ΠΡΟΣΦΑΤΕΣ ΔΙΕΘΝΕΙΣ ΣΥΣΤΑΣΕΙΣ ΣΤΑ ΡΕΥΜΑΤΙΚΑ ΝΟΣΗΜΑΤΑ

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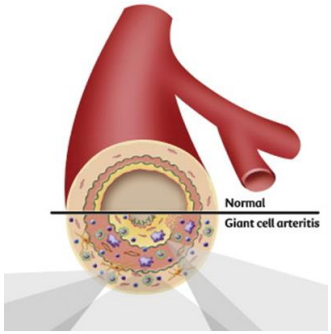
Αθήνα, 13/05/2022



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American College of Rheumatology
Empowering Rheumatology Professionals

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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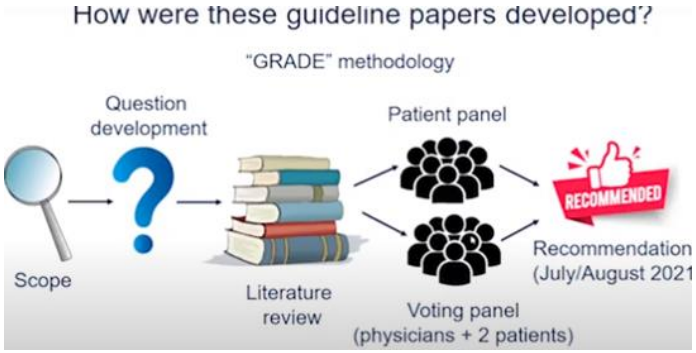
Η ανάγκη για νέες κατευθυντήριες οδηγίες προέκυψε καθώς υπάρχουν νεότερα δεδομένα από κλινικές μελέτες για την αποτελεσματικότητα και την ασφάλεια βιολογικών και μη βιολογικών ανοσοκατασταλτικών θεραπειών



- Για κάθε σύσταση απαιτείται >70% ομοφωνία
  - Strong recommendation
  - **Conditional recommendation**
  - Ungraded position statements

Ορισμοί

Table 1. Definitions of selected terms used in the recommendations and ungraded position statements for GPA, MPA, and EGPA*

Term	Definition
Disease states	
Active disease	New, persistent, or worsening clinical signs and/or symptoms attributed to GPA, MPA, or EGPA and not related to prior damage
Severe disease	Vasculitis with life- or organ-threatening manifestations (e.g., alveolar hemorrhage, glomerulonephritis, central nervous system vasculitis, mononeuritis multiplex, cardiac involvement, mesenteric ischemia, limb/digit ischemia)
Nonsevere disease	Vasculitis without life- or organ-threatening manifestations (e.g., rhinosinusitis, asthma, mild systemic symptoms, uncomplicated cutaneous disease, mild inflammatory arthritis)
Remission	Absence of clinical signs or symptoms attributed to GPA, MPA, or EGPA, on or off immunosuppressive therapy
Refractory disease	Persistent active disease despite an appropriate course of immunosuppressive therapy
Relapse	Recurrence of active disease following a period of remission
Treatments	
IV pulse GCs	IV methylprednisolone 500–1,000 mg/day (adults) or 30 mg/kg/day (children; maximum 1,000 mg/day) or equivalent for 3–5 days
High-dose oral GCs	Prednisone 1 mg/kg/day (adults; generally up to 80 mg/day) or 1–2 mg/kg/day (children; generally up to 60 mg/day) or equivalent
Remission induction therapy	
Methotrexate	Up to 25 mg/week (SC or oral)
Azathioprine	Up to 2 mg/kg/day
Mycophenolate mofetil	Up to 1,500 mg (oral) twice per day
Cyclophosphamide	Up to 2 mg/kg/day (oral) for 3–6 months; or intermittent 15 mg/kg (IV) every 2 weeks for 3 doses, followed by 15 mg/kg (IV) every 3 weeks for at least 3 doses (adults)
Rituximab	375 mg/m^2 (IV) weekly for 4 doses or 1,000 mg on days 1 and 15 (adults); or 375 mg/m^2 (IV) weekly for 4 doses or 575 mg/m^2 for patients with body surface area ≤1.5m^2 or 750 mg/m^2 for patients with body surface area >1.5m^2 with a typical maximum of 1 gm per infusion (both for 2 doses, days 1 and 15) (children)
Mepolizumab	300 mg (SC) every 4 weeks (adults)
Remission maintenance therapy	
Methotrexate, azathioprine, mycophenolate mofetil	Same dosing regimen as in remission induction therapy
Rituximab	500 mg (IV) every 6 months or 1 gm (IV) every 4 months (adults), 250 mg/m^2 (IV) every 6 months (children), or other doses
Mepolizumab	300 mg (SC) every 4 weeks
Omalizumab	300–600 mg (SC) every 2–4 weeks

