**SUPPLEMENTARY APPENDIX 2: Evidence Report**

**2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa**

# POLYARTERITIS NODOSA (PAN)

## Diagnosis

- **PICO question 1:** In patients with suspected PAN with and without gastrointestinal symptoms, what is the impact of non-invasive vascular imaging vs. conventional catheter-based imaging on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- **Critical Outcomes:** diagnostic accuracy, disease damage, clinical symptoms, death, adverse reaction to contrast, procedure complications

1. In patients with suspected PAN with and without gastrointestinal symptoms, what is the impact of non-invasive vascular imaging vs. conventional catheter-based imaging on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
   No comparative data available

2. In patients with suspected PAN with and without gastrointestinal symptoms, what is the impact of non-invasive vascular imaging on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
   No single arm data available

3. In patients with suspected PAN with and without gastrointestinal symptoms, what is the impact of conventional catheter-based imaging on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
   No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|

| | | | |
|---|---|---|---|
| M. Singhal | 2016 | Role of multidetector abdominal CT in the evaluation of abnormalities in polyarteritis nodosa | Exclude – descriptive study anatomy |
| C. Pagnoux | 2005 | Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis | Exclude. Does not address PICO question. |
| S. Ozen | 2004 | Juvenile polyarteritis: results of a multicenter survey of 110 children | Exclude. Does not address PICO question. |
| N. Gunal | 1997 | Cardiac involvement in childhood polyarteritis nodosa | Exclude. Does not address PICO question. |
| R. Gupta | 1997 | Outcome of polyarteritis nodosa in northern India | Exclude. Does not address PICO question. |
| L. Guillevin | 1996 | Antineutrophil cytoplasmic antibodies, abnormal angiograms and pathological findings in polyarteritis nodosa and Churg-Strauss syndrome: indications for the classification of vasculitides of the polyarteritis Nodosa Group | Exclude. Does not address PICO question. |
| M. Gordon | 1993 | Relapses in patients with a systemic vasculitis | Exclude. Does not address PICO question. |
| L. Guillevin | 1993 | Antineutrophil cytoplasm antibodies in systemic polyarteritis nodosa with and without hepatitis B virus infection and Churg-Strauss syndrome--62 patients | Exclude. Does not address PICO question. |
| P. Hekali | 1991 | Diagnostic significance of angiographically observed visceral aneurysms with regard to polyarteritis nodosa | Exclude. Does not address PICO question. |
| D. A. Albert | 1988 | The diagnosis of polyarteritis nodosa. II. Empirical verification of a decision analysis model | Exclude. Does not address PICO question. |
| L. Guillevin | 1988 | Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients | Exclude. Does not address PICO question. |
| E. A. Ewald | 1987 | Correlation of angiographic abnormalities with disease manifestations and disease severity in polyarteritis nodosa | Exclude. Does not address PICO question. |
| R. J. Sellar | 1986 | The incidence of microaneurysms in polyarteritis nodosa | Exclude. Does not address PICO question. |
| J. J. Vazquez | 1981 | Angiographic findings in systemic necrotizing vasculitis | Exclude. Does not address PICO question. |
| R. L. Travers | 1979 | Polyarteritis nodosa: a clinical and angiographic analysis of 17 cases | Exclude. Does not address PICO question. |
| E. B. Blau | 1977 | Polyarteritis nodosa in older children | Exclude. Does not address PICO question. |

# POLYARTERITIS NODOSA (PAN)

## Diagnosis

- **PICO question 2:** In patients with suspected cutaneous or systemic PAN involving the skin, what is the impact of a deep skin biopsy vs. skin punch biopsy on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- **Critical Outcomes:** diagnostic accuracy, disease damage, disease activity, death, pain, scarring, tissue injury

4. In patients with suspected cutaneous or systemic PAN involving the skin, what is the impact of a deep skin biopsy vs. skin punch biopsy on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
   No comparative data available

5. In patients with suspected cutaneous or systemic PAN involving the skin, what is the impact of a deep skin biopsy on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
   - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Diagnostic accuracy: There are a limited number of cases with no direct evidence. From what is available, deep biopsy is favored based. | Caorsi R, 2017 | Cross sectional design. | NA | Patients with a history of livedo reticularis and/or early stroke in the context of inflammation or PAN. | No intervention, purely observational. | 10 biopsies were performed:<br>- 7/10 (70%) showed PAN (i.e., medium vessel vasculitis) | Indirect evidence: The paper does not delineate what type of biopsy was performed (i.e., deep vs punch). Of note, medium vessel vasculitis is generally only diagnosed by deep skin biopsy. |

6. In patients with suspected cutaneous or systemic PAN involving the skin, what is the impact of a skin punch biopsy on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- **Patient important outcomes:**

| Outcomes | Author, year | Study type | Duration of follow up | Population | Intervention used in relevant population | Results | Comments |
|---|---|---|---|---|---|---|---|
| Diagnostic accuracy: There are a limited number of cases with no direct evidence. From what is available, deep biopsy is favored based, except in cases where LCV is expected. | Caorsi R, 2017 | Cross sectional design. | NA | Patients with a history of livedo reticularis and/or early stroke in the context of inflammation or PAN. | No intervention, purely observational. | 10 biopsies were performed:<br>- 3/10 (30%) showed LCV (i.e., small vessel vasculitis) | Indirect evidence: The paper does not delineate what type of biopsy was performed (i.e., deep vs punch). Of note, LCV can be seen with either a punch or deep skin biopsy. |
| | Albert D, 1988 | Cross sectional | NA | Patients with ICD code consistent with PAN. Mimics were excluded including infectious arteritis, PACNS and RA. Done in Chicago on patients seen between 1980-1985 | No intervention. | 2 punch skin biopsies done. 0/2 were positive for diagnosis. Both of these patients had confirmation of diagnosis by another means. | Indirect evidence: There is a limited number of skin biopsies performed and the indication for the skin biopsy was not described (e.g., palpable purpura vs nodular lesions). |

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

| Author | Year | Title | Comments |
|---|---|---|---|

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|---|---|---|---|
| R. Caorsi | 2017 | ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study | Include: This is indirect evidence as the paper does not mention which patients got deep vs punch skin biopsy. |
| D. A. Albert | 1988 | The diagnosis of polyarteritis nodosa. II. Empirical verification of a decision analysis model | Included: Only 2 punch skin biopsies reported. |

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| S. Ozen | 2004 | Juvenile polyarteritis: results of a multicenter survey of 110 children | Exclude: The article does not describe whether patients had a deep or punch skin biopsy. There is also no outcome data presented related to the skin biopsy. |
| N. Gunal | 1997 | Cardiac involvement in childhood polyarteritis nodosa | Exclude: Four patients in this small cohort (n=15) had skin biopsies, but the type and results of those biopsies is not mentioned. |
| R. Gupta | 1997 | Outcome of polyarteritis nodosa in northern India | Exclude: Only 2 skin biopsies were reported (with 1 positive), however it does not delineate what type of biopsies were performed. |
| M. Gordon | 1993 | Relapses in patients with a systemic vasculitis | Exclude: There were 12 classic PAN patients with 9 diagnosed based on skin, nerve or muscle biopsies. The article does not delineate how many had each and what type (i.e., deep vs punch skin biopsy). |
| L. Guillevin | 1993 | Antineutrophil cytoplasm antibodies in systemic polyarteritis nodosa with and without hepatitis B virus infection and Churg-Strauss syndrome--62 patients | Exclude: Article reports which patients were diagnosed by skin biopy, however, the biopsy type (i.e., deep vs punch) is not described. |

# POLYARTERITIS NODOSA (PAN)

## Diagnosis

- **PICO question 3:** In patients with suspected PAN and peripheral neuropathy (motor and/or sensory), what is the impact of nerve and muscle biopsy vs. nerve biopsy alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?

- **Critical Outcomes:** diagnostic accuracy, disease damage, disease activity, death, pain, scarring, tissue injury

7. In patients with suspected PAN and peripheral neuropathy (motor and/or sensory), what is the impact of nerve and muscle biopsy vs. nerve biopsy alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
   No comparative data available

8. In patients with suspected PAN and peripheral neuropathy (motor and/or sensory), what is the impact of nerve and muscle biopsy on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
   - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Diagnostic accuracy: Many of the studies include other forms of vasculitis and done prior to MPA being separated from PAN by CHCC. The majority of the evidence supports combination nerve/muscle biopsy. The article by Vital et al suggests that the number of positive biopsies can be increased from 16/202 (8% in nerve only) to 25/202 (12% | Pagnoux C, 2010 | Retrospective chart review | 68.3 ± 63.5 monhts | 348 PAN patients meeting ACR and CHCC diagnosed between 1963 and 2005. All participated in the French Vasculitis Study Group (FVSG) trials. | No intervention | Muscle/nerve biopsies:<br>-Total: 129 biopsies (108 with peripheral neuropathy and 21 without.<br>-Positive: 107 (65%) in all [90 (83%) with peripheral neuropathy and 17 (81%) without]<br><br>Muscle biopsy alone: 65/100 (65%) positive | Direct evidence: Article directly lists number of positive nerve/muscle biopies and demonstrates this to be superior to muscle biopsies alone.<br><br>Study includes both Hepatitis B virus positive and negative patients. |
| | Vital C, 2006 | Multicenter retrospective study | NA | 202 patients with nerve & muscle biopsy for suspected vasculitis neuropathy. 1989-2004 in Southwest France. CHCC used for diagnosis. | Whole superficial peronial nerve biopsy (2cm long) and 2-4 fragments from the peroneus brevis muscle. | 60/202 (29.7%) showed definite necrotizing vasculitis (56 with MPA lesions and 4 PAN). 16/60 (26.7%) with only nerve lesions, 19/60 (31.7%) with muscle only, and 25/60 (41.7%) with nerve and muscle lesions. | Direct evidence: Article directly looks at number of positive muscle/nerve biopsies in patients with suspected vasculitic neuropathy.<br><br>This is a mixed population of different forms of systemic vasculitis with only small percentage being PAN; |

