology clinic for joint pains and fatigue for 3-4 months. The pain involved both lower extremities and caused intermittent limping and night wakening. She began having spiking fevers 3 days a week 1 month prior to presentation and a 2-3 lb weight loss.

- Physical exam revealed marked tenderness of her right distal thigh and an antalgic gait.

- Initial laboratory evaluation at PMD:

```
6.8        288
32         ESR 86
LDH, Uric Acid  WNL
```
Phase 1 Diagnosis: 
Exclude Alternative Diagnoses – Malignancy (Cont’d)

Predictors of malignancy in children presenting with musculoskeletal pain:

- Limb/bone pain
- Night time pain, awakening
- Pain out of proportion to exam findings
- Abnormal CBC
- X-ray with metaphyseal lucent lines

[LOE: expert opinion; case-control studies] (Agodi, 2013; Cabral, 1999; Go, 2004; Gupta, 2010; Jones, 2006; Tafaghodi, 2009; Tamashiro, 2011)
Phase 1 Diagnosis: 
Exclude Alternative Diagnoses – Malignancy (Cont'd)

CLINICAL PEARL: What constitutes an ‘abnormal CBC’?

- Anemia is a common finding in patients with rheumatologic conditions as well as malignancies like leukemia.
- WBC counts may vary from high (e.g. SOJIA) to low (SLE) depending on the rheumatologic disorder in question. Low WBC and neutropenia in particular are concerning for leukemia.
- Platelets tend to be elevated in patients with inflammatory disorders. Even ‘low normal’ platelets (150-250K/mm3) in concert with signs of systemic inflammation markers is concerning for potential abnormal bone marrow production or peripheral destruction.

**NOTE:** No one CBC parameter has perfect sensitivity or specificity for detection of malignancy, however, the presence of multiple CBC abnormalities increases the likelihood of malignancy.

[LOE: expert opinion; case-control studies] (Agodi, 2013; Cabral, 1999; Gupta, 2010; Jones, 2006; Tamashiro, 2011)
Phase 1 Diagnosis:
Exclude Alternative Diagnoses – Malignancy (Cont'd)

Summary/Recommendations:

- CBC with differential and smear
  - Abnormalities in multiple cell lines should increase concern for malignancy
- Uric acid and LDH
- Chest X-ray
- Plain films of affected joints
- Consider Hematology Oncology Consult to assess need for bone-marrow biopsy or additional work-up.

[LOE: expert opinion; case-control studies] (Agodi, 2013; Cabral, 1999; Frick, 2006; Gedalia, 2002; Go, 2004; Gupta, 2010; Jones, 2006; Junnila, 2006; Mills, 2011; Radaelli, 2005; Southwood, 2008; Riccio, 2013; Thapa, 2007; Tafaghodi, 2009; Tamashiro, 2011; Wihlborg, 2001; Wittkowsi, 2008)
Phase 1 Diagnosis:
Assess Disease Extent

Rheumatologic Disease Associated Tests:

- Includes autoantibody tests (e.g. ANA, anti-dsDNA), and other biomarkers (chemistries, genetic markers)
- Tests are often ordered at admission to facilitate diagnosis of underlying rheumatologic disease
- Patterns of autoantibodies may be associated with certain rheumatologic disorders e.g.:
  - Anti-ds DNA and anti-Smith strongly associated with SLE
- Autoantibody sensitivity and specificity depends on specific disease in question

NOTE: No individual laboratory test can confirm or refute a rheumatologic diagnosis

Summary/Recommendations:

- No individual laboratory test can confirm or refute a rheumatologic diagnosis
- Rheumatic disease associated test results should be interpreted in context of physical findings and overall clinical picture

[LOE: ⬤⬤⬤ Low Quality] (Breda L, 2010; Solomon D, 2002; Shmerling R, 2005; local consensus)
EXAMPLE:

- A 12 yo female presents with joint pain, swelling and limited range of motion in multiple joints.