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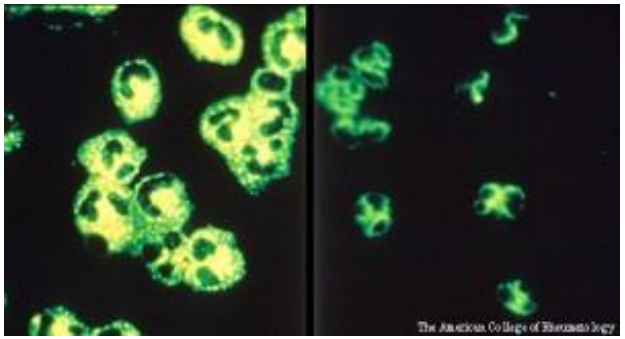
Recommendations and ungraded position statements for GPA and MPA



1. Επαγωγή ύφεσης σε ενεργό, σοβαρή νόσο

For patients with active, severe GPA/MPA, we conditionally recommend treatment with rituximab over cyclophosphamide for remission induction

LoE:Very low to moderate

- Όμοια αποτελεσματικότητα των δυο θεραπευτικών σχημάτων
- Μικρότερη τοξικότητα RTX, καλύτερα ανεκτό φάρμακο
- Και τα 2 δοσολογικά σχήματα του RTX θεωρούνται το ίδιο αποτελεσματικά
  (375 mg/m2 every week for 4 weeks and 1,000 mg on days 1 and 15)
- Υπό μελέτη ο συνδυασμός CYC + RTX

Επαγωγή ύφεσης σε ενεργό, σοβαρή νόσο
Πλασμαφαίρεση

In patients with GPA/MPA with active glomerulonephritis, we conditionally recommend *against* the routine addition of plasma exchange to remission induction therapy

LoE: Low to high

- Το όφελος της πλασμαφαίρεσης φαίνεται μεγαλύτερο στις περιπτώσεις με αυξημένο κίνδυνο για εξέλιξη σε ESRD
- Επίπεδα νεφρικής λειτουργίας στο baseline, ρυθμός έκπτωσης νεφρικής λειτουργίας, ανταπόκριση στη θεραπεία, status ασθενή (σοβαρές λοιμώξεις)
- Συστήνεται σε anti-GBM disease

In patients with active, severe GPA/MPA with alveolar hemorrhage, we conditionally recommend *against* adding plasma exchange to remission induction therapies

LoE: Low to high

- Δεν αναδεικνύεται διαφορά στην επίτευξη ύφεσης ή στη θνησιμότητα από τις κλινικές μελέτες
- Δεν έχει επιβεβαιωμένο όφελος, ενώ σχετίζεται με αυξημένο κίνδυνο λοιμώξεων
- Συστήνεται σε anti-GBM disease

Επαγωγή ύφεσης σε ενεργό, σοβαρή νόσο
Κορτικοστεροειδή

Ungraded position statement: For patients with active, severe GPA/MPA, either IV pulse GCs or high-dose oral GCs may be prescribed as part of initial therapy.

LoE:Very low to moderate

In patients with active, severe GPA/MPA, we conditionally recommend a reduced-dose GC regimen over a standard-dose GC regimen for remission induction.