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| with nerve/muscle biopsy) in those with suspected vasculitis neuropathy. | | | | | | | however, results are likely generalizable. |
| | Martinez AC, 1988 | Cross sectional | NA | 15 patients with systemic necrotizing vasculitis (SNV) of "PAN group" (article predates separation of MPA from PAN) | Nerve and/or muscle biopsy | 11/14 (78.6%) muscle biopsies showed SNV<br><br>12/13 (92.3%) nerve biopsies showed SNV | Indirect: The population is likely a mixture of forms of small vessel vasculitis and PAN. |
| | Wees SJ, 1981 | Retrospective observational | Not given | 17 patients with vasculitic neuropathy, 11 with PAN. PAN diagnosis based on 1) at least 2 organs involvement, 2) histologically proven necrotizing vasculitis and 3) other vasculitidies ruled out. (prior to separation of MPA from PAN by CHCC) | Muscle and sural nerve biopsies | 13/15 (86.7%) sural nerve biopsies positive.<br><br>6/11 (54.5%) muscle biopsies showed signs of vasculitis. | Indirect evidence: This is a mixed population of patients including secondary forms of vasculitis (2/2 to RA and SLE) and it is likely some of these are forms of small vessel vasculitis (i.e., MPA). |
| | Walker G, 1978 | Retrospective, observational | Mean f/u 3.3 years | 20 patients admitted to Royal Norh Shore Hospital with PAN over 8 year period. Excluded those with insufficient proof or likely EGPA. | No intervention | 2/2 sural nerve biopsies diagnostic<br><br>3/7 muscle biopsies diagnostic | Indirect: The number that had both biopsies together was not defined.<br><br>This may include patients with MPA (prior to CHCC defining MPA) |
| | Bennett, 2008 | Retrospective, observational | 5 years | 53 cases of biopsy proven peripheral nerve vasculitis. Clinicopathological | Nerve biopsy and muscle biopsy | Nerve biopsy demonstrated definite vasculitis in 36%, probable vasculitis in 62% and no vasculitis in | |

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| | | | | and neurophysiological data in these patients were reviewed. | | 2% of cases. In 24 patients a muscle biopsy (usually the vastus lateralis) was also performed and vasculitis was demonstrated in 46% of these (in 13% showing definite and 33% probable vasculitis). There was only one patient in whom vasculitis was demonstrated in muscle but not in peripheral nerve.<br><br>Combined nerve (usually sural) and vastus lateralis muscle biopsy di d not significantly increase the diagnostic yield compared with nerve biopsy alone | |
| | Said, 1988 | Retrosp ective, observat ional | 15 years | 100 patients in whom necrotizing arteritis was found in muscle and/or in nerve biopsy | Specimens to learn more about the clinicopathological aspects of the neu-ropathy associated with necrotizing arteritis and to compare the respective value of nerve and muscle biopsies in corroborating the diagnosis of necrotizing arteritis. | Among the **83** patients who underwent a muscle and a nerve biopsy, the muscle biopsy was diagnostic for necrotizing arteritis in *66* **(80%),** and the nerve biopsy was diagnostic in *46 (55%).* Observations plead for performance of nerve and muscle biopsies when the cause of a neuropathy has not been identified, even when | |

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| | | | | | | general symptoms are absent. | |
| Tissue injury: The (limited) data that is available suggests the addition of a muscle biopsy does not add to tissue damage over a nerve biopsy alone. | Wees SJ, 1981 | Retrospective observational | Not given | 17 patients with vasculitic neuropathy, 11 with PAN. PAN diagnosis based on 1) at least 2 organs involvement, 2) histologically proven necrotizing vasculitis and 3) other vasculitidies ruled out. (prior to separation of MPA from PAN by CHCC) | Muscle and sural nerve biopsies | All muscle biopsies (n=11) healed well<br><br>2 nerve biopsies were associated with infection and poor wound healing (both with vasculitis 2/2 to RA) | Indirect evidence: This is a mixed population of patients including secondary forms of vasculitis (2/2 to RA and SLE) and it is likely some of these are forms of small vessel vasculitis (i.e., MPA). |

9. In patients with suspected PAN and peripheral neuropathy (motor and/or sensory), what is the impact of nerve biopsy alone on diagnostic accuracy, disease-related outcomes, and diagnostic testing-related adverse events?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Diagnostic accuracy | Albert D, 1988 | Cross sectional | NA | Patients with ICD code consistent with PAN. Mimics were excluded including infectious arteritis, PACNS and RA. Done in Chicago on patients seen between 1980-1985 | No intervention | Muscle only: 5/9 (56%) confirmed diagnosis<br>Nerve only: 2/2 confirmed diagnosis<br>Muscle + nerve: ½ confirmed diagnosis<br><br>Including reference from literature:<br>Nerve bx alone: 8/11 (73%) | Indirect evidence: This does not include patients with mimics of PAN. Small number of patients included. |
| | Bennett, 2008 | Retrospective, observational | 5 years | 53 cases of biopsy proven peripheral nerve va | Nerve biopsy and muscle biopsy | Nerve biopsy demonstrated definite vasculitis in 36%, | |

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| | | | | sculitis. Clinicopathological and neurophysiological data in these patients were reviewed. | | probable vasculitis in 62% and no vasculitis in 2% of cases. In 24 patients a muscle biopsy (usually the vastus lateralis) was also performed and vasculitis was demonstrated in 46% of these (in 13% showing definite and 33% probable vasculitis). There was only one patient in whom vasculitis was demonstrated in muscle but not in peripheral nerve.<br><br>Combined nerve (usually sural) and vastus lateralis muscle biopsy di d not significantly increase the diagnostic yield compared with nerve biopsy alone | |

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
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| Author | Year | Title | Comments |
|---|---|---|---|
| C. Pagnoux | 2010 | Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database | Included. |
| C. Vital | 2006 | Combined nerve and muscle biopsy in the diagnosis of vasculitic neuropathy. A 16-year retrospective study of 202 cases | Included: Study includes a mixed population of vasculitis patients but generalizable to PAN. |
| D. A. Albert | 1988 | The diagnosis of polyarteritis nodosa. II. Empirical verification of a decision analysis model | Included: Limited number of patients. |
| A. Cruz Martinez | 1988 | Electrophysiological study in systemic necrotizing vasculitis of the polyarteritis nodosa group | Included: Likely a mixed population of patients with systemic necrotizing vasculitis. |
| S. J. Wees | 1981 | Sural nerve biopsy in systemic necrotizing vasculitis | Included: Mixed population of patients. |
| G. L. Walker | 1978 | Neurological features of polyarteritis nodosa | Included: Limited number of patients. It may include patients with MPA since done prior to CHCC defining MPA. |
| Bennet | 2008 | The use of nerve and muscle biopsy in the diagnosis of vasculitis: a 5 year retrospective study. | Included. |
| Said G | 1988 | The peripheral neuropathy of necrotizing arteritis: a clinicopathological study. | Included |

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| R. Caorsi | 2017 | ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study | Exclude: It does not appear that any of the cohort had a nerve and/or muscle biopsy. |
| S. Ozen | 2004 | Juvenile polyarteritis: results of a multicenter survey of 110 children | Exclude: There is no mention of nerve biospies. Muscle biopsies were mentioned to a limited degree, but not in combination with nerve biopsy. |
| N. Gunal | 1997 | Cardiac involvement in childhood polyarteritis nodosa | Exclude: There were no patients with neurologic involvement in this small cohort (n=15). |

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| S. H. Hawke | 1991 | Vasculitic neuropathy. A clinical and pathological study | Exclude: Some patients had nerve only and a small number had muscle biopsy as well. Outcomes are no delineated by the type of biopsies (i.e., nerve only vs nerve & muscle) |
| E. B. Blau | 1977 | Polyarteritis nodosa in older children | Exclude: No nerve biopsies are reported. |
| M. Sack | 1975 | Prognostic factors in polyarteritis | Exclude: No nerve biopsies reported. |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 4:** In patients with newly-diagnosed PAN with active and severe disease, what is the impact of pulse intravenous glucocorticoids compared to high dose oral glucocorticoids disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, serious adverse events, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)

10. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of pulse intravenous glucocorticoids compared to high dose oral glucocorticoids disease-related outcomes and treatment-related adverse events?
    No comparative data available

11. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of pulse intravenous glucocorticoids disease-related outcomes and treatment-related adverse events?
    No single arm data available

12. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of high dose oral glucocorticoids disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| M. Samson | 2014 | Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors | Exclude. This study was a long term follow up study of a prospective randomized trial. And many patients were already treated with Imuran or Cytoxan on follow up |
| M. Maeda | 1997 | Clinical observation of 14 cases of childhood polyarteritis nodosa in Japan | Exclude. Majority of patients were also treated with Imuran or Cytoxan. Also only a survey study. |
| M. Gordon | 1993 | Relapses in patients with a systemic vasculitis | Exclude. Prednisone were given together in combination with Cytoxan or imuran |
| L. Guillevin | 1992 | Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients | Exclude. Study included PAN and EGPA together and considered as same disease group. |
| L. Guillevin | 1988 | Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients | Exclude. Study included PAN and EGPA together and considered as same disease group |
| E. B. Blau | 1977 | Polyarteritis nodosa in older children | Exclude. Study included 2 patients who received IV pulse steroids and 9 had 2 mg/kg/day dose. Outcomes were not differentiated according to steroid dosing |
| M. Sack | 1975 | Prognostic factors in polyarteritis | Exclude. Study included “polyarteritis” patients. Cannot be classified as PAN |
| P. P. Frohnert | 1967 | Long-term follow-up study of periarteritis nodosa | Exclude. Study involved “periarteritis nodosa” and likely included EGPA patients |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 5:** In patients with newly-diagnosed PAN with active and severe disease, what is the impact of cyclophosphamide with high dose glucocorticoids vs. high dose glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hyperglycemia, decreased bone mineral density)

13. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of cyclophosphamide with high dose glucocorticoids vs. high dose glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | of cyclophosphamide with high dose glucocorticoid | high dose glucocorticoids alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Death within 2 years of disease onset** | | | | | | | | | | | | |
| 1 | observational studies | serious [a] | not serious | not serious | very serious [b] | strong association | 4/9 (44.4%) | 9/36 (25.0%) | **OR 2.40** (0.53 to 10.93) | **194 more per 1,000** (from 100 fewer to 535 more) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio

## Explanations

a. Patients may have received prior treatment at outside institutions, unclear how this was determined- patients may have received other treatments not documented

b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:

| Author | Year | Title |
|---|---|---|
| R. D. Cohen | 1980 | Clinical features, prognosis, and response to treatment in polyarteritis |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 6:** In patients with newly-diagnosed PAN with active and severe disease, what is the impact of cyclophosphamide vs. other non-glucocorticoid non-biologic immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia)

14. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of cyclophosphamide vs. other non-glucocorticoid non-biologic immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?
    No comparative data available

15. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of cyclophosphamide on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results |
|---|---|---|---|---|---|---|
| Survival was reported by one study with 24 patients followed up for 10 years, with 90% at 5 years and 80% at 10 years. | Samson, 2017 | RCT | 10 years | 24 PAN patients | CYC in 6 and 12 pulse doses + GC. | Overall 5-year survival 90%, 10-year survival 80%. Disease-free survival 5-10 years 58% |
| Sustained remission was reported by 6 studies with 114 patients and rates ranging from 100% at 2 years follow-up and 41% at 13 years of follow-up. | Samson, 2017 | RCT | 10 years | 24 PAN patients | CYC in 6 and 12 pulse doses + GC. | 15/24 (62.5%) |
| | Guillevin, 2013 | RCT | The mean (SD) followup was 32 (21) months | 18 PAN patients | CYC in 6 and 12 pulse doses + GC. | 100% |
| | Gayraud, 1997 | RCT | Mean follow-up 60.82 (14.5) months | 17 PAN patients | Oral or IV CYC + GC | 15/17 (88%) |
| | Boki, 1997 | Retrospective case-series | 13 years | 22 PAN patients | Oral or IV CYC + GC | 9/22 (41%) |
| | Gupta, 1997 | Retrospective case-series | 9 years | 17 PAN patients | IV CYC pulses + GC | 14/17 (82%) |

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| | Fauci, 1979 | Case-series | 11 years | 16 PAN patients | CYC 2mg/kg/day | 14/16 (87.5%) |
| Relapses were reported by 5 studies with 145 patients and rates ranging from 6% to 39% and follow-ups ranging from 32 months to 9 years. | Samson, 2017 | RCT | 10 years | 24 PAN patients | CYC in 6 and 12 pulse doses + GC. | 7/24 (29%) |
| | Eleftheriou, 2013 | Retrospective case-series | Median follow-up 6 years (range 1.5–16 years). | 69 pediatric patients with PAN | IV cyclophosphamide at 500–750 mg/m2 (maximum 1.2 gm) for a total of 3 or 6 doses | Lower risk of relapse with an increased cumulative CYC dose (HR 0.995 [95% CI 0.795–0.995], P 0.005), in a multivariable model HR 0.895 [95% CI 0.795–0.998], P 0.003. |
| | Guillevin, 2013 | RCT | The mean (SD) followup was 32 (21) months | 18 PAN patients | CYC in 6 and 12 pulse doses + GC. | 7/18 (39%) |
| | Gayraud, 1997 | RCT | Mean follow-up 60.82 (14.5) months | 17 PAN patients | Oral or IV CYC + GC | 1/17 (6%) |
| | Gupta, 1997 | Retrospective case-series | 9 years | 17 PAN patients | IV CYC pulses + GC | 2/14 (14%) |
| Death was reported by 5 studies with 98 patients and ranged from 6% to 18% with follow-ups from 32 months up to 13 years. | Samson, 2017 | RCT | 10 years | 24 PAN patients | CYC in 6 and 12 pulse doses + GC. | 2/24 (8%) |
| | Guillevin, 2013 | RCT | The mean (SD) followup was 32 (21) months | 18 PAN patients | CYC in 6 and 12 pulse doses + GC. | 2/18 (11%) |
| | Gayraud, 1997 | RCT | Mean follow-up 60.82 (14.5) months | 17 PAN patients | Oral or IV CYC + GC | 1/17 (6%) |
| | Boki, 1997 | Retrospective case-series | 13 years | 22 PAN patients | Oral or IV CYC + GC | 3/22 (14%) |
| | Gupta, 1997 | Retrospective case-series | 9 years | 17 PAN patients | IV CYC pulses + GC | 3/17 (18%) |
| SAE was reported by one study with 22 patients and follow-up | Boki, 1997 | Retrospective case-series | 13 years | 22 PAN patients | Oral or IV CYC + GC | 44% |

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| of 13 years and rate of 44%. | | | | | | |

16. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of. other non-glucocorticoid non-biologic immunosuppressive therapy on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Single arm studies and test accuracy studies:

| Author | Year | Title |
|---|---|---|
| M. Samson | 2017 | Microscopic polyangiitis and non-HBV polyarteritis nodosa with poor-prognosis factors: 10-year results of the prospective CHUSPAN trial |
| D. Eleftheriou | 2013 | Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years |
| L. Guillevin | 2003 | Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients |
| M. Gayraud | 1997 | Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides |
| K. A. Boki | 1997 | Necrotizing vasculitis in Greece: clinical, immunological and immunogenetic aspects. A study of 66 patients |
| R. Gupta | 1997 | Outcome of polyarteritis nodosa in northern India |
| A. S. Fauci | 1979 | Cyclophosphamide therapy of severe systemic necrotizing vasculitis |

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|

| | | | |
|---|---|---|---|
| K. A. Quinn | 2018 | Comparison of magnetic resonance angiography and (18)F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis | Exclude. Not clear how many patients had PAN, and all PAN patients were in control group only. |
| Y. J. Oh | 2017 | Birmingham vasculitis activity score at diagnosis is a significant predictor of relapse of polyarteritis nodosa | Exclude. Mixed treatments, no analysis of treatments. |
| C. Pagnoux | 2015 | Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy | Exclude. Most patients are not with PAN. |
| M. Samson | 2014 | Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors | Exclude. Mixed population and treatments. |
| M. Samson | 2014 | Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors | Exclude. Mixed populations and outcomes are not related to treatments. |
| C. Ribi | 2010 | Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients | Exclude. Mixed population. |
| D. Selga | 2006 | Polyarteritis nodosa when applying the Chapel Hill nomenclature--a descriptive study on ten patients | Exclude. Mixed and few patients. |
| C. Pagnoux | 2005 | Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis | Exclude. Mixed treatments. |
| M. Gordon | 1993 | Relapses in patients with a systemic vasculitis | Exclude. Mixed treatments. |
| S. H. Hawke | 1991 | Vasculitic neuropathy. A clinical and pathological study | Exclude. Mixed treatments. |
| R. D. Cohen | 1980 | Clinical features, prognosis, and response to treatment in polyarteritis | Exclude. Mixed treatments. |
| E. S. Leib | 1979 | Immunosuppressive and corticosteroid therapy of polyarteritis nodosa | Exclude. Mixed treatments. |
| G. Le Guenno | 2011 | Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides | Exclude. Mixed patients. |

# POLYARTERITIS NODOSA (PAN)

**Treatment**

- **PICO question 7:** In patients with newly-diagnosed PAN with active and severe disease, what is the impact of plasmapheresis combined with cyclophosphamide and glucocorticoids vs. cyclophosphamide and glucocorticoids alone on disease-related outcomes and treatment-related adverse events

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, toxicity leading to discontinuation (e.g., leukopenia, hyperglycemia, bleeding)

17. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of plasmapheresis combined with cyclophosphamide and glucocorticoids vs. cyclophosphamide and glucocorticoids alone on disease-related outcomes and treatment-related adverse events

| 18. Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | plasmapheresis combined with cyclophosphamide and glucocorticoids | cyclophosphamide and glucocorticoids alone | Relative (95% CI) | Absolute (95% CI) | | |
| **Relapse** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | very serious [b] | none | 4/28 (14.3%) | 3/34 (8.8%) | **OR 1.72** (0.35 to 8.44) | **54 more per 1,000** (from 55 fewer to 361 more) | ⨁◯◯◯ VERY LOW | |
| **Mortality** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | very serious [b] | strong association | 7/28 (25.0%) | 4/34 (11.8%) | **OR 2.50** (0.65 to 9.64) | **132 more per 1,000** (from 38 fewer to 445 more) | ⨁⨁◯◯ LOW | |
| **Cure - No vasculitis activity after 18 months of no treatment** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a] | not serious | not serious | very serious [b] | none | 16/28 (57.1%) | 22/34 (64.7%) | **OR 0.73** (0.26 to 2.03) | **75 fewer per 1,000** (from 324 fewer to 141 more) | ⨁◯◯◯ VERY LOW | |

**CI:** Confidence interval; **OR:** Odds ratio

## Explanations

a. There is no mention of the randomization process and of allocation concealment
b. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth, leading to very serious imprecision

- **References:**

- Randomized controlled trials:

| Author | Year | Title |
|---|---|---|
| L. Guillevin | 1995 | Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 8:** In patients with newly-diagnosed PAN with active and severe disease, what is the impact of using non-glucocorticoid non-biologic immunosuppressive therapy (excluding cyclophosphamide) with glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hyperglycemia, hepatotoxicity)

19. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of using non-glucocorticoid non-biologic immunosuppressive therapy (excluding cyclophosphamide) with glucocorticoids vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
    No comparative data available

20. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of using non-glucocorticoid non-biologic immunosuppressive therapy (excluding cyclophosphamide) with glucocorticoids on disease-related outcomes and treatment-related adverse events?
    No single arm data avaialble

21. In patients with newly-diagnosed PAN with active and severe disease, what is the impact of using glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Survival outcome | Leib, 1979 | Retrospective chart review | | 29 polyarteritis nodosa patients who received corticosteroids alone | Corticosteroids (prednisone, cortisone, methylprednisolone, betamethasone, ACTH) given at discretion of treating physician | Median survival time was 63 months. 5 year survival rate was 53%. | Indirect.<br><br>May have included EGPA patients (based on older vasculitis classificantion criteria<br><br>Other treatment group received cytoxan |
| | Cohen, 1980 | Retrospective chart review | Mean 3.3 years | 36 PAN patients who were treated with corticosteroids alone | Corticosteroids | Only 22 out of 36 patients were alive when last seen | Other treatment group received cytoxan |

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

| Author | Year | Title |
|---|---|---|
| R. D. Cohen | 1980 | Clinical features, prognosis, and response to treatment in polyarteritis |
| E. S. Leib | 1979 | Immunosuppressive and corticosteroid therapy of polyarteritis nodosa |

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| M. Samson | 2014 | Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors | Exclude. This study was a long term follow up study of a prospective randomized trial. And many patients were already treated with Cytoxan on follow up |
| S. H. Hawke | 1991 | Vasculitic neuropathy. A clinical and pathological study | Exclude. Some patients had received Cytoxan. Analysis also included patients with RA, lupus, EGPA, SS, GPA, cryo |
| L. Quint | 1991 | Hepatitis C virus in patients with polyarteritis nodosa. Prevalence in 38 patients | Exclude. Only 6 HBV negative PAN patients received steroids |
| M. Sack | 1975 | Prognostic factors in polyarteritis | Exclude. Study included "polyarteritis" patients. Cannot be classified as PAN |
| P. P. Frohnert | 1967 | Long-term follow-up study of periarteritis nodosa | Exclude. Study involved "periarteritis nodosa" and likely included EGPA patients |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 9:** In patients with newly-diagnosed PAN who have achieved remission with cyclophosphamide, what is the impact of transitioning to another non-glucocorticoid non-biologic immunosuppressive agent vs. continuing with cyclophosphamide on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

22. In patients with newly-diagnosed PAN who have achieved remission with cyclophosphamide, what is the impact of transitioning to another non-glucocorticoid non-biologic immunosuppressive agent vs. continuing with cyclophosphamide on disease-related outcomes and treatment-related adverse events?
    No comparative data available

23. In patients with newly-diagnosed PAN who have achieved remission with cyclophosphamide, what is the impact of transitioning to another non-glucocorticoid non-biologic immunosuppressive agent on disease-related outcomes and treatment-related adverse events?
    No single arm data available

24. In patients with newly-diagnosed PAN who have achieved remission with cyclophosphamide, what is the impact of continuing with cyclophosphamide on disease-related outcomes and treatment-related adverse events?

No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| M. Samson | 2017 | Microscopic polyangiitis and non-HBV polyarteritis nodosa with poor-prognosis factors: 10-year results of the prospective CHUSPAN trial | Exclude. Does not address PICO question. No maintenance therapy given/analyzed |
| C. Pagnoux | 2015 | Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy | Exclude. Only has 3 PAN patients in experimental group, 7 PAN patients in control group. Analysis were done as collectively with GPA/EGPA/MPA/PAN |
| L. Guillevin | 2003 | Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients | Exclude. No maintenance therapy was given after Cytoxan induction therapy |
| M. Gayraud | 1997 | Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides | Exclude. No maintenance therapy was given after Cytoxan induction therapy |
| A. S. Fauci | 1979 | Cyclophosphamide therapy of severe systemic necrotizing vasculitis | Excluded. Study included “systemic necrotizing vasculitis” and not classified as PAN |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 10:** In patients with newly-diagnosed PAN with active disease and severe manifestations, what is the impact of cyclophosphamide vs. rituximab on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

25. In patients with newly-diagnosed PAN with active disease and severe manifestations, what is the impact of cyclophosphamide vs. rituximab on disease-related outcomes and treatment-related adverse events?
    No comparative data available