QUESTION:

- Does this child have systemic lupus erythematosus?
  - ANA sensitivity: 93-100% (negative LR: 0.11)
  - ANA specificity: 57% (positive: LR 2.2)
EXAMPLE: (Cont’d)

A 12 yo female presents with joint pain, swelling and limited range of motion in multiple joints.

QUESTION:

• Does this child have juvenile idiopathic arthritis (JIA)?

  o ANA sensitivity: 57% (negative LR 1.08)
  o ANA specificity: 39% (positive LR 0.95)

ANSWER:

• A negative ANA means SLE would be very unlikely
• A positive ANA is one of 11 clinical criteria for SLE but is not diagnostic for SLE in isolation.
• Positive ANA's may be seen with other disorders (i.e. thyroid disease, psoriasis, certain infections) and up to 30% of healthy controls

(Breda, 2010; Solomon, 2002; Shmerling, 2005)
EXAMPLE: (Cont'd)
  • A 12 yo female presents with joint pain, swelling and limited range of motion in multiple joints.

QUESTION:
  • Does this child have juvenile idiopathic arthritis (JIA)?
    o ANA sensitivity: 57% (negative LR 1.08)
    o ANA specificity: 39% (positive LR 0.95)

ANSWER:
  • An ANA is not a good screening test to ‘rule-in’ or ‘rule-out’ JIA or rheumatologic disorders in general.

(Breda L, 2010; Solomon D, 2002; Shmerling R, 2005)
Phase 1 Diagnosis:
Assess Disease Extent

• Given multisystem involvement of rheumatologic disorders, a thorough organ screen is required
• Treatment is tailored to pattern of organ involvement and severity
• Organ threatening disease requires more aggressive regimen

Assess For Major Organ Involvement/Severe Disease
• Nephritis
• Pulmonary hemorrhage
• Pulmonary hypertension
• CNS involvement
• Severe myositis (JDMS)
• Macrophage activation syndrome

Back to Diagnosis
<table>
<thead>
<tr>
<th>Symptoms &amp; Clinical Findings</th>
<th>Consult Service</th>
<th>Common Clinical Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria, hematuria</td>
<td>Nephrology</td>
<td>• Need for renal biopsy to determine severity, chronicity?</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Nephrology</td>
<td>• Etiology (disease vs. medication related)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypertensive medication management</td>
</tr>
<tr>
<td>Seizures, altered mental status, stroke</td>
<td>Neurology</td>
<td>• Evaluation of CNS involvement</td>
</tr>
<tr>
<td>Respiratory Distress, pulmonary hemorrhage</td>
<td>Pulmonary</td>
<td>• Need for bronchoscopy for diagnosis?</td>
</tr>
<tr>
<td></td>
<td>Hematology, Anti-coagulation service</td>
<td>• Ongoing pulmonary management and surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypercoagulability evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anti-coagulant medication management</td>
</tr>
</tbody>
</table>

! Order additional consults based on organ involvement

Back to Diagnosis
Rheumatology New Diagnosis Pathway

PHASE 1: Diagnosis

Phase Change

PHASE 2: Treatment

Back to Diagnosis
Phase 2 Treatment:

Initial treatment involves parallel tracks:

- Induction immunosuppressive regimen
- Non-pharmacologic therapy
- Discharge planning

Initial treatment often includes IV methylprednisolone with transition to oral prednisone taper and disease specific steroid sparing agents.

**Induction Immunosuppressive Regimen**

- Initial treatment often includes IV methylprednisolone with transition to oral prednisone taper and disease specific steroid sparing agents.