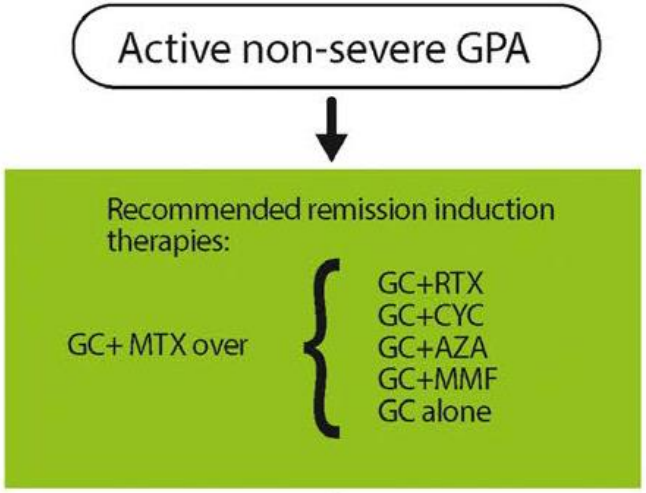
LoE:Very low to moderate

- Τοξικότητα από μακρόχρονη χρήση κορτικοστεροειδών
- Reduced dose regimen : pulse methylprednisolone (3 daily pulses) and 1 week of high-dose oral glucocorticoids.

2. Επαγωγή ύφεσης σε ενεργό, ΜΗ σοβαρή νόσο

We conditionally recommend

- Initiating treatment with methotrexate over cyclophosphamide or rituximab. (LoE: Very low to moderate)
- Initiating treatment with methotrexate and GCs over GCs alone. (LoE:low)
- Initiating treatment with methotrexate and GCs over azathioprine and GCs or mycophenolate mofetil and GCs. (LoE:low)
- Initiating treatment with methotrexate and GCs over trimethoprim/sulfamethoxazole and GCs. (LoE:low)



3. Διατήρηση ύφεσης

For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with rituximab over methotrexate or azathioprine for remission maintenance.

LoE:Very low to moderate

Δοσολογικά σχήματα RTX
500 mg κάθε 6 μήνες
1,000 mg κάθε 4 μήνες
1,000 mg κάθε 6 μήνες

For patients with GPA/MPA who are receiving rituximab for remission maintenance, we conditionally recommend scheduled re-dosing over using ANCA titers or CD19+ B cell counts to guide re-dosing.

LoE:Very low to low

3. Διατήρηση ύφεσης

For patients with severe GPA/MPA whose disease has entered remission after treatment with cyclophosphamide or rituximab, we conditionally recommend treatment with methotrexate or azathioprine for remission maintenance over

- mycophenolate mofetil (LoE: Very low to moderate)
- leflunomide (LoE: Very low to low)

For patients with GPA whose disease has entered remission, we conditionally recommend treatment with methotrexate or azathioprine over trimethoprim/sulfamethoxazole for remission maintenance.

(LoE: Very low to low)

Recommended remission maintenance therapies in order of preference:
1. RTX
2. MTX or AZA
3. MMF or LEF

3. Διατήρηση ύφεσης

In patients with GPA whose disease has entered remission, we conditionally recommend *against* adding trimethoprim/sulfamethoxazole to other therapies (e.g., rituximab, azathioprine, methotrexate, etc.) for the purpose of remission maintenance.

LoE: Low to moderate

Όφελος σε συμμετοχή ανώτερου αναπνευστικού
Αυξημένη τοξικότητα
Ένδειξη σε προφύλαξη έναντι PCP

For patients with GPA/MPA receiving remission maintenance therapy with rituximab who have hypogammaglobulinemia (e.g., IgG <3 gm/liter) and recurrent severe infections, we conditionally recommend immunoglobulin supplementation

LoE: Very low

3. Διατήρηση ύφεσης

Ungraded position statement
1. The duration of non-GC remission maintenance therapy in GPA/MPA should be guided by the patient's clinical condition, preferences, and values.
2. The duration of GC therapy for GPA/MPA should be guided by the patient's clinical condition, preferences, and values.

