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2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Guideline Summary

A panel of adult and pediatric rheumatologists and endocrinologists updated the systematic literature review and included currently available medications for the prevention and treatment of glucocorticoid (GC)-induced osteoporosis. A patient panel was included in this update.

Similar to the 2017 guideline, we recommend risk stratifying patients as being at low, moderate, or high risk of fracture (Adults ≥ 40 years, FRAX® 10-year probability of major osteoporotic fracture < 10 %,10-19%, or ≥ 20% respectively). These cut points were used to stratify PICO questions and weigh potential benefits versus harms, when considering osteoporosis (OP) therapy. For all adults initiating or continuing GC therapy ≥ 2.5mg/day for > 3 months, who have never had fracture risk assessment or been treated with OP therapy, initial clinical fracture risk assessment is strongly recommended over no assessment. Clinical fracture risk factor assessment includes the dose, duration, and pattern of GC use, alcohol use, smoking history, hypogonadism, history of prior fractures, low body weight, significant weight loss, parental history of hip fracture, fall history, thyroid disease, hyperparathyroidism, rheumatoid arthritis, malabsorption, chronic liver disease, inflammatory bowel disease, and height loss. If available, BMD testing is recommended within 6 months of starting GC therapy for adults and every 1-2 years thereafter while continuing GC therapy.

A strong recommendation was made to use oral bisphosphonates (BPs) for adults ≥ 40 years receiving long-term GCs, at high risk for fracture, based on available fracture data in GIOP populations. Other agents including intravenous BPs, PTH/PTHrP, and denosumab (DEN) are also options and are conditionally recommended given lack of fracture prevention data in GIOP populations. The selection between oral and IV BP, PTH/PTHrP, and DEN should be based on patient and physician preferences. Selective estrogen receptor modulators (SERMs) and romosozumab (ROM) may be used in selected patients, after careful consideration of potential harms including thrombosis, stroke, and cardiovascular events.

Table 1: Definitions of selected terms used in the recommendations and upgraded position statements for GIOP

Term	Adults ≥ 40 years of age	Adults < 40 years of age
Major osteoporotic fracture (MOF)	Non-traumatic or pathological fractures of the spine, hip, wrist, or humerus	Non-traumatic or pathological fractures of the spine, hip, wrist, or humerus
Clinical fracture risk assessment	History of GC use, evaluation for falls, fractures, frailty, secondary causes of osteoporosis, FRAX® with GC adjustment, BMD testing	History of GC use, evaluation for falls, fractures, frailty, secondary causes of osteoporosis, BMD testing (FRAX® not validated at age <40 years)

Follow up risk assessment during GC treatment	FRAX® and BMD testing every 1-2 years for untreated patients; BMD testing every 1-2 years for OP-treated patients, whether receiving or completed OP therapy	BMD testing every 1-2 years
FRAX® GC correction	If GC dose is > 7.5 mg/day, multiply the 10-year risk of major osteoporotic fracture by 1.15 and the hip fracture risk by 1.2 *	Not applicable
Fracture risk categories in patients not yet receiving OP treatment		
High	Prior OP fracture (s) **OR** Hip or spine BMD T ≤ -2.5 **OR** FRAX® (GC-Adjusted) 10-year risk of MOF ≥ 20%, hip ≥ 3% **OR** GC ≥ 30mg/day or cumulative GC doses ≥ 5 grams/year	Prior OP fracture (s) **OR** GC ≥ 30mg/day **OR** cumulative GC doses ≥ 5 grams/year
Moderate	FRAX® (GC-Adjusted) 10-year risk of MOF ≥ 10 and < 20%, hip > 1 and < 3%	Continuing GC treatment ≥ 7.5mg/day for ≥ 6 months **AND** (Hip or spine BMD Z score < -3) **OR** (rapid bone loss ≥ 10% at the hip or spine over 1-2 years)
Low	FRAX® (GC-Adjusted) 10-year risk of MOF < 10%, hip ≤ 1%	None of the above risk factors other than GC treatment
Treatments	***Recommended pharmacological treatment strategy***	
Calcium and Vitamin D	In addition to lifestyle modifications, optimized intake of dietary and supplemental calcium and vitamin D based on age-appropriate U.S. Recommended Dietary Allowances.	
Bisphosphonates (BP) Alendronate (oral) Risedronate (oral) Ibandronate (oral/ IV) Zoledronic acid (IV) **PTH & PTHrP Agonists** Teriparatide (TER) Abaloparatide (ABL) **Anti-RANKL** Denosumab (DEN) **SERM** Raloxifene (RAL) Bazedoxifene (BAZ) **Anti-sclerostin** Romosozumab (ROM)	*First line:* *Strong recommendation based on fracture data in GIOP:* Oral BP *Conditional recommendation due to lack of fracture data in GIOP:* IV BP[$], DEN, PTH/PTHrP Conditionally *recommended against due to CVD and thrombosis risk unless first-line therapies are contraindicated or not tolerated: ROM, SERM*	*First line:* *Conditional recommendation* Oral or IV BP[$], PTH/PTHrP or DEN Conditionally *recommended against due to CVD and thrombosis risk unless first-line therapies are contraindicated or not tolerated:* SERM and ROM

BP = bisphosphonate; PTH = parathyroid hormone; PTHrP = PTH-related protein; RANKL = Receptor activator of NF-κβ-Ligand; SERM = Selective estrogen receptor modulator; BMD = bone mineral density; GC= glucocorticoid; FRAX® = https//www.shef.ac.uk/FRAX/Tool.jsp; MOF = major osteoporotic fracture; * FRAX® GC correction example: if hip fracture risk is 2.0% multiply by 1.2 for adjusted risk =2.4%; [$] = IV BP not preferred in women of child-bearing potential

Osteoporosis Medications for Patients with Chronic Kidney Disease or Following Renal Transplant

Bisphosphonates should generally not be used in patients with an eGFR < 35 ml/min. When eGFR is < 35 ml/min, the risk of renal osteodystrophy, including adynamic bone disease, osteomalacia, osteitis fibrosa cystica and mixed uremic osteodystrophy, is increased. As such, metabolic bone disease expert evaluation for chronic kidney disease-mineral and bone disorder (CKD-MBD) is conditionally recommended to exclude these conditions. Once excluded, no dose adjustment is needed when prescribing DEN, PTH/PTHrP, or romosozumab (ROM).

Table 2. Recommendations for initial treatment for prevention of GIOP in adults beginning long-term GC therapy

Recommendations for patients taking prednisone ≥ 2.5mg/day for > 3months	Certainty of evidence	PICO evidence report basis	Page no(s). of evidence tables
For adults and children beginning or continuing chronic GC treatment at low, moderate, or high risk of fracture, optimizing dietary and supplemental calcium and vitamin D in addition to lifestyle modifications (CAL/VIT D/LM) is **conditionally** recommended. All additional recommendations are in addition to CAL/VIT D/LM).	Low or Very Low	1.1a,b,c-1.3a,b,c, 2.1-2.3, 7.16-7.26	6-8, 47-48, 63-65, 141-144,148-151
In adults ≥ 40 years			
With ***LOW*** fracture risk, adding any OP medications to CAL/VIT D /LM based on known harms with no evidence of benefit is **strongly** recommended ***against***.	Very Low	1.4a-1.28a	8-46
With ***MODERATE*** fracture risk, oral or IV BP, PTH/PTHrP, or DEN over no OP therapy is **conditionally** recommended.	Moderate to Very Low	1.4b-1.28b	42-47
With ***MODERATE*** fracture risk, using ROM or SERM is **conditionally** recommended *against* except for in patients intolerant of other agents, due to risk of life-threatening harms.	Very Low	1.12b, 1.16b,1.17b,1.21b-1.25b, 1.28b	40-41, 44-47
With ***HIGH*** fracture risk, oral BP over not giving OP therapy is **strongly** recommended[#]. IV BP, PTH/PTHrP, or DEN over no OP therapy is **conditionally** recommended[$].	Low or Very Low	1.5c-1.28c	48-53
With ***HIGH*** fracture risk, using ROM or SERM is **conditionally** recommended ***against*** except for patients intolerant of other agents due to risk of life- threatening harms	Very Low	1.16c, 1.21c, 1.28c	50, 52-53

With ***HIGH*** fracture risk, using two different OP medications at the same time is **conditionally** recommended ***against***.	Very Low	1.29-1.35	53-62
For *post-menopausal* women at moderate or ***HIGH*** fracture risk, SERM is **conditionally** recommended ***against*** except for in patients intolerant of other agents, due to risk of life- threatening harms.	Very Low	1.12b,c, 1.17b,c 1.22b,c-1.25b,c	43-46, 50-52
Adults ≥ 40 years receiving high-dose GC (initial dose ≥ 30 mg/day or cumulative dose ≥ 5 gm in 1 year)			
Treating with oral or IV BP, PTH/PTHrP, DEN, SERM, or ROM is **conditionally** recommended.	Low	6.4a-6.19a	120-130
In adults <40 years			
With ***LOW*** fracture risk, adding OP medications over CAL/VIT D/ LM alone is **strongly** recommended ***against*** due to known risk of harms and no evidence of benefit.	Very Low	4.4a-4.13a	91-101
With ***MODERATE or HIGH*** fracture risk, oral or IV BP[%], DEN, or PTH/PTHrP therapy is **conditionally** recommended.	Low or Very Low	2.4-2.22, 3.4-3.17	65-76, 79-84.
With ***MODERATE or HIGH*** fracture risk, using ROM is **conditionally** recommended ***against*** due to risk of life-threatening harms.	Very Low	2.9, 3.9	70, 86
Adults < 40 years[#] receiving high-dose GC (initial dose ≥ 30 mg/day > 30 days or cumulative dose ≥ 5 gm in 1 year)			
Treating with oral or IV BP[%], PTH/PTHrP or DEN is **conditionally** recommended over SERM or ROM due to risk of life-threatening harms	Low	6.1b-6.19b	133-141
For adults with solid organ transplants, glomerular filtration rate ≥ 35 ml/minute, and no evidence of chronic kidney disease-mineral and bone disorder (CKD-MBD)*			
Expert evaluation for CKD-MBD in renal transplant recipients is **conditionally** recommended.	Low	5.1-5.26	103-118
Personalized treatment with oral or IV BP, DEN, PTH/PTHrP, or SERM based on individual patient factors is **conditionally** recommended.	Low	5.1-5.26	103-118
Using ROM due to CVD risk and lack of safety in this population is **conditionally** recommended ***against***.	Very Low	5.9	112
Children ages 4-17 years treated with GCs at any dose for > 3 months (Low or moderate risk)			
Optimization of dietary and supplementation of CAL and VIT D is **conditionally** recommended as recommended by U.S. RDA depending on the age of the child.	Very Low	7.1a-7.4a	141-144
Starting oral or IV BP is **conditionally** recommended ***against*** due to low risk of OP fractures in this age group.	Very Low	7.5a	144