**Treatment**

**Induction immunosuppression**

- Methylprednisolone 30mg/kg IV q 18-24 hours x 1-3 doses
- Gastroprotective agent (H2 Blocker or PPI)
- Steroid sparing medications
  - Add immunosuppressive agents based on diagnosis
- Oral Steroid Taper
- Calcium/Vitamin D supplements
CLINICAL PEARL: High Dose IV Methylprednisolone Safety

- Elevated blood pressures (> 2 SD above norms for size) may occur during or after methylprednisolone infusions.
- Patients with kidney involvement as part of their rheumatologic disease (e.g., SLE nephritis, vasculitis) are at increased risk for hypertension related to infusions.
- Elevated blood pressure plus symptoms (headache, chest pain, abdominal pain) or new signs of acute renal failure (decreasing urine output) require urgent response.
Oral Steroids

- Patients requiring IV steroids at treatment onset will likely require an oral steroid taper over several months.
- Starting dose range and taper speed depends on disease severity, anticipated time frame for response, and time to effect for steroid sparing agents.
- Prednisone Dose Ranges:
  - High dose: 1-2 mg/kg/day (max 80 mg/day)
  - Moderate dose: 0.5 mg/kg/day
  - Low dose: < 0.3 mg/kg/day
Steroid Sparing Agents:

- Selected based on underlying disease and organs affected

<table>
<thead>
<tr>
<th>Disease</th>
<th>Common Steroid Sparing Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>JIA</td>
<td>Methotrexate, TNF-a antagonists</td>
</tr>
<tr>
<td>SLE</td>
<td>Azathioprine, mycophenolate mofetil</td>
</tr>
<tr>
<td>JDMS</td>
<td>Methotrexate, Plaquenil</td>
</tr>
<tr>
<td>SOJIA/MAS</td>
<td>Anakinra, Cyclosporin</td>
</tr>
<tr>
<td>small vessel vasculitis</td>
<td>Azathioprine, mycophenolate mofetil</td>
</tr>
</tbody>
</table>

- Require patient/family education for administration (subcutaneous injections, etc) and monitoring
- Refer to Rheum Maintenance Medications Orderset for guidelines and assistance with ordering
Manage Severe Disease:

- Organ or life threatening disease requires initial treatment with additional IV agents such as cyclophosphamide, IVIG, or Rituximab.
- Refer to the Cyclophosphamide Recurring Infusion Clinical Standard Work Pathway for more details around cyclophosphamide infusions.
Supportive Medications:

- **Supplemental Calcium/Vitamin D are recommended for patients on chronic steroids***:
  - Calcium
    - Age ≥4 yrs: Elemental calcium 1000mg daily (=2500mg calcium carbonate) in divided doses
  - Vitamin D
    - Age 1 yr-adult: Vitamin D 600iu daily

* If renal insufficiency, dose Calcium/Vitamin D per nephrology

[LOE: Very low quality, with local expert opinion] (Bak, 2006; Talalaj, 1996; USRDA)
## Phase 2 Treatment: Non-Pharmacologic Therapies

<table>
<thead>
<tr>
<th>Service</th>
<th>Common Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical therapy</td>
<td>Lower extremity arthritis, joint contractures, weakness, general de-conditioning</td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>Upper extremity arthritis, joint contractures, weakness</td>
</tr>
<tr>
<td>Speech therapy</td>
<td>Swallowing difficulties, aspiration risk</td>
</tr>
<tr>
<td>Nutrition Consult</td>
<td>Dietary changes for high dose steroids, renal failure</td>
</tr>
<tr>
<td>Social Work</td>
<td>Adjustment to chronic illness, school accommodations, transportation issues</td>
</tr>
</tbody>
</table>
Discharge planning should occur alongside initial evaluation and treatment.

Discussion of discharge criteria in family-centered rounds helps families to plan ahead, deal with uncertainty of diagnosis and hospitalization.

**Discharge Criteria**

- Adequate ambulation
- Able to swallow (nutrition plan in place)
- Prescriptions ordered and ready
  - Oral Steroid taper 1-2mg/kg/day divided into 2 doses/day
  - Disease specific steroid sparing agents
  - Calcium/vitamin D supplements
  - Consider gastroprotective agent (H2 blocker or PPI)
- Medication teaching (e.g. subcutaneous injection)
- Follow-up appointments: rheumatology clinic, primary MD, PT/OT, infusions, next cyclophosphamide admission
EXAMPLE:

• A 2 yo female was admitted with a 2 month history of weakness, rash and difficulty handling secretions.
• A thorough evaluation revealed Juvenile Dermatomyositis with prominent pharyngeal muscle weakness and she was started on IV methylprednisolone and IVIG.

