



## Complete Summary

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### GUIDELINE TITLE

Multiple myeloma (MM).

### BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Multiple myeloma (MM). In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007 May 30 [Various].

### GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Finnish Medical Society Duodecim. Multiple myeloma (MM). In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2005 May 1 [Various].

## \*\* REGULATORY ALERT \*\*

### FDA WARNING/REGULATORY ALERT

**Note from the National Guideline Clearinghouse:** This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [July 31, 2008, Erythropoiesis Stimulating Agents \(ESAs\)](#): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- [November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents \(ESAs\)](#): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

## COMPLETE SUMMARY CONTENT

\*\* REGULATORY ALERT \*\*

SCOPE

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## SCOPE

### **DISEASE/CONDITION(S)**

Multiple myeloma (MM)

### **GUIDELINE CATEGORY**

Diagnosis  
Evaluation  
Management  
Treatment

### **CLINICAL SPECIALTY**

Family Practice  
Hematology  
Oncology

### **INTENDED USERS**

Health Care Providers  
Physicians

### **GUIDELINE OBJECTIVE(S)**

Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.

### **TARGET POPULATION**

- Patients with multiple myeloma (MM)
- Patients requiring evaluation for possible multiple myeloma

### **INTERVENTIONS AND PRACTICES CONSIDERED**

#### **Evaluation/Diagnosis**

1. Use of World Health Organization (WHO) Diagnostic Criteria

2. Differential diagnosis
3. Laboratory tests: blood picture, serum calcium, potassium, sodium and creatinine, and erythrocyte sedimentation rate (ESR); bone marrow examination; serum and urine protein electrophoresis
4. Additional investigations, as indicated:
  - X-ray (skull, thorax/ribs, backbone, scapulae, pelvis and long bones of the extremities)
  - Serum/plasma total protein, albumin, potassium, sodium, calcium, ionised calcium, creatinine, urate and immunoglobulins (IgG, IgA, IgM)
  - Identification of M component heavy and light chains by immunofixation or by other means
  - Magnetic resonance imaging as indicated

### **Treatment/Management**

1. Early treatment of complications
2. Follow-up, including assessment of:
  - The amount of M component (serum and/or urine)
  - Degree of bone marrow infiltrates
  - General condition and symptoms, infections and (bone) pains
  - Osteolytic lesions (x-ray)
  - Renal function, hypercalcaemia and blood picture
3. Pharmacologic treatment
  - Cytotoxic drugs (vincristine, melphalan, cyclophosphamide, adriamycin), often combined with corticosteroids
  - Corticosteroids (dexamethasone or methylprednisolone)
  - Thalidomide or lenalidomide
  - Bortezomib
  - Interferon
4. Supportive therapy
  - Maintenance of fluid and electrolyte balance
  - Treatment of hypercalcaemia
  - Treatment of infections
  - Maintenance of mobility
  - Treatment of anaemia and thrombocytopenia (red blood cell and platelet transfusions, erythropoietin)
  - Analgesia for pain relief
  - Radiotherapy for focal skeletal foci
  - Bisphosphonates for hypercalcaemia
5. Intensive treatment with the support of autologous stem cell transplantation
6. Allogeneic stem cell transplantation

### **MAJOR OUTCOMES CONSIDERED**

- Survival (lifetime and progression-free)
- Mortality
- Adverse effect associated with treatment

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

## **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

The evidence reviewed was collected from the Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effectiveness (DARE). In addition, the Cochrane Library and medical journals were searched specifically for original publications.

## **NUMBER OF SOURCE DOCUMENTS**

Not stated

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Given)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

### **Levels of Evidence**

#### **A. Quality of Evidence: High**

Further research is very unlikely to change confidence in the estimate of effect

- Several high-quality studies with consistent results
- In special cases: one large, high-quality multi-centre trial

#### **B. Quality of Evidence: Moderate**

Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

- One high-quality study
- Several studies with some limitations

#### **C. Quality of Evidence: Low**

Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

- One or more studies with severe limitations

#### **D. Quality of Evidence: Very Low**

Any estimate of effect is very uncertain.

- Expert opinion
- No direct research evidence
- One or more studies with very severe limitations

## **METHODS USED TO ANALYZE THE EVIDENCE**

Review of Published Meta-Analyses  
Systematic Review

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

Not stated

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Not stated

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

Not stated

# **RECOMMENDATIONS**

## **MAJOR RECOMMENDATIONS**

The levels of evidence [A-D] supporting the recommendations are defined at the end of the "Major Recommendations" field.

### **Aim**

To recognize symptoms that require early intervention

### **Pathology**

- Multiple myeloma (MM) is a clonal bone marrow proliferation of mature B cells (plasma cells) characterized by a monoclonal immunoglobulin fraction (M

component, a paraprotein) in the serum or sometimes only in urine protein electrophoresis.

- "Benign" disease forms (MGUS or monoclonal gammopathy with unknown significance) are about 100 times more common than myeloma.