26. In patients with newly-diagnosed PAN with active disease and severe manifestations, what is the impact of cyclophosphamide on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Remission<br><br>56/75 (~75%) of PAN patients treated with CYC were able to achieve remission. Favors use of Cyc | Samson M, 2017 | Prospective, randomized, multicenter | 10 years | 64 patients with non-HBV PAN or MPA with poor prognosis (based on FFS> or equal to 1) randomized to 12 (23 MPA, 10 PAN) or 6 (17 MPA, 14 PAN) pulses of CYC followed up after 10 years. Total of 24 PAN patients in trial. 11 patients lost to follow up | All patients rec'd pulse MP II15mg/kg/d) followed by pred 1mg/kg/d (progressively tapered). Randomized to either 12 or 6 CYC pulses (every 2 weeks for 1 month, then q 4 weeks)<br><br>Remission=absence of disease activity attributable to vasculitis for 3 months with bvas of 0, not requiring being off or on a specified GC dose. | 14 PAN patients received 6 IV pulses of CYC. 1/14 failed and 13/14 achieved remission<br><br>10 PAN patients received 12 pulses of IV cyc. 8/10 achieved remission, and 2 failed<br><br>Total of 21/24(88%) PAN patients achieved remission with IV CYC | *11/64 patients lost to follow up |
| | Boki, 1997 | Single center retrospective | | Review of 36 GPA, 22 PAN, 7 EGPA patients. Evaluated demographics, immunogenetic background, treatment. | Treatment group 1: 19 PAN patients, monthly IV pulse CYC)<br>Treatment group 2: 4 PAN patients (oral cyc) | 9/22 patients with PAN treated with cyc (IV or oral) experienced remisson at a median of 9-24 months. | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Gupta, 1997 | Single center retrospective | 5 years (median) | 17 patients with PAN (HBsAg negative) | Treated with oral pred 1mg/kg/d for 6 weeks and tapered over 6 mos. Monthly IV Cyc (15mg/kg) for first 6 months, followed by 3 monthly pulses for a total of 2 years | 14/17 achieved remission after a median of 5 months | |
| | Gordon, 1993 | Single center prospective | Median 33 months | 150 patients with vasculitis (WG-28 limited GPA-15, PAN 12, MPA 95) | Treatment was either 3 doses IV steroid followed by oral CYC for 3-6 months, then aza OR pulse intermittent cyclophosphamide and pred IV x 3 doses switched to oral pred and continued for 18 months. Patients with pulm hem or diffuse crescentic GC were given plasma exchange as well.<br><br>*Of the cPAN patients, 11/12 had the IV regimen | 12/12 PAN patients achieved remission<br><br>Remission=absence of clinical sx's of vasculitis, resolution of pulm changes or stable changes c/w scarring and stabilization or improvement of renal disease | |
| Relapse-<br><br>48 patients in total studies with 14 relapses (29% of PAN patients who achieve remission have a | Samson M, 2017 | Prospective, randomized, multicenter | 10 years | 64 patients with non-HBV PAN or MPA with poor prognosis (based on FFS> or equal to 1) randomized to 12 (23 MPA, 10 PAN) or 6 (17 MPA, 14 PAN) pulses of CYC followed up after 10 years. Total of 24 PAN patients in trial. 11 | All patients rec'd pulse MP II15mg/kg/d) followed by pred 1mg/kg/d (progressively tapered). Randomized to either 12 or 6 CYC pulses (every 2 weeks for 1 month, then q 4 weeks)<br><br>Relapse=recurrence, worsening or new clinical PAN/MPA manifestations following at least 3 months in remission | Of the 13 PAN patients who achieved remission, 8 had sustained remission and 5 had relapses (in the 6 dose group).<br>Of the 9 who achieved remission with 12 doses, 7 had sustained remission and 2 had relapses. | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| relapse). Favors using cyc, but still signif relapse rate | | | | patients lost to follow up | | In total, 7 of the 22 (32%) PAN patients suffered from relapses | |
| | Eleftheriou, 2013 | Single center, retrospective | | 69 children with PAN (median age 8.5). Cutaneous PAN excluded. Followed for at least 1 year. | Demographics, labs, treatments, relapse, morbitities/SAEs reviewed and recorded<br><br>57/69 (83%) rec'd CYC—33 oral and 24 IV.<br><br>Pulse cyc was 500-750mg/m2 for 6 doses monthly in 17 patients. In 10 patients regimen was 500-750mg/m2 q 14 days for 3 doses and then montly for 2-4doses.<br><br>Oral Cyc was given at 1-2mg/kg/d for 2-4 months.<br><br>All patients got IV pulse steroids of 30mg/kg/d x 3 days followed by taper of oral steroids over 12-28 months | Cumulative cyc dose associated with risk of relapse HR 0.895 (0.792-0.998), p=0.005 | |
| | Gupta, 1997 | Single center retrospective | 5 years (median) | 17 patients with PAN (HBsAg negative) | Treated with oral pred 1mg/kg/d for 6 weeks and tapered over 6 mos. Monthly IV Cyc (15mg/kg) for first 6 months, followed by 3 monthly pulses for a total of 2 years | 2 of the 14 who achieved remission experienced a relapse during follow up | |
| | Gordon, 1993 | Single center prospective | Median 33 months | 150 patients with vasculitis (WG-28 limited GPA-15, PAN 12, MPA 95) | Treatment was either 3 doses IV steroid followed by oral CYC for 3-6 months, then aza OR | Relapses occurred in 5/12 (41.7%) of PAN patients after a median of 33 months (7-57) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | pulse intermittent cyclophosphamide and pred IV x 3 doses switched to oral pred and continued for 18 months. Patients with pulm hem or diffuse crescentic GC were given plasma exchange as well.<br><br>*Of the cPAN patients, 11/12 had the IV regimen | Relapse= re-emergence of new clinical sx's of vasculitis or worsening original manifestations | |
| Death<br><br>8/31 PAN patients tx's with CYC died | Samson M, 2017 | Prospective, randomized, multicenter | 10 years | 64 patients with non-HBV PAN or MPA with poor prognosis (based on FFS > or equal to 1) randomized to 12 (23 MPA, 10 PAN) or 6 (17 MPA, 14 PAN) pulses of CYC followed up after 10 years. Total of 24 PAN patients in trial. 11 patients lost to follow up | All patients rec'd pulse MP II15mg/kg/d) followed by pred 1mg/kg/d (progressively tapered). Randomized to either 12 or 6 CYC pulses (every 2 weeks for 1 month, then q 4 weeks) | Of the total PAN patients treated with CYC (n=24), 5 died (4 in the 6 dose group) | |
| | Gupta, 1997 | Single center retrospective | 5 years (median) | 17 patients with PAN (HBsAg negative) | Treated with oral pred 1mg/kg/d for 6 weeks and tapered over 6 mos. Monthly IV Cyc (15mg/kg) for first 6 months, followed by 3 monthly pulses for a total of 2 years | 3/17 died | |
| | Gordon, 1993 | Single center prospective | Median 33 months | 150 patients with vasculitis (WG-28 | Treatment was either 3 doses IV steroid followed by oral CYC for 3-6 | 0/12 with PAN died | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | limited GPA-15, PAN 12, MPA 95) | months, then aza OR pulse intermittent cyclophosphamide and pred IV x 3 doses switched to oral pred and continued for 18 months. Patients with pulm hem or diffuse crescentic GC were given plasma exchange as well.<br><br>*Of the cPAN patients, 11/12 had the IV regimen | | |
| VDI<br><br>24 patients with VDi of 2.0 (no comparato r group of VDI w/o tx). Favors use of CYC | Samson M, 2017 | Prospective, randomized, multicenter | 10 years | 64 patients with non-HBV PAN or MPA with poor prognosis (based on FFS> or equal to 1) randomized to 12 (23 MPA, 10 PAN) or 6 (17 MPA, 14 PAN) pulses of CYC followed up after 10 years. Total of 24 PAN patients in trial. 11 patients lost to follow up | All patients rec'd pulse MP II15mg/kg/d) followed by pred 1mg/kg/d (progressively tapered). Randomized to either 12 or 6 CYC pulses (every 2 weeks for 1 month, then q 4 weeks) | Of the 24 PAN patients, VDI at 120 months was 2.0 +/-1.6 | |
| Adverse Events (Major/Infe ction)<br><br>3/17 with TB (1 disemmina ted). Still | Gupta, 1997 | Single center retrospective | 5 years (median) | 17 patients with PAN (HBsAg negative) | Treated with oral pred 1mg/kg/d for 6 weeks and tapered over 6 mos. Monthly IV Cyc (15mg/kg) for first 6 months, followed by 3 monthly pulses for a total of 2 years | 2/17 developed pulmonary TB, 1 developed disseminated TB | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| favors use of CYC | | | | | | | |
| Minor AEs<br><br>17 total patients, minor SEs, favors using CYC | Gupta, 1997 | Single center retrospective | 5 years (median) | 17 patients with PAN (HBsAg negative) | Treated with oral pred 1mg/kg/d for 6 weeks and tapered over 6 mos. Monthly IV Cyc (15mg/kg) for first 6 months, followed by 3 monthly pulses for a total of 2 years | 14/17 developed SE of GI intolerance, 7 had alopecia | |
| Disease Progression<br><br>Of 22 PAN patients, 4 developed nephritis/renal failure and 7 developed mononeuritis. Does not fully favor use of Cyc | Boki, 1997 | Single center retrospective | | Review of 36 GPA, 22 PAN, 7 EGPA patients. Evaluated demographics, immunogenetic background, treatment. | Treatment group 1: 19 PAN patients, monthly IV pulse CYC)<br>Treatment group 2: 4 PAN patients (oral cyc) | 4/22 developed nephritis/ renal failure and required dialysis<br><br>7/22 developed mononeurtitis | |

27. In patients with newly-diagnosed PAN with active disease and severe manifestations, what is the impact of rituximab on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Single arm studies and test accuracy studies: (9)

| Author | Year | Title |
|---|---|---|
| M. Samson | 2017 | Microscopic polyangiitis and non-HBV polyarteritis nodosa with poor-prognosis factors: 10-year results of the prospective CHUSPAN trial |
| D. Eleftheriou | 2013 | Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years |
| K. A. Boki | 1997 | Necrotizing vasculitis in Greece: clinical, immunological and immunogenetic aspects. A study of 66 patients |
| R. Gupta | 1997 | Outcome of polyarteritis nodosa in northern India |
| M. Gordon | 1993 | Relapses in patients with a systemic vasculitis |

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| C. Pagnoux | 2015 | Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy | Exclude: Only 3 patients with PAN and outcomes for that subgroup not separately reported |
| L. Guillevin | 2003 | Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients | Exclude: Same population as M. Samson 2017 (Microscopic polyangiitis and non-HBV polyarteritis with poor prognostic factors: 10-year results of the prospective CHUSPAN trial), without extra relevant data |
| M. Gayraud | 1997 | Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides | Exclude: Only included FFS of 0, so non-severe disease. |
| L. Guillevin | 1988 | Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients | Exclude: Results reported for combination of EGPA and PAN and no clear separation in results of those who rec'd CYC as induction |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 11:** In patients with newly-diagnosed PAN in remission after remission induction therapy, what is the impact of a rapid taper of glucocorticoids (<6 months) vs. a slow taper (≥ 6 months) on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, infection, toxicity leading to discontinuation (e.g., hyperglycemia), other glucocorticoid toxicity (e.g., decreased bone mineral density)

28. In patients with newly-diagnosed PAN in remission after remission induction therapy, what is the impact of a rapid taper of glucocorticoids (<6 months) vs. a slow taper (≥ 6 months) on disease-related outcomes and treatment-related adverse events?
    No comparative data available

29. In patients with newly-diagnosed PAN in remission after remission induction therapy, what is the impact of a rapid taper of glucocorticoids (<6 months) on disease-related outcomes and treatment-related adverse events?
    No single arm data available

30. In patients with newly-diagnosed PAN in remission after remission induction therapy, what is the impact of a slow taper (≥ 6 months) on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| P. P. Frohnert | 1967 | Long-term follow-up study of periarteritis nodosa | Did not abstract data from article. Very unclear which patients achieved remission and what the actual steroid course length was in those who did |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 12:** In patients with newly diagnosed PAN with active and non-severe disease, what is the impact of adding of non-glucocorticoid non-biologic immunosuppressive therapy to glucocorticoids vs. using glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hyperglycemia, decreased bone mineral density)