LoE: Low to moderate

Παράγοντες που επηρέαζουν την απόφαση για τη διάρκεια της αγωγής
- Ιστορικό υποτροπών
- Χαρακτηριστικά νόσου πχ PR3 ANCA

Συστηματική παρακολούθηση για ανεπιθύμητες ενέργειες από GC

4. Υποτροπή νόσου

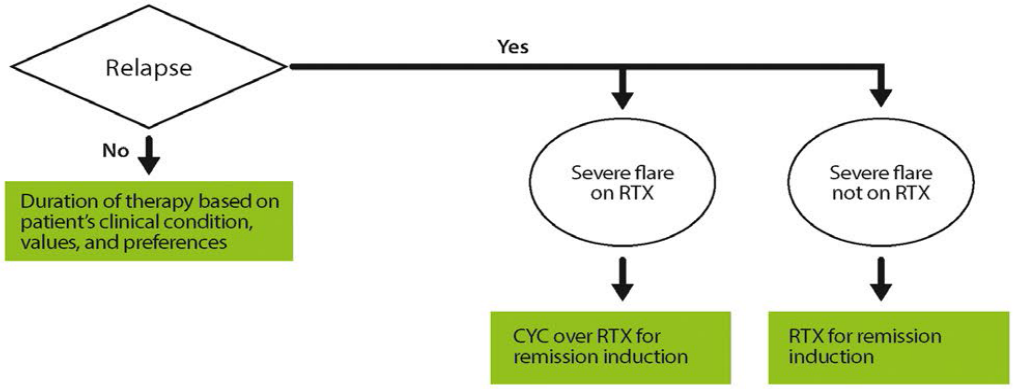
For patients with GPA/MPA who have experienced relapse with severe disease manifestations and are not receiving rituximab for remission maintenance, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction.

LoE: Low

For patients with GPA/MPA who experienced relapse with severe disease manifestations while receiving rituximab for remission maintenance, we conditionally recommend switching from rituximab to cyclophosphamide over receiving additional rituximab for remission re-induction.

LoE: Very Low

Αθροιστική δόση CYC
Διάστημα από τελευταία έγχυση RTX (πρόσφατο ή μη)
Σε συνδυασμό με κορτικοστεροειδή



5. Ανθεκτική νόσος

For patients with severe GPA/MPA that is refractory to treatment with rituximab or cyclophosphamide for remission induction, we conditionally recommend switching treatment to the other therapy over combining the 2 therapies.

LoE : Very low

❖ Απαραίτητος αποκλεισμός καταστάσεων που μιμούνται αγγειίτιδα πχ **λοίμωξη**

For patients with GPA/MPA that is refractory to remission induction therapy, we conditionally recommend adding IVIG to current therapy.

LoE: Low to moderate

6. Ειδικές καταστάσεις (sinonasal, airway, and mass lesions)

- Ungraded position statement: For patients with sinonasal involvement in GPA, **nasal rinses and topical nasal therapies** (antibiotics, lubricants, and glucocorticoids) **may be beneficial**

  LoE: Very low to low

- For patients with GPA in remission who have nasal septal defects and/or nasal bridge collapse, we **conditionally recommend reconstructive surgery**, if desired by the patient. LoE: Low

- For patients with GPA and actively inflamed subglottic and/or endobronchial tissue with stenosis, we **conditionally recommend treating with immunosuppressive therapy over surgical dilation** with intralesional glucocorticoid injection alone.

  LoE: Low

- For patients with GPA and mass lesions (e.g.,orbital pseudotumor or masses of the parotid glands, brain, or lungs), we **conditionally recommend treatment with immunosuppressive therapy** over surgical removal of the mass lesion with immunosuppressive therapy LoE: Very low to low

7. Άλλες καταστάσεις

❖ In patients with GPA/MPA, we **conditionally recommend *against* dosing immunosuppressive therapy based on ANCA titer results alone.**
LoE :Very low

❖ For patients with GPA who are receiving rituximab or cyclophosphamide, we **conditionally recommend prophylaxis to prevent *Pneumocystis jirovecii* pneumonia**.
LoE : Low

❖ For patients with GPA/MPA in remission and **stage 5 chronic kidney disease**, we **conditionally recommend evaluation for renal transplantation**.
LoE : Low

❖ For patients with active GPA/MPA who are **unable to receive other immunomodulatory therapy**, we conditionally recommend **administering IVIG**.
LoE : Low **(ex. Sepsis, pregnancy)**

Ungraded position statement: The optimal duration of **anticoagulation** is unknown for patients with GPA/MPA who experience venous thrombotic events
LoE : Very low