### **Epidemiology**

- Approximately 3 to 4 new cases/100,000/year
- Diagnosis is usually made at the age of 50 to 70 years, rarely before the age of 40 years.
- No sex differences

### **Aetiology**

- Unknown.
- Ionizing radiation slightly increases the risk.

### **Diagnosis**

- The main diagnostic difficulty is to make a distinction between early cases of MM and "benign" paraproteinaemias.

### **Criteria for Diagnosis of Multiple Myeloma (World Health Organization [WHO] Classification)**

- A. The diagnosis of multiple myeloma requires one main criterion and at least one additional criterion OR three additional criteria, which include C1 and C2. In addition, the disease has to be symptomatic and progressive.
- B. Main criteria
  1. Bone marrow plasmacytosis (>30%)
  2. Plasmacytoma in biopsy
  3. M component
    - Serum/plasma: Immunoglobulin G (IgG) >35 g/L, IgA >20 g/L
    - Urine: >1 g/24 h
- C. Additional criteria
  1. Bone marrow plasmacytosis (10–30%)
  2. M component (smaller than in point B)
  3. Osteolytic lesions
  4. Decrease of polyclonal immunoglobulins in serum
    - IgG <6 g/L
    - IgA <1 g/L
    - IgM <0.5 g/L

### **Differential Diagnostics**

- MGUS (plasma cells in bone marrow <10%; IgG <35 g/L or IgA <20 g/L, no osteolytic foci, no symptoms). The WHO classification 2001 also includes the traditional "benign" paraproteinaemia in this group.
- Waldenström's macroglobulinaemia (See Finnish Medical Society Duodecim guideline "Waldenström's macroglobulinaemia [WM]")

- Lymphomas with an M component in some cases
- Other rare diseases where there is an M component

### **Clinical Picture**

- Often:
  - Osteolytic lesions and bone pains
  - Mild anaemia, hypercalcaemia, hyperuricaemia
  - Renal insufficiency
- Rarely:
  - Hyperviscosity syndrome (IgA myeloma)

### **Typical Laboratory Findings**

- Increased erythrocyte sedimentation rate (ESR) (not in light-chain myeloma)
- M component in serum and/or urine
- Decreased haemoglobin level, often also leuco- and thrombocytopenia
- Malignant plasma cell infiltrates in the bone marrow
- Osteolytic lesion in bone x-ray
- Often increased serum urate and calcium but diminished albumin concentration

### **Basic Examinations**

- Blood picture, serum calcium, potassium, sodium and creatinine, and ESR
- Bone marrow examination
- Serum and urine protein electrophoresis (M component can be found exclusively in urine in only 10 to 20% of MM patients)

### **Additional Investigations when MM is Likely**

- X-ray (skull, thorax/ribs, vertebrae, scapulae, pelvis, and long bones of the extremities)
- Serum/plasma total protein, albumin, potassium, sodium, calcium, ionised calcium, creatinine, urate, and immunoglobulins (IgG, IgA, IgM, sometimes IgD)
- Identification of M component heavy and light chains by immunofixation or by other means
- Magnetic resonance imaging is more sensitive than radiography, but is seldom indicated in basic diagnosis. Scintigraphy does not reveal lytic changes.

### **Complications Requiring Attention Preferably Within 24 Hours (Particularly in New Patients)**

- Sepsis or pneumonia (intravenous broad-spectrum antibiotics)
- Renal insufficiency (dialysis or haemofiltration)
- Hyperviscosity (plasmapheresis)
- Hypercalcaemia (fluid replacement, bisphosphonates, steroids)
- Spinal cord compression (surgical decompression, radiotherapy)
- Pathological fractures (pain medication, stabilization)

- Vertebral compression (orthopaedic treatment)

### **Disease Progression and Prognosis**

- With traditional therapies, median life expectancy at diagnosis is about 3.5 to 4 years and somewhat longer with more intensive treatments. Marked individual variation exists.
- Myeloma cells become gradually resistant to chemotherapy.
- Myeloma cell infiltrates occupy the bone marrow causing anaemia, thrombocytopenia, and leucopenia.
- Infections, haemorrhages, and renal insufficiency are frequent complications.

### **Follow-up and Treatment**

- If the patient is symptomless, no chemotherapy is usually given, as it does not improve the patient's well being or prolong life.
- Symptomatic patients are treated actively.