QUESTION:

• What are the other components of her initial treatment regimen, including pharmacologic and non-pharmacologic interventions?

ANSWER:

• Initial Treatment Plan:
  o IVIG + IV Methylprednisolone
  o Oral Prednisone taper
  o Ca/Vit D supplements
  o Steroid Sparing Agent: Methotrexate SQ injections
  o Speech Therapy Evaluation: Feeding modifications
  o Physical/Occupational therapy: Range of motion, home exercise plan
  o Child Life: Adjustment to chronic illness, coping with injections
Phase 2 Treatment:
Discharge Planning (Cont'd)

See Rheumatology Patient Education Toolkit for patient education and reference materials:

Discharge Instructions
- Rheum toolkit
- Medic alert bracelet
- Medication teaching

[Back to Treatment](#)
Rheumatology New Diagnosis Follow-Up Guidelines:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PMD</th>
<th>Rheum Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Poly JIA</td>
<td>1-2 weeks</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>New Systemic Onset JIA (no MAS)</td>
<td>1-2 weeks</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>New SLE</td>
<td>&lt; 1 week</td>
<td>2-4 weeks</td>
</tr>
<tr>
<td>New JDMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Diagnosis + MAS</td>
<td></td>
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</tr>
</tbody>
</table>

- Including the PMD in discharge communications is essential
- Exact timing of follow-up may be affected by patient specific factors such as disease severity, language barriers, geographic considerations.
Summary

Now that this module has been completed, when evaluating a child with suspected rheumatologic disease, participants should be better able to:

1. Describe reasons for a thorough evaluation for infectious entities as part of the initial diagnostic approach
2. Identify symptoms and laboratory findings concerning for possible malignancy in these patients
3. Recognize the appropriate use and limitations of rheumatologic disease associated tests in the initial evaluation
4. Apply the Rheumatology New Diagnosis Pathway to develop an initial management plan when admitting these patients
5. Discuss the general approach to the initial evaluation with patient families
## Follow-up Guidelines

### Rheumatology New Diagnosis Admission

#### Follow-up Guidelines

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>PMD</th>
<th>Rheum Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Poly JIA</td>
<td>1-2 weeks</td>
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</tr>
<tr>
<td>New Systemic JIA (no MAS)</td>
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<tr>
<td>New SLE</td>
<td>&lt; 1 week</td>
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<td></td>
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</tr>
<tr>
<td>New Vasculitis</td>
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For questions concerning this pathway, contact: rheumatologynewdiagnosis@seattlechildrens.org

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Executive Summary

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Objectives
- To facilitate timely evaluation, treatment, and discharge of patients admitted for suspicion of new Rheumatologic Diagnoses
- To improve familiarity and competency with appropriate evaluation of new rheumatology patients for care providers interfacing with the Rheumatology service (Residents, Nursing Staff)

Recommendations
- The Rheumatology Admit order set will be utilized for all patients admitted to the Rheumatology Service with suspicion of a new Rheumatologic Diagnosis (Juvenile Idiopathic Arthritis, Systemic Lupus Erythematosus, Juvenile Dermatomyositis, Primary Vasculitis, Macrophage Activation Syndrome)
- The Rheumatology New Diagnosis Pathway provides an overview of the appropriate evaluation process for these patients as well as providing guidance for treatment initiation and discharge planning.

Rationale
VARIATION: There is currently considerable variation with regards to care for patients admitted for suspected new Rheumatologic diagnoses. Due to relative rarity of Rheumatologic disorders and frequent rotation of resident and nursing staff, these front-line providers may have little familiarity with the disorders in question which may lead to confusion around plan of care and a fragmented experience for patients and families. The intent of this project is to establish a standardize approach to the admission process.