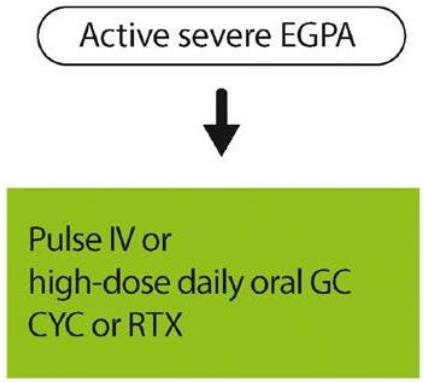
Short term anticoagulation>lifelong

Recommendations and ungraded position statements for EGPA

1. Επαγωγή ύφεσης σε ενεργό, σοβαρή νόσο

Ungraded position statement

- For patients with active, severe EGPA, either IV pulse glucocorticoids or highdose oral glucocorticoids may be prescribed as initial therapy.
- For patients with active, severe EGPA, either cyclophosphamide or rituximab may be prescribed for remission induction.



CYC	RTX
Προσβολή καρδιάς	ANCA (+)
ANCA (-)	Σπειραματονεφρίτιδα
Προσβολή ΓΕΣ	Προηγηθείσα αγωγή με CYC
Προσβολή ΠΝΣ/ΚΝΣ	Αναπαραγωγική ηλικία

For patients with active, severe EGPA, we conditionally recommend treatment with cyclophosphamide or rituximab over mepolizumab for remission induction.

LoE: Low

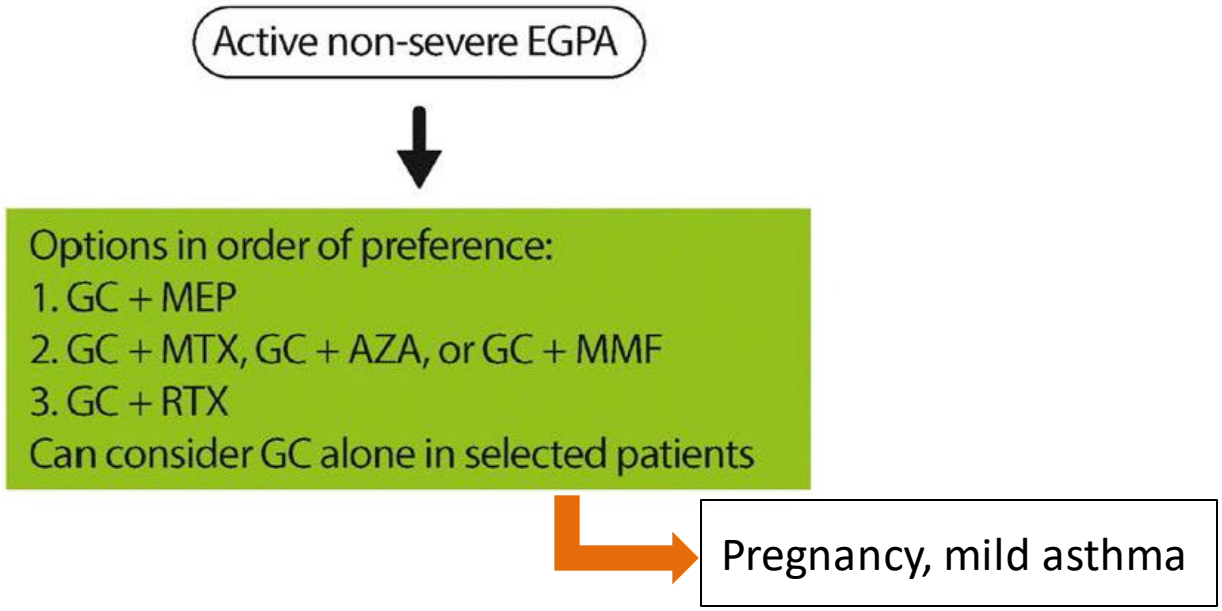
2. Επαγωγή ύφεσης σε ενεργό, ΜΗ σοβαρή νόσο

For patients with active, nonsevere EGPA, we conditionally recommend:

- initiating treatment with mepolizumab and glucocorticoids over methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids (LoE :Very low to low)

- initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids over glucocorticoids alone. (LoE : low)

- initiating treatment with methotrexate, azathioprine, or mycophenolate mofetil and glucocorticoids over cyclophosphamide or rituximab and glucocorticoids. (LoE :Very low to low)



3. Διατήρηση ύφεσης

For patients with severe EGPA whose disease has entered remission with cyclophosphamide therapy, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over rituximab for remission maintenance.