Children ages 4-17 years with *an osteoporotic fracture* who are continuing treatment with GCs at a dose of ≥ 0.1 mg/kg/day for > 3 months (high risk)			
Treating with an oral or IV BP is **conditionally** recommended.	Very Low	7.1b-7.2b	147-253

GIOP = Glucocorticoid-induced osteoporosis, BMD = Bone mineral density, GC = glucocorticoids, BP = bisphosphonate, IV = intravenous, DEN = denosumab, PTH/PTHrP = parathyroid hormone/ parathyroid hormone related protein, RAL = raloxifene, ROM = romosozumab, OP = osteoporosis; PICO = Patients, intervention, comparison, outcome; CAL/VIT D/LM = calcium/ vitamin D/ lifestyle modifications; # strong recommendation based on fracture data, $ conditional due to lack of fracture data, % who are not planning on pregnancy during the OP treatment period or are using effective birth control if sexually active; CAL = calcium; CVD = cardiovascular disease; SERM = selective estrogen receptor modulator; U.S. RDA = United States Recommended Dietary Allowances; CKD-MBD = chronic kidney disease-mineral and bone disorder; *includes osteomalacia, adynamic bone disease, osteitis fibrosa cystica, mixed uremic osteodystrophy

This updated guideline includes recommendations on abaloparatide (PTHrP) and romosozumab (ROM), which are newly available since the 2017 guideline. It also addresses sequential therapy, which was not addressed in the past. Patients should know that osteoporosis therapy with denosumab (DEN), teriparatide (PTH), PTHrP, or ROM will need sequential osteoporosis therapy to prevent rapid bone loss after these drugs are discontinued. Recommendations for sequential therapies are based in part on initial study designs, long term follow-up studies, and new clinical trials. Patients completing a course of DEN should transition to 1-2 years of a BP. Patients completing a course of PTH, PTHrP, or ROM need to transition to a BP or DEN. Discontinuation of DEN after two or more doses has been associated with rapid bone loss and development of new vertebral compression fractures as soon as 7-9 months after the last dose. As such, BP therapy is recommended beginning at 6-7 months after the last dose of DEN. The precise timing, dose and duration of BP use after DEN cessation is under study, but treatment for a least 1 year seems prudent, until additional research is available. Stopping PTH/PTHrP without transition to another therapy can also result in rapid bone loss and new fractures, which can be prevented by institution of oral or IV BP or DEN. Stopping ROM without transition to another therapy can result in bone loss, which can be prevented by the institution of oral or IV BP or DEN.

Sequential Treatments Recommended When Initial OP Therapy and GC are Discontinued and at Low or Moderate Risk

Initial OP therapy	**Subsequent OP therapy options**
Oral/IV Bisphosphonate	No subsequent OP therapy needed
SERM	No subsequent OP therapy needed
PTH/PTHrP	Oral or IV Bisphosphonate, **OR** Denosumab followed by Bisphosphonate
Denosumab	Oral or IV Bisphosphonate
Romosozumab	Oral or IV Bisphosphonate, **OR** Denosumab followed by Bisphosphonate

Sequential Treatments Recommended When Initial OP Therapy and GC are Discontinued and Patient Remains High Risk

Continue current therapy or switch to IV Bisphosphonate, DEN, PTH/PTHrP, SERM or romosozumab

This summary was initially approved by the ACR Board of Directors on August 13, 2022 and updated on November 9, 2022. These recommendations are included in a full manuscript, which will be submitted for publication in Arthritis & Rheumatology and Arthritis Care and Research.