  - Safety may be enhanced by improving staff understanding of plan of care and reducing opportunities for error related to variations in practice.
  - Costs may be reduced by streamlining diagnostics studies and early anticipation of discharge needs, potentially decreasing length of stay.
  - Delivery of care will be improved by expediting patient flow through the inpatient setting and facilitating transition to outpatient care in the Rheumatology Clinic.
  - Quality of care will improve by ensuring completeness of appropriate evaluation and consistency in medication education and discharge preparation.
  - Engagement is grounded in the fact that the pathway has been developed by RNs and MDs in response to frequent requests for a consolidated Rheumatology order set by rotating resident MD’s.
  - Patient/Family Satisfaction will be addressed by implementing clinical standard work that will assure the highest quality of care, including consistent messaging from nursing, resident and attending Rheumatology Staff.

Evidence
- The literature review yielded thirty-eight studies for inclusion in the pathway
Executive Summary

- The Rheumatology New Diagnosis Pathway was developed by the physicians in the Seattle Children’s Rheumatology Division and reflects consensus as to sound practices for evaluation, treatment initiation and discharge preparation for this patient population.

Implementation Items
- Seven powerplans with diagnosis and treatment orders
- Web-based training on approach to initial rheumatology evaluation for medical trainees
- Communication to resident staff, nursing staff, physical/occupational therapy, nutrition services, ongoing staff support and education

Metrics Plan
- CSW Core Metrics
  1. Count of Inpatient/Observation discharges
  2. Median Length of Stay
  3. % of patients admitted to Team 6 with specified order set
  4. Average charges per case
  5. Readmission
- Effectiveness of web-based training for resident education
- Family Experience Survey

PDCA Plan
The pathway owner and committee will follow metrics, continue to review medical literature, and make alterations to the pathway as needed.

Revision History
Date Approved: May 2014
Next Review Date: May 2017
Approved by the Rheumatology New Diagnosis Clinical Standard Work Team
May 2014

CSW Rheumatology New Diagnosis Team:

Rheumatologist and Owner: Kristen Hayward, MD, MS
Medical Floor Nurse: Kristi Klee, DNP, RN, CPN

Clinical Effectiveness Team:

Consultant: Jennifer Hrachovec, PharmD, MPH
KM Analyst: Suzanne Spencer, MBA, MHA
CIS Informatician: Michael Leu, MD, MS, MHS
CIS Analyst: Heather Marshall
Librarian: Jamie Gray, MLS
Program Coordinator: Asa Herrman
Completion qualifies you for 1 hour of Category II CME credit. If you are taking this self-assessment as a part of required departmental training at Seattle Children's Hospital, you MUST logon to Learning Center.

1) A 6 yo male presents with fevers and joint pain of 2 weeks duration. Outpatient evaluations are unrevealing for the source of illness and he is admitted due to progressive difficulty with ambulation.

*It is important that his initial admission include a thorough evaluation for infectious etiologies because:*
A) Occult infections are identified in 23-51% of patients with fever of unknown origin
B) Viral infections such as EBV and CMB may present with signs and symptoms that mimic rheumatologic disorders
C) An ANA was negative therefore he has a low likelihood of having an underlying rheumatologic diagnosis such as systemic onset juvenile arthritis
D) A and B
E) All of the above

2) A 6 yo male presents with fevers and joint pain of 2 weeks duration. Outpatient evaluations are unrevealing for the source of illness and he is admitted due to progressive difficulty with ambulation.

*Admission labs reveal a CRP of 3.0 mg/dl (nml < 0.8) and ESR of 72 mm/h (nml < 10). Please choose the most appropriate interpretation from the following:*
A) A CRP of 3.0 reliably excludes an occult bacterial infection.
B) An ESR > 50 is seen only in rheumatologic conditions.
C) Inflammatory markers cannot adequately distinguish between different causes of an inflammatory process.
D) A and B
E) All of the above

3) A 6 yo male presents with fevers and joint pain of 2 weeks duration. Outpatient evaluations are unrevealing for the source of illness and he is admitted due to progressive difficulty with ambulation.