LoE : Very low

Μικρή εμπειρία από χρήση RTX για διατήρηση ύφεσης σε EGPA.

- RTX remission induction therapy ⟶ RTX remission maintenance therapy

For patients with severe EGPA whose disease has entered remission, we conditionally recommend treatment with methotrexate, azathioprine, or mycophenolate mofetil over mepolizumab for remission maintenance.

LoE : Very low

- **Ungraded position statement**: The duration of glucocorticoid therapy in EGPA should be guided by the patient's clinical condition, values, and preferences.
  - Στόχος η μικρότερη δυνατή δόση

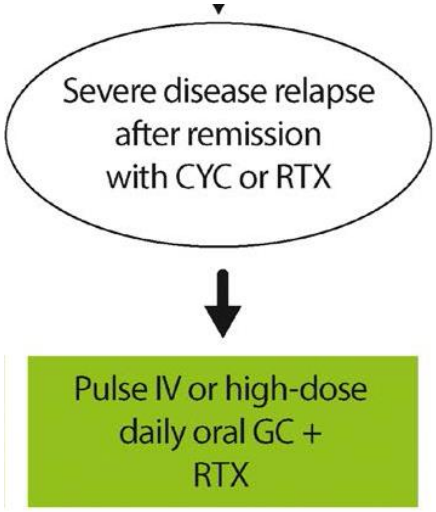
4. Υποτροπή νόσου

For patients with EGPA who have experienced relapse with **severe disease** manifestations after prior successful remission induction with cyclophosphamide, we conditionally recommend treatment with rituximab over cyclophosphamide for remission re-induction

LoE : Very low

For patients with EGPA who have experienced relapse with **severe disease** manifestations after prior successful remission induction with rituximab, we conditionally recommend treatment with rituximab over switching to cyclophosphamide for remission re-induction.

LoE : Very low



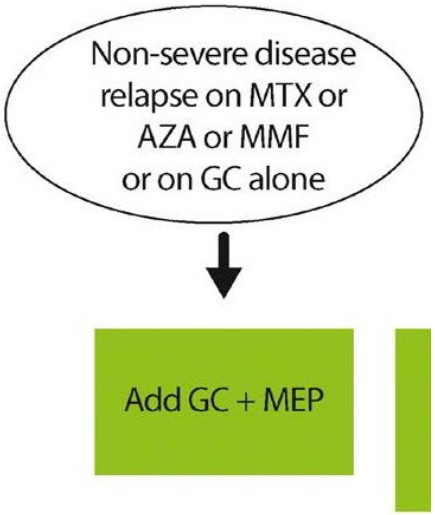
4. Υποτροπή νόσου

For patients with EGPA who have experienced relapse with **nonsevere disease** manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil, we conditionally recommend adding mepolizumab over switching to another agent

LoE : Very low

For patients with EGPA who have experienced relapse with **nonsevere disease** manifestations (asthma and/or sinonasal disease) while receiving low-dose GCs and no other therapy, we conditionally recommend adding mepolizumab over adding methotrexate, azathioprine, or mycophenolate mofetil

LoE : Very low



4. Υποτροπή νόσου

For patients with EGPA and high serum IgE levels who have experienced relapse with nonsevere disease manifestations (asthma and/or sinonasal disease) while receiving methotrexate, azathioprine, or mycophenolate mofetil,
we conditionally recommend adding mepolizumab over adding omalizumab

LoE : Very low

5. Άλλες καταστάσεις

Recommendation: For patients with newly diagnosed EGPA receiving leukotriene inhibitors, we conditionally recommend continuing leukotriene inhibitors over discontinuing them.

LoE : Very low

Ungraded position statement: Use of leukotriene inhibitors is not contraindicated for patients with EGPA with active asthma and/or sinonasal disease.

Recommendation: For patients with EGPA,
we conditionally recommend obtaining an echocardiogram at the time of diagnosis.

LoE : Very low

5. Άλλες καταστάσεις

Recommendation: For patients with EGPA, we conditionally recommend using the Five-Factor Score to guide therapy.