31. In patients with newly diagnosed PAN with active and non-severe disease, what is the impact of adding of non-glucocorticoid non-biologic immunosuppressive therapy to glucocorticoids vs. using glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
    No comparative data available

32. In patients with newly diagnosed PAN with active and non-severe disease, what is the impact of adding of non-glucocorticoid non-biologic immunosuppressive therapy to glucocorticoids on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| **Relapse**<br><br>9/12 PAN patients tx'd with non-GC non-giologic IS had a relapse. Favors not using this interventio n | Oh Y, 2017 | Retrospective, single center | Mean follow up 64.1 months | 30 patients with newly diagnosed PAN (6 with cutaneous PAN, 14 Hep B associated and 10 generalized idiopathic) followed for >12 months. Mean BVAS of 10.1 +/-9.5 | Of the 30 PAN patients, induction with non biologic, non-GC agent was used in 7 patients (4 aza, 1 MTX, 1 mycophenolate, 1 colchicine). GC monotherapy was used for induction in 14 | 3/7 patients treated with non-GC, non-biologic IS did NOT relapse, 4/7 did relapse | *did not stratify tx strategy based on disease severity, so does not exactly answer the pico |
| | Selga, 2006 | Retrospective, single center | Median follow up 14 years (14-45) | 10 patients with PAN. 6 had FFS=0 | Of the 6 PAN patients with FFS=0, 2 were treated with AZA (+GC) and 4 were treated with CYC (+GC) | Of the 5 PAN patients who achieved remission with CYC or AZA +GC, all of them suffered a relapse (after a mean of | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 3 years, range 0.7 years-6.8 years) | |
| Remission<br><br>5/6 achieved remission with non GC and non-biologic IS. Favors using the drug | Selga, 2006 | Retrospective, single center | Median follow up 14 years (14-45) | 10 patients with PAN. 6 had FFS=0 | Of the 6 PAN patients with FFS=0, 2 were treated with AZA (+GC) and 4 were treated with CYC (+GC) | 1/6 died and did not achieve remission (tx with cyc)<br><br>5/6 achieved remission | |
| Survival<br><br>Poor data as noted in comments and not all in analysis were on the non-GC non-bio regeimen. However of 22 PAN pts, survival at 5 years was 80% | Leib, 1979 | Retrospective, single center | | 64 patients with PAN with multisystem involvement. No cutaneous PAN (only). Confirmed by bx in 34, by autopsy in 13 and angiography in 10 | Group 1: 8 received supportive therapy, Group 2: 34 received GC alone, Group 3: 22 received both GC + IS agent.<br><br>*5 patients in group 2 and 1 patient in group 3 excluded from survival studies 2/2 insufficient length of therapy | Median survival in GC +other group was 149 months with 5 year survival of 80%. 16/22 were on non bio non GC med (14 aza, 1 6mp, 1 MTX) | Includes severe and non-severe PAN. Did not differentiate outcomes of therapies in non-severe cohort |

33. In patients with newly diagnosed PAN with active and non-severe disease, what is the impact of using glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

- **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Remission<br><br>115 patients. 93 achieved remission with CS alone (80%). Favors using CS along | Samson 2014 | Retrospective, multicenter | 97.6 +/- 39.6 months | 193 patients (75 EGPA, 61 MPA and 57 non-HBV PAN) with FFS=0. 86/193 required additional IS | All patients received CS alone as initial induction tx. 24/57 PAN patients required add on therapy. | 48/57 (84%) of PAN patients achieved remission with CS alone. (remission >3 months) | Additional IS tx added only after relapse or failure (not up front) |
| | Ribi 2010 | Prospective multicenter therapeutic trial | 62+/-33 months | 124 patients with newly diagnosed PAN (n=58) or MPA (n=66) (FFS of 0). No alveolar hemorrhage or severe renal impairment | Treatment with steroids alone. At time of treatment failure or relapse (or unable to wean pred below 20mg/d), patients were randomized to oral azathioprine 2mg/kg or cyclophosphamide 6 IV pulses (600mg/m2). One IV methyl pred pulse of 15mg/kg was allowed followed by dose of 1mg/kg/day for 3 weeks. Tapered by 5mg every 10 days to dose of 0.5mg/kg/day, then by 2.5mg every 10 days until a dose of 15mg/day, and finally by 1mg every 10 days to the minimal effective dose or when possible, until withdrawal | 45/58 patient with PAN achieved remission with CS alone | |
| Death | Cohen, 1980 | Retrospective, single center | At least 2 years. | 53 patients with PAN. At least 2 | 36 treated with GC alone, 14 with combination of GC +cytotoxic agent (CYC | 14/36 treated with GC alone died. 7 from active | Includes severe and non-severe PAN. Did not differentiate outcomes |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 14/36 treated with GC alone died (of note they included severe AND non-severe PAN in their cohort). Does not favor intervention but weak data | | | Mean 3.3 years | organ systems involved. | n=9 or aza n=5), 3 with no tx.<br>In those treated with GC, initial dose was >40mg/d. those who were started on steroids prior to evaluation at this center (n=19, were seen ~6 months prior). When activity of disease was controlled, the steroid dose was reduced to lowest possible (usually between 10-15mg/d) | vasculitis, 7 from other causes | of therapies in non-severe cohort |
| Survival<br><br>144 patients tx'd with GC alone, 5 year survival was 48-53%. Not very high. Does not favor intervention but included severe and non-severe PAN | Leib, 1979 | Retrospective, single center | | 64 patients with PAN with multisystem involvement. No cutaneous PAN (only). Confirmed by bx in 34, by autopsy in 13 and angiography in 10 | Group 1: 8 received supportive therapy, Group 2: 34 received GC alone, Group 3: 22 received both GC + IS agent.<br><br>*5 patients in group 2 and 1 patient in group 3 excluded from survival studies 2/2 insufficient length of therapy | Median survival in GC alone was 63 moths<br>5 year survival was 53%<br><br>22/34 GC only were on >50mg pred/d equivalent | Includes severe and non-severe PAN. Did not differentiate outcomes of therapies in non-severe cohort |
| | Frohnert, 1967 | Retrospective single center | | Records of 130 patients with periarteritis nodosa seen at mayo from 1946-1962 reviewed | Intensive corticosteroid or ACTH therapy had been given to 110 of these patients. Usual course was 200mg cortisone/d for 6 weeks then decreased by 12.5 to 25mg every 4-5 days | 5 year survival was 48% in those treated with GC (n=110) | Includes severe and non-severe PAN. Did not differentiate outcomes of therapies in non-severe cohort |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | until discontinued or maintenance dose established | | |
| Side effects<br><br>18/110 had SE of hypercortisolism and 2 osteoporosis. Not bad SE profile. Poor data overall | Frohnert, 1967 | Retrospective single center | | Records of 130 patients with periarteritis nodosa seen at mayo from 1946-1962 reviewed | Intensive corticosteroid or ACTH therapy had been given to 110 of these patients. Usual course was 200mg cortisone/d for 6 weeks then decreased by 12.5 to 25mg every 4-5 days until discontinued or maintenance dose established | 18/110 patients on steroids had sx's of hypercortisonism and osteoporosis in 2 | Includes severe and non-severe PAN. Did not differentiate outcomes of therapies in non-severe cohort |
| Relapse<br><br>4/14 with GC monotherapy relapsed. Favors the intervention | Oh Y, 2017 | Retrospective, single center | Mean follow up 64.1 months | 30 patients with newly diagnosed PAN (6 with cutaneous PAN, 14 Hep B associated and 10 generalized idiopathic) followed for >12 months. Mean BVAS of 10.1 +/-9.5 | Of the 30 PAN patients, induction with non biologic, non-GC agent was used in 7 patients (4 aza, 1 MTX, 1 mycophenolate, 1 colchicine). GC monotherapy was used for induction in 14 | 10/14 with GC monotherapy did not relapse, 4/14 did relapse | Includes severe and non-severe PAN. Did not differentiate outcomes of therapies in non-severe cohort |

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

| Author | Year | Title | Comments |
|---|---|---|---|
| Y. J. Oh | 2017 | Birmingham vasculitis activity score at diagnosis is a significant predictor of relapse of polyarteritis nodosa | Did not evaluate treatment/medications differences based on BVAS (non severe disease) |

| | | | |
|---|---|---|---|
| M. Samson | 2014 | Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors | Include |
| M. Samson | 2014 | Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors | Same PAN population as 16597 so didn't re-abstract data. Additional IS tx added only after relapse or failure (not up front) |
| C. Ribi | 2010 | Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients | Include |
| D. Selga | 2006 | Polyarteritis nodosa when applying the Chapel Hill nomenclature--a descriptive study on ten patients | Include |
| R. D. Cohen | 1980 | Clinical features, prognosis, and response to treatment in polyarteritis | Includes severe and non-severe PAN. Did not differentiate outcomes of therapies in non-severe cohort |
| E. S. Leib | 1979 | Immunosuppressive and corticosteroid therapy of polyarteritis nodosa | Includes severe and non-severe PAN. Did not differentiate outcomes of therapies in non-severe cohort |
| P. P. Frohnert | 1967 | Long-term follow-up study of periarteritis nodosa | Includes severe and non-severe PAN. Did not differentiate outcomes of therapies in non-severe cohort |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 13:** In patients with PAN in remission on non-glucocorticoid non-biologic immunosuppressive therapy, what is the impact of discontinuation of non-glucocorticoid non-biologic immunosuppressive therapy after 18 months vs. continued treatment on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hepatotoxicity)