*Findings in this child which would raise concern for possible underlying leukemia would include anemia and:*
A) platelet count of 150K/mm3
B) night time wakening due to pain
C) limb pain with or without associated arthritis
D) A and B
E) All of the above

4) A 12 yo female presents with a facial rash, joint swelling and pain for 3 weeks. As part of her initial laboratory evaluation she is found to have a positive ANA with a titer of 1:320.

*The most appropriate interpretation of this laboratory finding is:*
A) the positive ANA is very specific for SLE and effectively excludes a diagnosis of malignancy
B) a positive ANA is very sensitive for SLE but is only 1 of 11 clinical criteria used to diagnose SLE.
C) an ANA of this titer is unlikely to be found in the context of an infectious illness.
D) A and B
E) All of the above
Completion qualifies you for 1 hour of Category II CME credit. If you are taking this self-assessment as a part of required departmental training at Seattle Children’s Hospital, you MUST logon to Learning Center.

5) A 16 yo female is admitted due to persistent fevers, body aches, cough and vomiting/dehydration. She fails to respond to initial interventions such as broad spectrum antibiotics for community acquired pneumonia and develops a malar rash. There is increasing concern for a possible underlying rheumatologic disorder and she is admitted for further evaluation.

In addition to a thorough investigation for alternative infections or an underlying malignancy, important elements of her admission evaluation include:
A) urinalysis and BUN/ Cr to assess for any evidence of renal system abnormalities
B) an echocardiogram to assess for pericardial effusion
C) AST/ALT to look for hepatic involvement or myositis
D) A and B
E) All of the above

6) A 16 yo female is admitted due to persistent fevers, body aches, cough and vomiting/dehydration. She fails to respond to initial interventions such as broad spectrum antibiotics for community acquired pneumonia and develops a malar rash. There is increasing concern for a possible underlying rheumatologic disorder and she is admitted for further evaluation.

An organ screen reveals hematuria and proteinuria. A nephrology consultation is obtained and a kidney biopsy is recommended. The family voices concerns about the procedure and wants to know why it is important. You tell them:
A) A biopsy will determine the severity and pattern of kidney involvement which will affect the choice of initial induction treatment regimen
B) A kidney biopsy is the only way to definitively diagnose SLE
C) The pattern of kidney involvement on biopsy helps to determine whether or not the child’s SLE will be a lifetime disease or resolve by adulthood.
D) A and B
E) all of the above

7) A 16 yo female is admitted due to persistent fevers, body aches, cough and vomiting/dehydration. She fails to respond to initial interventions such as broad spectrum antibiotics for community acquired pneumonia and develops a malar rash. There is increasing concern for a possible underlying rheumatologic disorder and she is admitted for further evaluation.

After initial treatment with high dose IV methylprednisolone and cyclophosphamide the patient is preparing for discharge. The family has questions about their home medication regimen. You tell them they should expect:
A) their child will likely not need any oral steroids after the three days of high dose methylprednisolone
B) their child will likely not be on oral steroids long enough to have to worry about dietary modifications.
C) their child will likely be on a tapering dose of oral steroids over the next several months
D) their child will likely be on oral steroids for the rest of their lives
E) All of the above
Completion qualifies you for 1 hour of Category II CME credit. If you are taking this self-assessment as a part of required departmental training at Seattle Children’s Hospital, you MUST logon to Learning Center

8) A 3 yo M is admitted due to swallowing difficulties, rashes and weakness. A thorough evaluation reveals Juvenile Dermatomyositis and he is started on IV methylprednisolone and IVIG.

*Which of the following would be appropriate element(s) of his initial treatment plan:*
- A) Speech therapy evaluation to determine safety for oral feeds
- B) Physical therapy to provide range of motion exercise
- C) Calcium/Vitamin D supplementation to mitigate effects of chronic steroids on bone metabolism
- D) A and B
- E) All of the above

9) A 3 yo M is admitted due to swallowing difficulties, rashes and weakness. A thorough evaluation reveals Juvenile Dermatomyositis and he is started on IV methylprednisolone and IVIG.