LoE : Very low

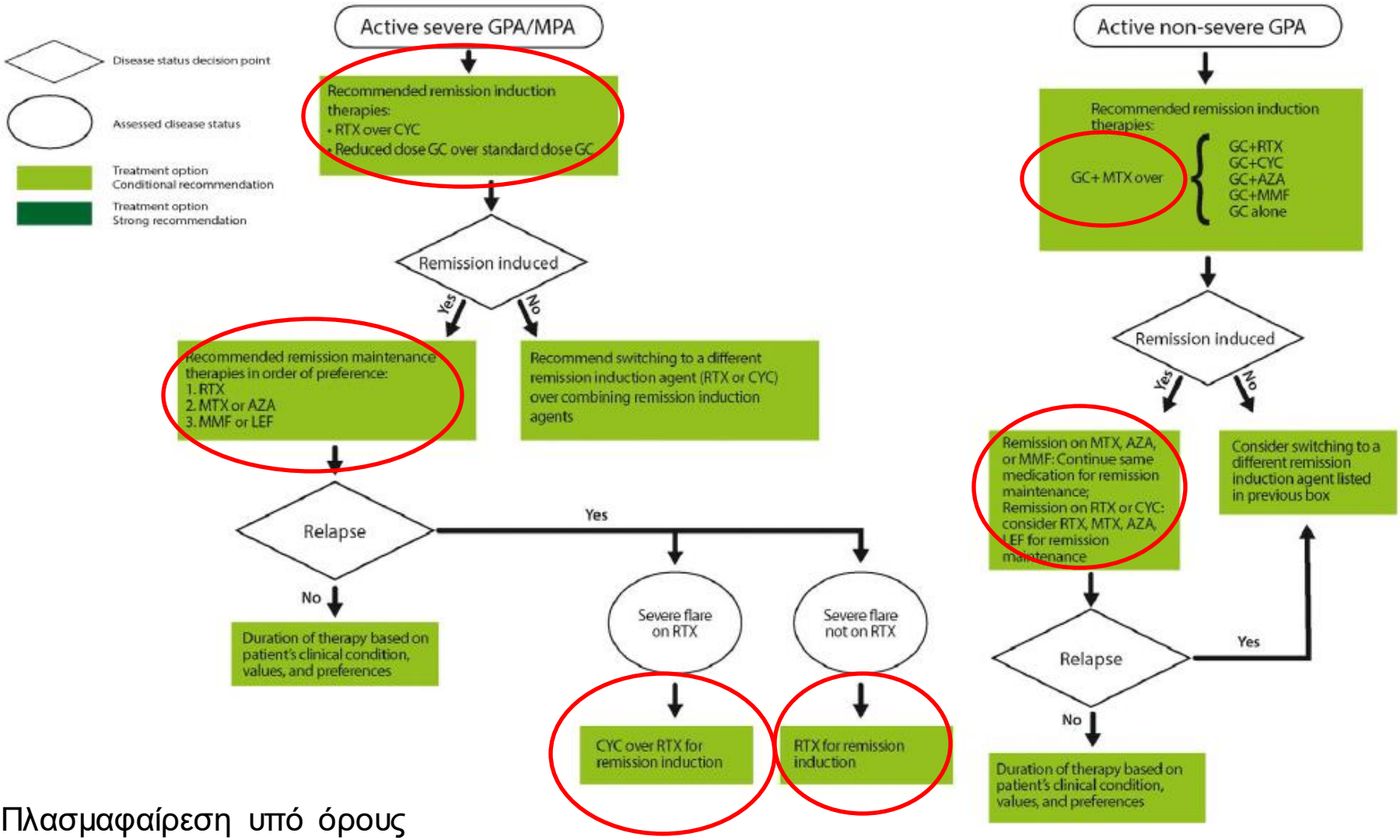
1. proteinuria>1gr/d
2. renal insufficiency
3. GI involvement
4. cardiomyopathy
5. CNS involvement

Ungraded position statement: In patients with sinonasal involvement in EGPA, treatment with nasal rinses and topical therapies (e.g., antibiotics, lubricants, and GCs) may be considered.

Recommendation: For patients with EGPA who are receiving cyclophosphamide or rituximab, we conditionally recommend prescribing medications for prophylaxis to prevent *Pneumocystis jirovecii* pneumonia.

LoE : low

Συμπεράσματα GPA/MPA

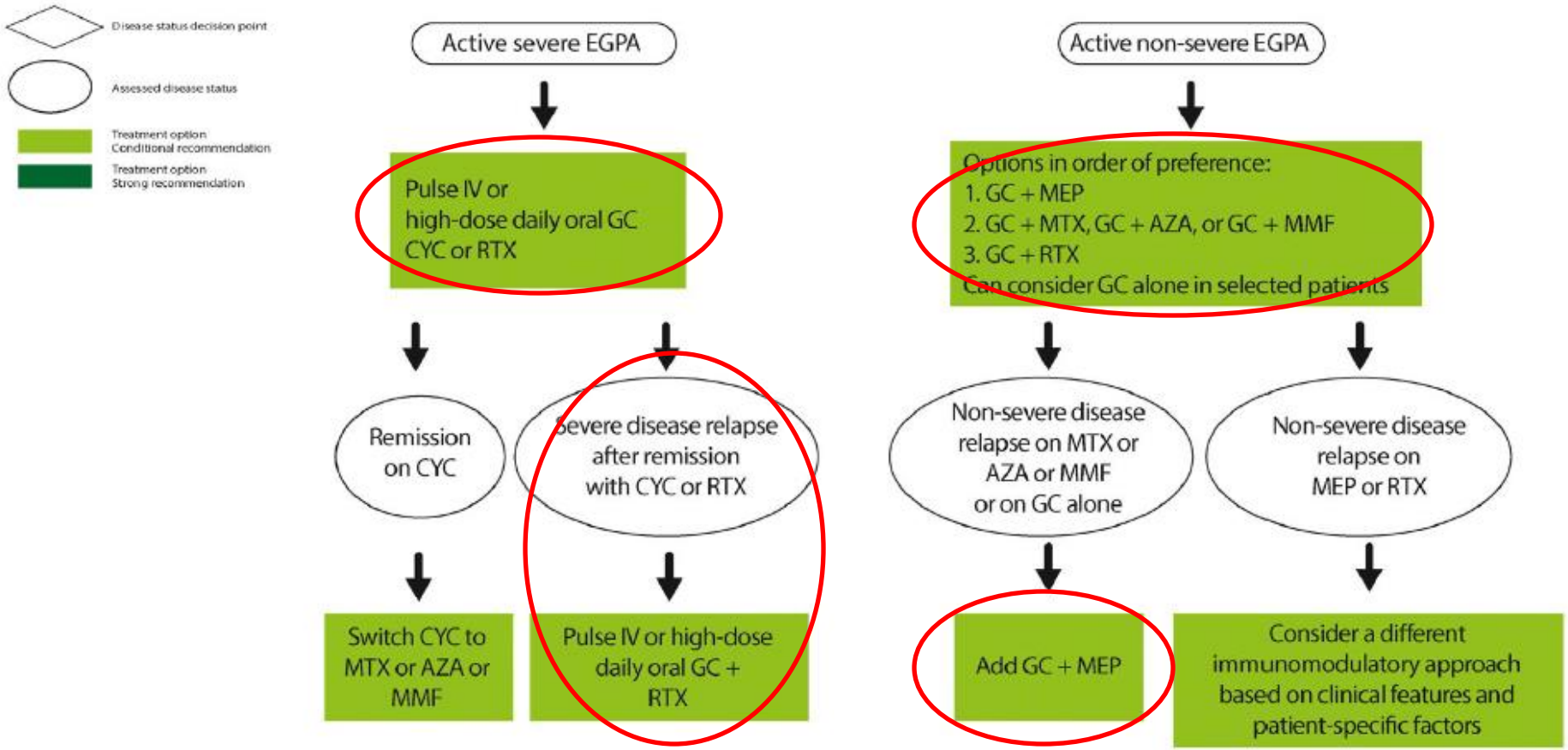


Πλασμαφαίρεση υπό όρους

Μειωμένο δοσολογικό σχήμα κορτικοστεροειδών

Όχι θεραπεία ανάλογα με επίπεδα ANCA και Bcells

Συμπεράσματα EGPA



- Υπερηχοκαρδιογράφημα στο baseline