### **In Follow-up, Attention is Paid to:**

- The amount of M component (serum and/or urine)
- The blood picture (reflects the degree of bone marrow infiltrates)
- General condition and symptoms, infections and (bone) pains
- Osteolytic lesions (x-ray)
- Renal function and hypercalcaemia

### **Pharmacological Treatment of Myeloma**

- According to instructions given by a haematologist or a specialist in internal medicine who is familiar with the treatment of haematological diseases. The aim is usually intensive therapy with the support of autologous stem cell transplantations (patients under 70 years).
- Cytotoxic drugs (cyclophosphamide, melphalan, vincristine or adriamycin), often combined with corticosteroids
- Corticosteroid alone (either dexamethasone or methylprednisolone)
- Thalidomide (or lenalidomide) either alone or in combination with other drugs
- Bortezomib (proteasome inhibitor)
- Interferon in individual cases, usually in order to sustain the achieved treatment response

### **Supportive Therapy Includes:**

- Maintenance of fluid and electrolyte balance (to prevent renal failure)
- Treatment of hypercalcaemia
- Treatment of infections
- Maintenance of mobility in order to prevent osteoporosis and pathological fractures
- If necessary, treatment of anaemia and thrombocytopenia (red blood cell and platelet transfusions, erythropoietin)
- Alleviation of pain with analgesics
- Radiotherapy for local skeletal foci is quite common.

- Bisphosphonates (Djulbegovic et al., 2002) [**A**] to prevent and to decelerate the progression of bony changes and to treat hypercalcaemia

### **Stem Cell Transplantation**

- Intensive treatment with the support of autologous stem cell transplantation is used increasingly and is often the first-line treatment for patients over 70 years of age (Johnson et al., 1998; DARE-989011, 2000) [**C**].
- Allogeneic stem cell transplantation is also used increasingly, but it is still possible only for few patients.

### **Related Resources**

#### **Cochrane Reviews**

- Early treatment of early stage multiple myeloma appears to inhibit disease progression and reduce vertebral compression. However, early treatment may increase the risk of acute leukemia (He et al., 2003) [**B**].
- Bisphosphonates (clodronate and pamidronate) prevent pathological vertebral fractures and reduce pain in multiple myeloma (Djulbegovic et al., 2002) [**A**].

#### **Other Evidence Summaries**

- There appears to be no significant survival advantage of interferon in the maintenance treatment of multiple myeloma (Trippoli et al., 1997) [**B**].
- Osteonecrosis of the jaw may be associated with the use of high doses of intravenous aminobisphosphonates in patients with myeloma or metastatic cancer (Woo, Hellstein, & Kalmar, 2006) [**C**].

Refer to the original guideline document for other Internet resources, resources for the patient, and other literature.

#### **Definitions:**

#### **Levels of Evidence**

##### **A. Quality of Evidence: High**

Further research is very unlikely to change confidence in the estimate of effect

- Several high-quality studies with consistent results
- In special cases: one large, high-quality multi-centre trial

##### **B. Quality of Evidence: Moderate**

Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

- One high-quality study

- Several studies with some limitations

**C. Quality of Evidence: Low**

Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

- One or more studies with severe limitations

**D. Quality of Evidence: Very Low**

Any estimate of effect is very uncertain.

- Expert opinion
- No direct research evidence
- One or more studies with very severe limitations

**CLINICAL ALGORITHM(S)**

None provided

**EVIDENCE SUPPORTING THE RECOMMENDATIONS**

**REFERENCES SUPPORTING THE RECOMMENDATIONS**

[References open in a new window](#)

**TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS**

Concise summaries of scientific evidence attached to the individual guidelines are the unique feature of the Evidence-Based Medicine Guidelines. The evidence summaries allow the clinician to judge how well-founded the treatment recommendations are. The type of supporting evidence is identified and graded for select recommendations (see the "Major Recommendations" field).

**BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS**

**POTENTIAL BENEFITS**

Reduction of symptoms and prevention of complications through early diagnosis and treatment

**POTENTIAL HARMS**

Osteonecrosis of the jaw may be associated with the use of high doses of intravenous aminobisphosphonates in patients with myeloma or metastatic cancer

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Multiple myeloma (MM). In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007 May 30 [Various].

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2001 Dec 27 (revised 2007 May 30)

### GUIDELINE DEVELOPER(S)

Finnish Medical Society Duodecim - Professional Association

### SOURCE(S) OF FUNDING

Finnish Medical Society Duodecim

### GUIDELINE COMMITTEE

Editorial Team of EBM Guidelines

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

Not stated

## **GUIDELINE STATUS**

This is the current release of the guideline.

This guideline updates a previous version: Finnish Medical Society Duodecim. Multiple myeloma (MM). In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2005 May 1 [Various].

## **GUIDELINE AVAILABILITY**

This guideline is included in a CD-ROM titled "EBM Guidelines. Evidence-Based Medicine" available from Duodecim Medical Publications, Ltd, PO Box 713, 00101 Helsinki, Finland; e-mail: [info@ebm-guidelines.com](mailto:info@ebm-guidelines.com); Web site: [www.ebm-guidelines.com](http://www.ebm-guidelines.com).

## **AVAILABILITY OF COMPANION DOCUMENTS**

None available

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This summary was completed by ECRI on December 17, 2002. The information was verified by the guideline developer as of February 7, 2003. This NGC summary was updated by ECRI on October 5, 2004, June 24, 2005, and January 3, 2008. This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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