*Which of the following are essential components of his discharge plan?*
- A) Education around home medication regimen
- B) Rheumatology clinic follow-up
- C) PMD appt to review recent hospitalization and new diagnosis
- D) A and B
- E) All of the above

10) A previously healthy 15 yo boy is admitted for persistent fever and increasing respiratory distress. He is found to have pulmonary hemorrhage concerning for small vessel vasculitis.

*As part of the rheumatology new diagnosis pathway, an infectious disease consult is:*
- A) Indicated because infections may trigger the initial presentation of an underlying rheumatologic condition
- B) Indicated because rheumatologic disorders may lead to impaired immune function, resulting in increased susceptibility to infections
- C) Not indicated because his rheumatology associated disease tests revealed a positive ANCA
- D) Not indicated because he is likely to receive 3 days of high dose intravenous methylprednisolone
- E) A and B

[Links to Back to Diagnosis, Back to Treatment, View Answers]
Q1 Explanation: Answer is D. This child’s presentation is consistent with fever of unknown origin (FUO). Occult infections are a common cause for FUO and certain infectious or post-infectious processes may present with fever, joint pain and swelling mimicking an underlying rheumatologic disorder. Systemic onset juvenile arthritis (SOJIA) is another potential cause for FUO, however, ANA testing is not diagnostic for SOJIA and maybe positive or negative in this condition, thus a negative ANA does not rule out SOJIA.

Q2 Explanation: Answer is C. Although highly elevated CRP’s are often found in bacterial infections and certain rheumatologic disorders may present with a highly elevated ESR, there can be considerable overlap between levels of inflammatory markers in patients with these disorders. Levels of standard inflammatory markers cannot reliably differentiate between infectious versus rheumatologic conditions.

Q3 Explanation: Answer is E. Relative thrombocytopenia, night time wakening and limb pain with or without arthritis have all been identified as red flags for underlying malignancies such as leukemia or lymphoma in patients presenting with musculoskeletal complaints.

Q4 Explanation: Answer is B. A positive ANA is very sensitive for systemic lupus erythematosus (SLE) meaning that a negative test is helpful to rule out the disease. However, a positive ANA is not specific for SLE alone and is not useful to rule out alternative diagnoses. Positive ANA’s may be seen in up to 20-30% of the healthy population as well as transiently in the context of infection and have been reported positive in patients with underlying malignancies. Because of the relatively low specificity of an ANA, diagnosis of SLE requires additional clinical criteria.

Q5 Explanation: Answer is E. Since rheumatologic diseases are often multisystemic disorders, patients undergoing evaluated for a potential new rheumatologic diagnosis should undergo a thorough organ screen. In particular, the patient in this question has fevers, myalgia and skin findings concerning for systemic lupus erythematosus which may result in nephritis, myositis and/or pericarditis. The pattern of organ involvement at diagnosis of a rheumatologic disorder such as SLE is important to help guide appropriate treatment regimens and to follow response to therapy.

Q6 Explanation: Answer is A because the treatment of SLE nephritis is tailored to the pattern and severity of kidney involvement with more aggressive kidney disease requiring more aggressive induction medications such as monthly intravenous cyclophosphamide. Although finding on kidney biopsy may support the diagnosis of SLE, a biopsy is not required for diagnosis as SLE can be diagnosed by clinical and laboratory parameters alone. SLE is considered a chronic lifetime disorder. Though some patients experience periods of disease remission it is not possible to predict future disease course based on kidney biopsy findings.
**Q7** Explanation: Answer is C. A dose of intravenous methylprednisolone exerts systemic effects for approximately 7 to 10 days. Steroid sparing medications such as cyclophosphamide require weeks to months to reach full efficacy. Thus, after initial induction treatment, children with a new rheumatologic diagnosis require several months of either oral or additional intravenous steroids to maintain disease control. This level of exposure to corticosteroids is significant enough to cause side effects such as weight gain, salt and water retention and alteration of blood pressure as well as osteopenia thus dietary modifications are an important consideration during this time. Although some children may require some amount of oral steroids for prolonged periods, they are not universally committed to a lifetime steroid requirement.