34. In patients with PAN in remission on non-glucocorticoid non-biologic immunosuppressive therapy, what is the impact of discontinuation of non-glucocorticoid non-biologic immunosuppressive therapy after 18 months vs. continued treatment on disease-related outcomes and treatment-related adverse events?
    No comparative data available

35. In patients with PAN in remission on non-glucocorticoid non-biologic immunosuppressive therapy, what is the impact of discontinuation of non-glucocorticoid non-biologic immunosuppressive therapy after 18 months on disease-related outcomes and treatment-related adverse events?
No single arm data available

36. In patients with PAN in remission on non-glucocorticoid non-biologic immunosuppressive therapy, what is the impact of continued treatment on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Glucocorticoid reduction – One study of 8 patients who received long term CYC or AZA showed that 5 were able to discontinue GC. | Fauci, 1979 | Single Center, Retrospective study | Of the 8/17 that continued treatment for 18+ months follow up was 25 months – 5 years | 17 patients with "systemic necrotizing vasculitis" 8/17 continued treatment (i.e., had been followed) for greater than 18 months. | 7/8 received long term CYC 1/8 received AZA | 5/8 were able to discontinue glucocorticoids during their course | Indirect Pre-ANCA, but most patients likely represent PAN phenotype |
| Death – One study of 8 patients who received long term CYC or AZA showed that 2 died over the | Fauci, 1979 | Single Center, Retrospective study | Of the 8/17 that continued treatment for 18+ months follow up was 25 months – 5 years | 17 patients with "systemic necrotizing vasculitis" 8/17 continued treatment (i.e., had been followed) for greater than 18 months. | 7/8 received long term CYC 1/8 received AZA | 2/8 died during the course (one after 2 years of pneumonia, one at 5 years due to end stage renal and hepatic failure) | Indirect Pre-ANCA, but most patients likely represent PAN phenotype |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| observation period. | | | | | | | |

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:

  None

- Single arm studies and test accuracy studies:

| Author | Year | Title | Comments |
|---|---|---|---|
| A. S. Fauci | 1979 | Cyclophosphamide therapy of severe systemic necrotizing vasculitis | Included for PAN PICO 13, Indirect |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 14 :** In patients with PAN who has nerve and/or muscle involvement, what is the impact of physical therapy vs. no physical therapy on disease-related outcomes?

- **Critical Outcomes:** patient reported outcomes (SF36, EQ-5D, CHQ, Patient global assessment, PROMIS, RAPID3, or MDHAQ)

37. In patients with PAN who has nerve and/or muscle involvement, what is the impact of physical therapy vs. no physical therapy on disease-related outcomes?
    No comparative data available

38. In patients with PAN who has nerve and/or muscle involvement, what is the impact of physical therapy on disease-related outcomes?
    No single arm data available

39. In patients with PAN who has nerve and/or muscle involvement, what is the impact of no physical therapy on disease-related outcomes?
    No single arm data available

- **References:**

- Randomized controlled trials:

  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 15:** In patients with PAN with refractory disease on glucocorticoids alone, what is the impact of adding of cyclophosphamide vs. increasing the glucocorticoid dose alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hyperglycemia, decreased bone mineral density)

40. In patients with PAN with refractory disease on glucocorticoids alone, what is the impact of adding of cyclophosphamide vs. increasing the glucocorticoid dose alone on disease-related outcomes and treatment-related adverse events?
    No comparative data available

41. In patients with PAN with refractory disease on glucocorticoids alone, what is the impact of adding of cyclophosphamide on disease-related outcomes and treatment-related adverse events?
    - **Patient important outcomes:**

| Outcomes (Name + Summary) | Author, year | Study type | Duration of follow up | Population (number and description) | Intervention used in relevant population (Describe the intervention) | Results | Comments |
|---|---|---|---|---|---|---|---|
| Remission – Two heterogeneous study populations with 35 patients total who received CYC for | Fauci, 1979 | Single Center, retrospective study | Range 3 months to 5 years) | 17 patients with "systemic necrotizing vasculitis"<br>16/17 patients had been receiving GC and had "clear cut subjective and objective evidence of progression of | 16/17 received CYC 2mg/kg/d (titrated to maintain total neutrophil count no lower than 1000-1500 per $mm^3$)<br>1/17 received AZA | 13/16 achieved received "complete remission"<br>Mean duration of remission induced by CYC was 22 months (range two to 61 months) | Indirect<br>Pre-ANCA study, but most patients represent PAN/medium vessel phenotype<br>No definitions for "remission" |

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| refractory PAN, show that ~70% of patients will achieve remission. | | | | disease" when they entered the study (attn.: PICO population) | | | |
| | Ribi, 2010 | Population is from a multicenter, prospective, randomized, open label trial in France and UK (1993-2005) | Mean 66 months for PAN population in total | 58/124 had PAN (rest were MPA) – not distinguished at enrollment, only later by ANCA, histology, clinical features | 19 patients (7 with PAN, 12 MPA) were randomized to CYC when GC alone failed<br><br>All patients had FFS=0 initially<br>All patients treated with GC alone initially and then if/when that failed patients were randomized to receive 6 months of IV CYC or AZA | 13/19 patients achieved disease remission | Indirect<br>Heterogenous population<br>Complete remission was defined as the absence of clinical andbiologic manifestations of active vasculitis for at least 3 months |
| Reduction or cessation of glucocorticoids – One heterogenous study shows that around 2/3 of patients can reduce glucocortoicds if CYC is used in cases of refractory PAN. | Fauci, 1979 | Single Center, retrospective study | Range 3 months to 5 years) | 17 patients with "systemic necrotizing vasculitis"<br>16/17 patients had been receiving GC and had "clear cut subjective and objective evidence of progression of disease" when they entered the study (attn.: PICO population) | 16/17 received CYC 2mg/kg/d (titrated to maintain total neutrophil count no lower than 1000-1500 per $mm^3$)<br>1/17 received AZA | 11/16 patients were able to taper or cease use of glucocorticoids during their course<br>(if patients were only "converted" to alternate day regimens, these were not counted) | Indirect<br>Pre-ANCA study, but most patients represent PAN/medium vessel phenotype |
| | Ribi, 2010 | Population is from a multicenter, prospective, randomized, open label trial in France and UK (1993-2005) | Mean 66 months for PAN population in total | 58/124 had PAN (rest were MPA) – not distinguished at enrollment, only later by ANCA, histology, clinical features | 19 patients (7 with PAN, 12 MPA) were randomized to CYC when GC alone failed<br><br>All patients had FFS=0 initially<br>All patients treated with GC alone initially and | 4/13 who achieved remission had relapse (8 months, 19 months, 32 months, 63 months) | Indirect<br>Heterogenous population<br><br>Relapses were defined as therecurrence of at least 1 vasculitis manifestation. |

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| | | | | | then if/when that failed patients were randomized to receive 6 months of IV CYC or AZA | | |
| Death – Two heterogeneous study populations with 35 patients total who received CYC for refractory PAN demonstrate mortality rates between 19-32% over observation period. | Fauci, 1979 | Single Center, retrospective study | Range 3 months to 5 years) | 17 patients with "systemic necrotizing vasculitis"<br>16/17 patients had been receiving GC and had "clear cut subjective and objective evidence of progression of disease" when they entered the study (attn.: PICO population) | 16/17 received CYC 2mg/kg/d (titrated to maintain total neutrophil count no lower than 1000-1500 per $mm^3$)<br>1/17 received AZA | 3/16 died (one at 5 years of liver and kidney failure – disease in remission, one at 2 years due to pneumonia – disease in remission, one at 1 month from unknown cause – had leukopenia) | Indirect<br>Pre-ANCA study, but most patients represent PAN/medium vessel phenotype |
| | Ribi, 2010 | Population is from a multicenter, prospective, randomized, open label trial in France and UK (1993-2005) | Mean 66 months for PAN population in total | 58/124 had PAN (rest were MPA) – not distinguished at enrollment, only later by ANCA, histology, clinical features | 19 patients (7 with PAN, 12 MPA) were randomized to CYC when GC alone failed<br><br>All patients had FFS=0 initially<br>All patients treated with GC alone initially and then if/when that failed patients were randomized to receive 6 months of IV CYC or AZA | By end of follow up, 6/19 had died (5 of vasculitis, 1 of cardiac failure) | Indirect<br>Heterogenous population |
| Adverse Events – One study with heterogenous population of 19 patients | Ribi, 2010 | Population is from a multicenter, prospective, randomized, open label trial in France and UK (1993-2005) | Mean 66 months for PAN population in total | 58/124 had PAN (rest were MPA) – not distinguished at enrollment, only later by ANCA, histology, clinical features | 19 patients (7 with PAN, 12 MPA) were randomized to CYC when GC alone failed<br><br>All patients had FFS=0 initially<br>All patients treated with GC alone initially and | Data available on only 10 patients randomized to CYC<br>4 – Infection<br>5 – ophtho complications<br>2 – Osteoporotic fractures<br>2 – Thrombotic events | Indirect<br>Heterogenous population |

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| that received CYC (and GC) for refractory PAN shows treatment related adverse events of CYC and GC. | | | | | then if/when that failed patients were randomized to receive 6 months of IV CYC or AZA | | |

42. In patients with PAN with refractory disease on glucocorticoids alone, what is the impact of increasing the glucocorticoid dose alone on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Single arm studies and test accuracy studies:

| Author | Year | Title | Comments |
|---|---|---|---|
| C. Ribi | 2010 | Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients | Included for PAN PICO 15, Heterogenous population of PAN and MPA based on convention at the time of enrollment |
| A. S. Fauci | 1979 | Cyclophosphamide therapy of severe systemic necrotizing vasculitis | |

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|

| | | | |
|---|---|---|---|
| M. Samson | 2014 | Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors | Excluded for PAN PICO 15 single arm<br>No data available at the level of PAN patients that got CYC (analysis is of all patients – EGPA/PAN/MPA - that got "add on" – half CYC/half AZA) |
| M. Gordon | 1993 | Relapses in patients with a systemic vasculitis | Exclude for PAN PICO 15, not a refractory population |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 16:** In patients with PAN with refractory disease on glucocorticoids and cyclophosphamide, what is the impact of adding plasmapheresis vs. increasing immunosuppression on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, bleeding, hepatotoxicity)

43. In patients with PAN with refractory disease on glucocorticoids and cyclophosphamide, what is the impact of adding plasmapheresis vs. increasing immunosuppression on disease-related outcomes and treatment-related adverse events?
    No comparative data available

44. In patients with PAN with refractory disease on glucocorticoids and cyclophosphamide, what is the impact of adding plasmapheresis on disease-related outcomes and treatment-related adverse events?
    No single arm data available

45. In patients with PAN with refractory disease on glucocorticoids and cyclophosphamide, what is the impact of increasing immunosuppression on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| G. de Luna | 2015 | Plasma exchanges for the treatment of severe systemic necrotizing vasculitides in clinical daily practice: Data from the French Vasculitis Study Group | Excluded for PAN PICO 16 single arm, Only 5/152 patients were PAN |
| M. Samson | 2014 | Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors | Excluded for PAN PICO 16, only 3 PAN patients received PLEX, data not available at that level |
| M. Samson | 2014 | Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors | Excluded for PAN PICO 16, only 2 PAN or MPA patients received PLEX, data not available at that level |
| L. Guillevin | 1992 | Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients | Excluded from PAN PICO 16, not a refractory population |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 17:** In patients with PAN with refractory disease on glucocorticoids and non-glucocorticoid nonbiologic immunosuppressive therapy (excluding cyclophosphamide), what is the impact of switching to cyclophosphamide vs. increasing glucocorticoid dose alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hyperglycemia, hepatotoxicity)

46. In patients with PAN with refractory disease on glucocorticoids and non-glucocorticoid nonbiologic immunosuppressive therapy (excluding cyclophosphamide), what is the impact of switching to cyclophosphamide vs. increasing glucocorticoid dose alone on disease-related outcomes and treatment-related adverse events?
    No comparative data available

47. In patients with PAN with refractory disease on glucocorticoids and non-glucocorticoid nonbiologic immunosuppressive therapy (excluding cyclophosphamide), what is the impact of switching to cyclophosphamide on disease-related outcomes and treatment-related adverse events?

No single arm data available

48. In patients with PAN with refractory disease on glucocorticoids and non-glucocorticoid nonbiologic immunosuppressive therapy (excluding cyclophosphamide), what is the impact of increasing glucocorticoid dose alone on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
None

- Comparative observational studies:
None

- Single arm studies and test accuracy studies:
None

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| M. Gordon | 1993 | Relapses in patients with a systemic vasculitis | Excluded for PAN PICO 17, no relevant population to inform the PICO. All 12 PAN patients were receiving CYC. |

# POLYARTERITIS NODOSA (PAN)

## Treatment

- **PICO question 18:** In patients with PAN and Adenosine Deaminase 2 deficiency what is the impact of TNF-alpha inhibitors (e.g., infliximab, etanercept, adalimumab) versus glucocorticoids alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** disease activity, disease damage, relapse, death, malignancy, infection, toxicity leading to discontinuation (e.g., leukopenia, hyperglycemia)

49. In patients with PAN and Adenosine Deaminase 2 deficiency what is the impact of TNF-alpha inhibitors (e.g., infliximab, etanercept, adalimumab) versus glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
No comparative data available

50. In patients with PAN and Adenosine Deaminase 2 deficiency what is the impact of TNF-alpha inhibitors (e.g., infliximab, etanercept, adalimumab) on disease-related outcomes and treatment-related adverse events?
No single arm data available

51. In patients with PAN and Adenosine Deaminase 2 deficiency what is the impact of glucocorticoids alone on disease-related outcomes and treatment-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
None

- Comparative observational studies:
None

- Single arm studies and test accuracy studies:
None

- Studies reviewed and excluded:

| Author | Year | Title | Comment |
|---|---|---|---|
| Caorsi | 2017 | ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study | Exclude study, no data about treatment, although it is the population in question |

# POLYARTERITIS NODOSA (PAN)

## Monitoring

- **PICO question 19:** In patients with a history of severe PAN who is clinically asymptomatic but has newly elevated inflammatory markers without a clear etiology, what is the impact of vascular imaging (both invasive and non-invasive) vs. clinical assessment alone on disease-related outcomes and diagnostic testing-related adverse events?

- **Critical Outcomes:** radiation exposure, adverse reaction to contrast, disease activity, disease damage, relapse, death, adverse reaction to sedation (if needed)

52. In patients with a history of severe PAN who is clinically asymptomatic but has newly elevated inflammatory markers without a clear etiology, what is the impact of vascular imaging (both invasive and non-invasive) vs. clinical assessment alone on disease-related outcomes and diagnostic testing-related adverse events?
    No comparative data available

53. In patients with a history of severe PAN who is clinically asymptomatic but has newly elevated inflammatory markers without a clear etiology, what is the impact of vascular imaging (both invasive and non-invasive) on disease-related outcomes and diagnostic testing-related adverse events?
    No single arm data available

54. In patients with a history of severe PAN who is clinically asymptomatic but has newly elevated inflammatory markers without a clear etiology, what is the impact of clinical assessment alone on disease-related outcomes and diagnostic testing-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Single arm studies and test accuracy studies:
    None

# POLYARTERITIS NODOSA (PAN)

## Monitoring

- **PICO question 20 :** In patients with a history of severe PAN who is clinically asymptomatic, what is the impact of routine vascular imaging (both invasive and non-invasive) every 6 months vs. vascular imaging only prompted by clinical symptoms/signs on disease-related outcomes and diagnostic testing-related adverse events?

- **Critical Outcomes:** radiation exposure, adverse reaction to contrast, disease activity, disease damage, relapse, death, adverse reaction to sedation (if needed)

55. In patients with a history of severe PAN who is clinically asymptomatic, what is the impact of routine vascular imaging (both invasive and non-invasive) every 6 months vs. vascular imaging only prompted by clinical symptoms/signs on disease-related outcomes and diagnostic testing-related adverse events?
    No comparative data available

56. In patients with a history of severe PAN who is clinically asymptomatic, what is the impact of routine vascular imaging (both invasive and non-invasive) every 6 months prompted by clinical symptoms/signs on disease-related outcomes and diagnostic testing-related adverse events?
No single arm data available

57. In patients with a history of severe PAN who is clinically asymptomatic, what is the impact of vascular imaging only prompted by clinical symptoms/signs on disease-related outcomes and diagnostic testing-related adverse events?
No single arm data available

- **References:**

- Randomized controlled trials:
  None

- Comparative observational studies:
  None

- Single arm studies and test accuracy studies:
  None

- Studies reviewed and excluded:

| Author | Year | Title | Comments |
|---|---|---|---|
| P. Bouche | 1986 | Peripheral neuropathy in systemic vasculitis: clinical and electrophysiologic study of 22 patients | Excluded for PAN PICO 20. No relevant intervention to inform PICO. |

# POLYARTERITIS NODOSA (PAN)

## Monitoring

- **PICO question 21:** In patients with a history of peripheral motor neuropathy secondary to PAN, what is the effect of routine EMG/NCS every 6 months vs. routine neurologic exam alone on disease-related outcomes and treatment-related adverse events?

- **Critical Outcomes:** adverse reaction to EMG/NCS, disease activity, neurologic damage, relapse, death

58. In patients with a history of peripheral motor neuropathy secondary to PAN, what is the effect of routine EMG/NCS every 6 months vs. routine neurologic exam alone on disease-related outcomes and treatment-related adverse events?

No comparative data available

59. In patients with a history of peripheral motor neuropathy secondary to PAN, what is the effect of routine EMG/NCS every 6 months on disease-related outcomes and treatment-related adverse events?
    No single arm data available

60. In patients with a history of peripheral motor neuropathy secondary to PAN, what is the effect of routine neurologic exam alone on disease-related outcomes and treatment-related adverse events?
    No single arm data available

- **References:**

- Randomized controlled trials:
    None

- Comparative observational studies:
    None

- Single arm studies and test accuracy studies:
    None