**Q8** Explanation: Answer is E. Juvenile dermatomyositis (JDMS) may affect the skeletal muscle in the proximal esophagus, leading to swallowing dysfunction and aspiration. Given the proximal muscle inflammation associated with JDMS, physical therapy is imperative to preserve joint range of motion and eventually to work on regaining muscle strength. Treatment of JDMS involves chronic corticosteroids which have deleterious effects on bone metabolism.

**Q9** Explanation: Answer is E. Treatment of JDMS often involves multiple home medications such as oral corticosteroids and subcutaneous methotrexate which require family education for administration and monitoring. It is important to establish appropriate follow up with both PMD as well as Rheumatology for ongoing care prior to discharge.

**Q10** Explanation: Answer is E. Infections may be a trigger for the initial presentation of underlying rheumatologic disorder such as small vessel vasculitis. Having a positive ANCA could support a diagnosis of vasculitis but does not rule out a concomitant infection. Patients with active rheumatologic disorders also require a thorough infectious evaluation for concomitant infection particularly in anticipation of immunosuppressive medications such as pulse methylprednisolone as well as due to impaired immune function from their underlying disease.
We used the GRADE method of rating evidence quality. Evidence is first assessed as to whether it is from randomized trial, or observational studies. The rating is then adjusted in the following manner:

Quality ratings are *downgraded* if studies:
- Have serious limitations
- Have inconsistent results
- If evidence does not directly address clinical questions
- If estimates are imprecise OR
- If it is felt that there is substantial publication bias

Quality ratings can be *upgraded* if it is felt that:
- The effect size is large
- If studies are designed in a way that confounding would likely underreport the magnitude of the effect OR
- If a dose-response gradient is evident

**Quality of Evidence:**
- 🌟🌟🌟🌟 High quality
- 🌟🌟🌟 Moderate quality
- 🌟🌟 Low quality
- 🌟🌟🌟 Very low quality
- ⭐⭐⭐⭐ Expert Opinion (E)

Summary of Version Changes

- **Version 1 (11/07/2011):** Go live
- **Version 2 (5/20/2014):** Added citations and enhanced clinical training content
- **Version 2.1(11/18/14):** Updated answer key for learning assessment.
Medical Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required.

The authors have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication.

However, in view of the possibility of human error or changes in medical sciences, neither the authors nor Seattle Children’s Healthcare System nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information.

Readers should confirm the information contained herein with other sources and are encouraged to consult with their health care provider before making any health care decision.
Studies were identified by searching electronic databases using search strategies developed and executed by a medical librarian, Jamie Graham. Searches were performed in April and May 2012. The following databases were searched - on the Ovid platform: Medline (1996 to date), Cochrane Database of Systematic Reviews (2005 to date), Cochrane Central Register of Controlled Trials (1996 to date); elsewhere - Embase (1997 to date), Clinical Evidence, National Guideline Clearinghouse, and TRIP. Retrieval was limited to ages 0-18, 10 years and English language. In Medline and Embase, appropriate Medical Subject Headings (MeSH) and Emtree headings were used respectively, along with text words, and the search strategy was adapted for other databases using their controlled vocabularies, where available, along with text words. The project owner consulted on appropriate MeSH to include. Both a scout search and a secondary search were performed. At times certain limiters were eliminated due to small retrieval within the secondary search. All retrieval was further limited to certain evidence categories, such as relevant publication types, Clinical Queries, index terms for study types and other similar limits when possible. Alerts were set up on September 28, 2012 in Medline and Embase to monitor current literature on an ongoing basis.

Jamie Graham, MLS
October 14, 2013

Flow diagram adapted from Moher D et al. BMJ 2009;339:bmj.b2535


Title: Rheumatology New Diagnosis Pathway

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Date: March 2014


Example: