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Immunotherapy guidelines in neuromuscular diseases

Quick guide for Physicians

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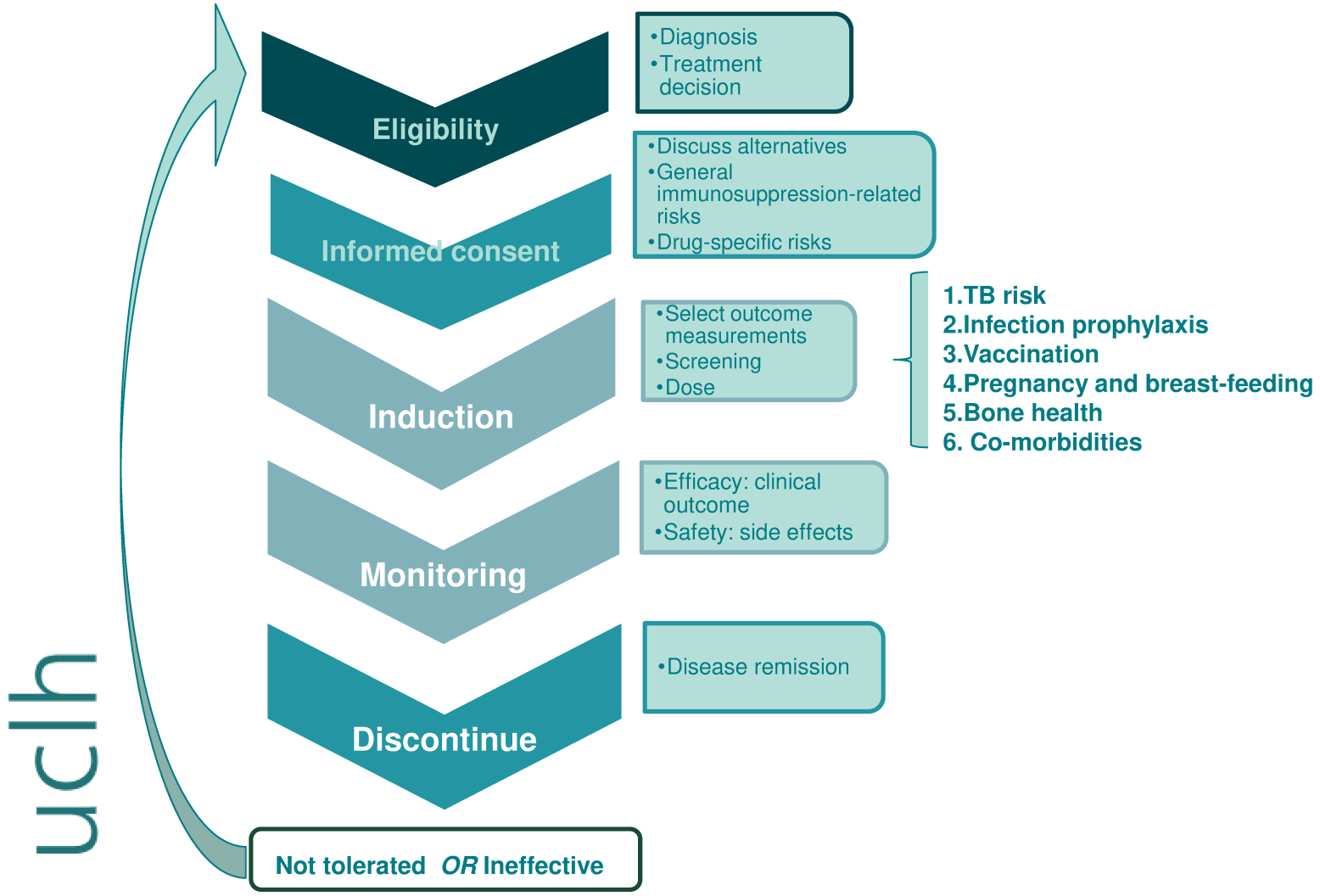
General recommendations



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Informed consent

* Discussion of adverse events: www.gmc-uk.org/guidance	
1.	Inform patients of all potential minor adverse events if they occur frequently (1/10 – 1/100)
2	In form patient of any **serious adverse event** even if likelihood is very small (<1/10,000).
Serious adverse event	An adverse outcome resulting in death, permanent or long-term physical disability or disfigurement, medium or long-term pain, or admission to hospital; or other outcomes with a long-term or permanent effect on a patient's employment, social or personal life (WHO, 1972).

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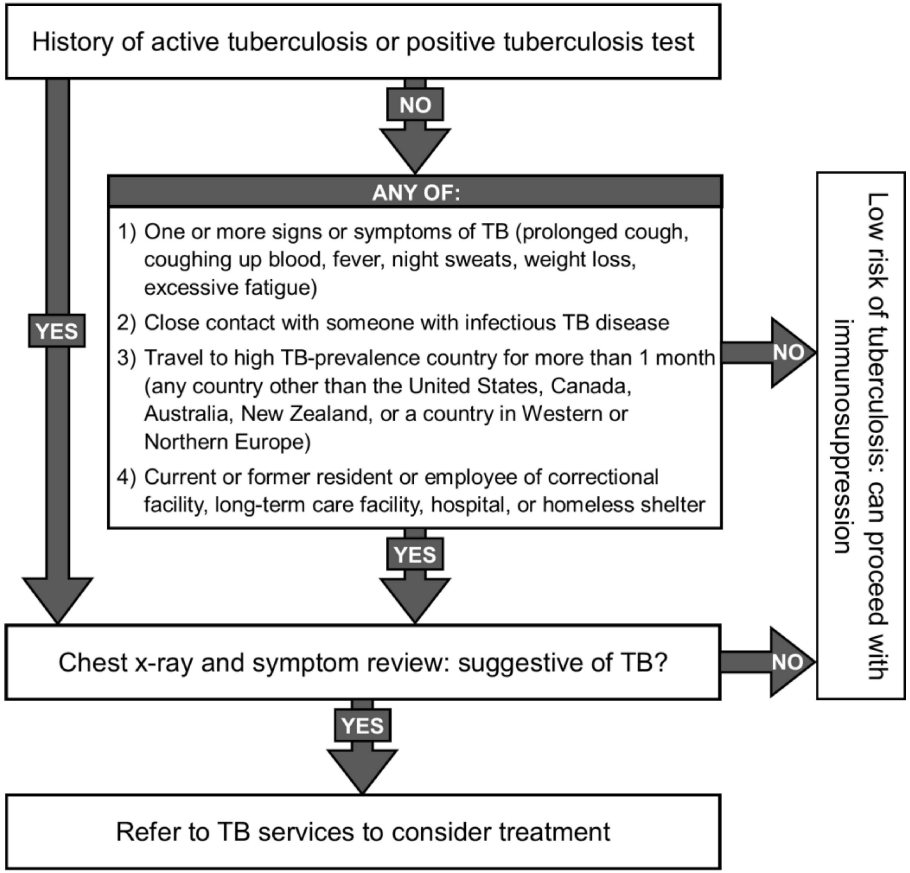
TB Treatment



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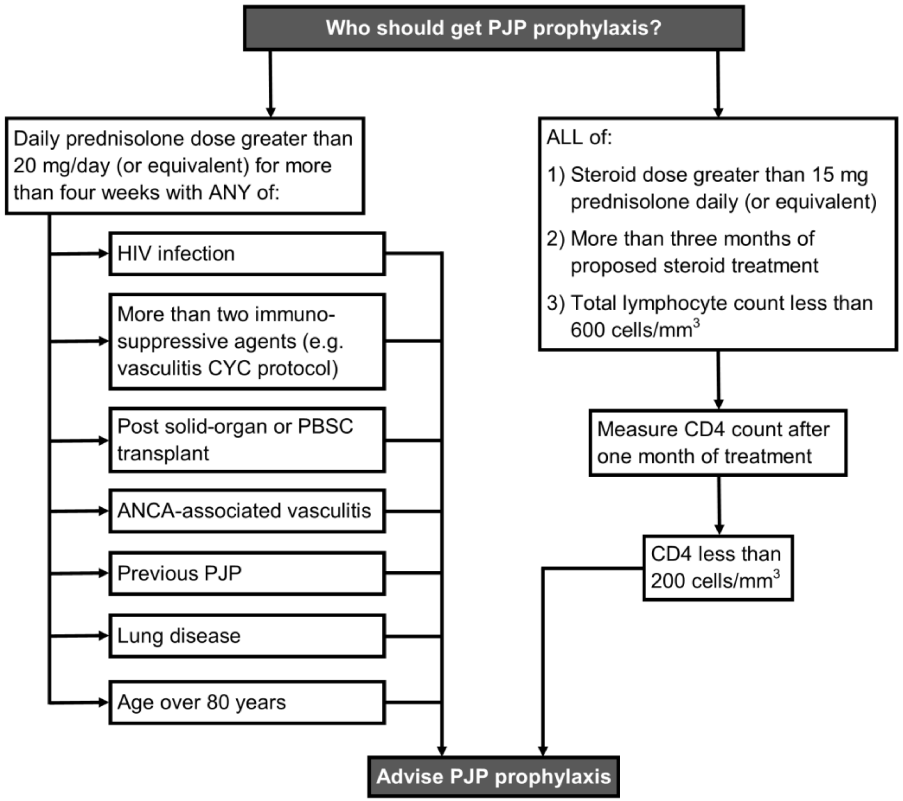
PJP Prophylaxis



Primary and Secondary PJP prophylaxis	
First line	**Co-trimoxazole 960mg PO 3/week** • 3/12x FBC, U&E. Stop if or ↓ rash (480mg OD or 960mg alt. days). • 5% annual risk of SJS or TEN
Alternatives *significantly less effective*	Dapsone 50-200mg PO OD AND pyrimethamine 75mg OD once weekly *OR* Pentamidine 300mg nebulised every 4 weeks *OR* Atovoquone 750mg PO BD

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Reduction of infection risk

Vaccination recommendations*
• Pneumococcus
• Influenza (annual)
• Avoid live vaccines
• Varicella: check status, VZIg if exposed

Peri-operative recommendations*
• Minimise steroid dose pre-op
• Do not increase steroid dose peri-op to avoid adrenal insufficiency
• Do not routinely stop immunosuppressant pre-op (decision depends on procedure)

Intercurrent infection recommendations*
• Discontinue oral immunosuppressant (not steroids) until patient recovers from serious infection
• Postpone regular IVIg during infective symptoms to reduce clotting risk

Procedures with high infection risk:	Discuss with microbiology team

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**Ledingham J et al. Rheumatology (Oxford). 2017 Jun 1;56(6):865-868.*

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Pregnancy and breastfeeding

	Peri-conception	T1	T2/T3	Breast-feeding	Paternal exposure
Prednisolone	yes	yes	yes	yes	yes
IVMP	yes	yes	yes	yes	yes
AZA	yes	yes	yes	yes	yes
MTX ≤25 mg /week	stop 1 month in advance	no	no	no	yes
MMF	stop 6 weeks in advance	no	no	no	yes
CYC	no	no[a]	no[a]	no	no
IVIg	yes	yes	yes	yes	yes[b]
Rituximab	consider stopping at conception[c]	severe disease if no alternatives[c]	severe disease if no alternatives[d]	yes[b]	yes[b]

[a] Only consider in severe life or organ-threatening maternal disease; [b] Limited data available; [c] can consider in severe maternal disease if no pregnancy-compatible alternatives available; [d] if used in third trimester, avoid live vaccinations in infant until six months of age; *Russell M et al. Rheumatology 2022*

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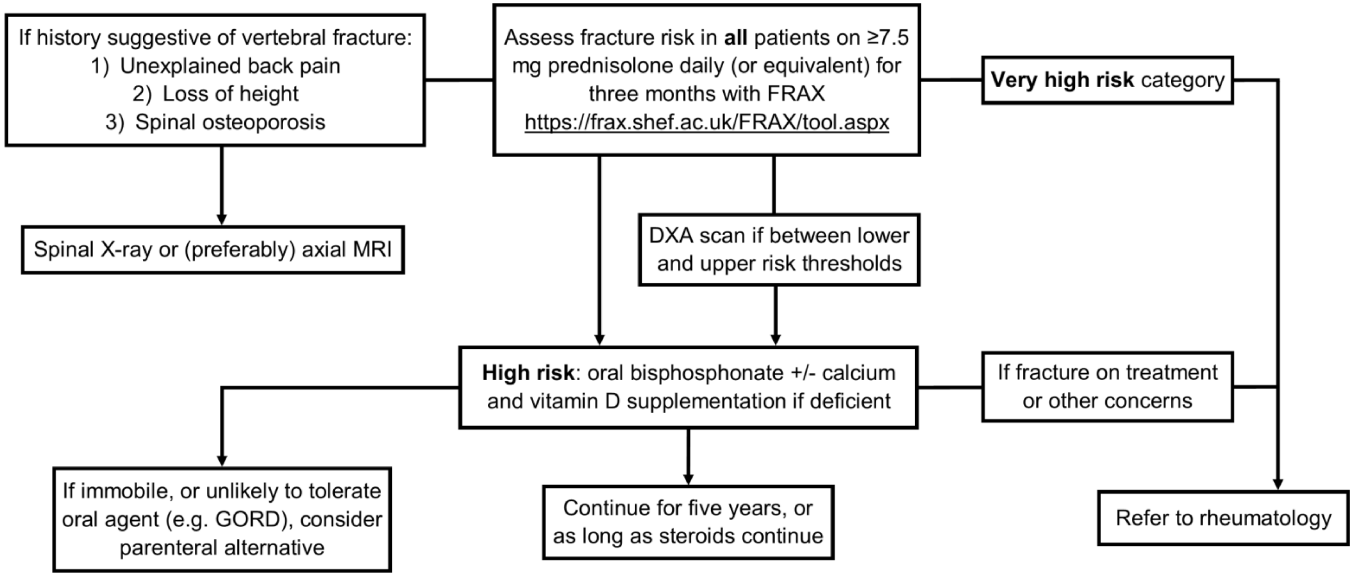
Bone health

https://www.nogg.org.uk, 2021



Review at 3 years zoledronic acid or 5 years oral bisphosphonate.
Longer treatment recommended if:

- age >75 years;
- history of hip or vertebral fracture;
- fracture while on treatment;
- oral glucocorticoids.

If bone protection discontinued:

- Reassess risk after new fracture, regardless of when this occurs;
- If no new fracture occurs, reassess risk at 18 months to 3 years.

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Screen for significant co-morbidities

Pre-treatment screening	**Height, weight, blood pressure and vascular risk assessment**
	FBC, creatinine/calculated GFR, ALT and/or AST, albumin
	Blood-borne viruses (HIV, HBV, HCV)
	History and examination for respiratory disease

Situation	Recommendation
Suspicion of parenchymal lung disease: *Consider referral to respiratory physician* *(*Particularly important with MTX or cyclophosphamide use)	• Smoking cessation advice • Lung function tests • CXR +/- high resolution CT chest
HIV, HBV and HCV:	• Consider anti-viral treatment prior to immuno-suppression (discuss with specialist)
Abnormal liver biochemistry: *AST or ALT>100*	• **Not an absolute contraindication** • Select less hepatotoxic drug: MMF>AZA
Abnormal synthetic liver function:	• **Not an absolute contraindication** • Increased risk of toxicity: Except MMF
Chronic renal impairment	• Increased toxicity and direct nephrotoxicity • Investigate cause for newly identified CRI • Alter dose/ frequency and monitoring *(Page 9)*
Cardiovascular risk	Primary prevention pre-treatment
Previous malignancy	**Not an absolute contraindication;** routine population screening recommended

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Dose adjustment in Chronic renal impairment

Drug	Accumulates in CRI	Potential for nephrotoxicity	Chronic renal impairment		
			III	IV	V
			Recommended adjustment (% of standard dose)		
AZA	No	No	Normal	75-100%	50-100%
MTX	Yes	Yes	50%	Contraindicated	Contraindicated
MMF	Yes	No	Normal dose	1mg BD max.	1mg BD max.
CYC	Yes	Yes	According to age and creatinine (Page 14)		

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Established outcome measures in NM disease

Condition	Established disability measure
CIDP	MRC sum score
	CIDP-RODS*
	Dynometer (kPa)**
	10m timed walk (seconds)
	ONLS
Other neuropathy/ neuromyotonia	INCAT sensory sum score*
	Berg balance scale*
	ABC balance score *
	Tremor scale*
	Myotonia behaviour scale*
MMN	MRC sum score
	Dynometer (kPa)**
	MMN-RODS*
	ONLS
Inflammatory myopathy	MRC sum score
	Up and go 3 m walk (seconds)
	CK
	HAQ score*
	Physician global activity assessment
	Patient/parent global activity assessment
	Manual muscle testing (MMT)
	MDAAT
MG	MG composite*
	MG-ADL score
	Respiratory function, e.g. forced vital capacity

* Validated; ** Responsive

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Corticosteroids

CONSENT
Common S/E
- Diabetes
- Gastritis
- ↑appetite
- ↑ weight
- Osteopenia
- Mood alteration
- Sleep disturbance
- Adrenal insufficiency
- Infections
- VZV reactivation/ infection risk
- Glaucoma/ cataract risk

Rare/ SAE:
- Avascular necrosis of femoral head (1:100-1:1000)

	INDUCTION	MAINTENANCE	REDUCTION
IVMP	**1g/day x3 days** *or* **500mg/day x5 days**	***1g / 1 day every 3 weeks x6*****	***No down titration required*****
PO Pred.	**1mg/kg/day** *or* **2mg/kg/alt days**	**1mg/kg/day PO Prednisolone X 4-6 weeks**	**See WITHDRAWAL***

CO-PRESCIBE: Bone protection (oral or IV bisphosphonate), D3 and calcium and PPI or H2-antagonist

Cautions	Drug interactions	Contraindications
Hepatic dysfunction Diabetes Hypertension CCF Recent MI Pregnancy	Digoxin, Warfarin NSAIDs Carbemazepine, phenytoin, phenobarbital Methotrexate Bronchodilators, diuretics (K+) Anti-retrovirals, macrolides, antifungals, rifampicin	Systemic infections Psychosis, severe depression, BPAD Wounds Live vaccines

MONITORING

When	What
Pre-treatment	BP, weight, HbA1C, TG, K, CXR, HIV
	Signs of adrenal insufficiency
	Assess fracture risk (Vit D and Ca^{2+})
	HIV, HBV, HCV.Document VZV status
Monitoring	BP, weight, HbA1C, TG, K+ at one month, then 3 monthly
	Glaucoma and cataract screening 6-12 monthly
	Signs of adrenal insufficiency

WITHDRAWAL*

Circumstance	Suggestion
Problem resolved and treatment<3 weeks	↓by 2.5 mg/ 3–4 days, to 7.5 mg per day, then ↓by 2.5 mg/ week, fortnight, or month.
disease resolution and/or treatment>1 month	↓by 5mg month to 10 mg per day, then ↓by 1 mg/ month.
Abnormal bruising or severe sore throat	Rapidly to 7.5mg/ day then ↓by 1 mg/ month.

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Monitoring in ALL steroid-sparing agents

CONSENT
Common S/E
- Nausea
- GI symptoms
- Infection risk
- Potential for hepatic and renal toxicity
- Potential for bone marrow failure
- Potential for teratogenicity

When	What
Pre-treatment	FBC, U&E, eGFR , LFT, albumin, BhCG, HIV, HBV, HCV, EBV. Assess TB risk. Document VZV status.
Monitoring	FBC, U&E, eGFR, LFT, albumin x 2 weeks until stable dose for at least 6weeks
	On stable dose: monthly FBC, U&E, LFT, albumin x3 months
	Then 3 monthly FBC, U&E, LFT, albumin
Following dose change	FBC, U&E, eGFR, LFT, albumin x 2 weeks until stable dose for at least 6weeks

ACTIONABLE EVENTS

Event	Action
WBC< 3.5 x10^9/L	Withhold until discussion with specialist team.
Neutrophils < 1.6 x10^9/L	
Unexplained eosinophilia >0.5 x10^9L	
Platelets< 140 x10^9/L	
Cr>30% above baseline or eGFR<60	
AST, ALT> 100 units/L	
Unexplained fall in serum albumin	
Rash or oral ulceration	
MCV > 105fL	Check and treat B12, folate, TFT. If normal: Withhold until discussion with specialist team.
Abnormal bruising or severe sore throat	Withhold until FBP available and discuss with specialist team

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Azathioprine

Starting dose	**1 mg/kg/ day**	Increase at 4 weeks to 2mg/day and then as necessary	Target dose	**2-3 mg/kg/day**

CONSENT

Common S/E
- GI disturbance
- Hepatic and renal dysfunction
- Dose related bone marrow suppression
- Skin: fungal infection/ reactivation and BCC
- Infections
- VZV reactivation

Rare/ SAE:
- Hepatic veno-occlusive disease
- Pure red cell aplasia
- pancreatitis

Cautions	Drug interactions	Contraindications
Non-melanoma skin cancer	**Allopurinol, aminosalicylates , Co-trimoxazole, trimethoprim (Severe)**	Homozygous TMPT deficiency
Pancreatitis	Warfarin	Live vaccine
TB, Hepatitis B and C	ACE-inhibitors	Lesch-Nyhan syndrome
Heterozygous TMPT deficiency	Phenytoin, carbamazepine, sodium valproate	

SPECIFIC MONITORING

When	What
Pre-treatment	TMPT
Monitoring	As per All steroid sparing agents Except if TMPT low metaboliser: at least monthly monitoring

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Methotrexate

CONSENT
Common S/E
- GI disturbance
- Skin, nail and hair changes
- Hepatic and renal dysfunction
- Dose related bone marrow suppression
- Infection: VZV reactivation

Rare/ SAE:
- Pneumonitis
- Hypersensitivity/ SJS

Starting dose	**5-10 mg/week**	Increase by 2.5-5mg every 2-6 weeks	Target dose	**7.5-25 mg/weeky**
CO-PRESCIBE WITH 5mg FOLIC ACID PER WEEK on ALTERNATE DAY TO MTX				

Cautions	Drug interactions	Contraindications
Renal impairment	Phenytoin (↑anti-folate effect)	Suspected infection
TB, Hepatitis B and C	Probenecid, NSAIDs, Penicillin (↓excretion)	Pregnancy and breast feeding
Anaemia, cytopenia with bone marrow failure	Co-trimoxazole, trimethoprim (↑marrow failure)	Bone marrow failure or unexplained anaemia/ cyptopenia
	Tolbutamide (↑MTX concentration)	

SPECIFIC MONITORING

When	What
Pre-treatment	CXR
Monitoring	Annual CXR

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Mycophenolate mofetil

CONSENT
Common S/E
- GI disturbance
- Hepatic and renal dysfunction
- Dose related bone marrow suppression
- Skin: fungal infection/ reactivation and BCC
- Infections
- VZV reactivation

Rare/ SAE:
- PML (with concomitant immunosuppressant)

Starting dose	**500mg/ day**	Then 500mg BD, increase by 500mg per week to efficacy/ as tolerated	Target dose	**Max.: 3g/day**

Beware	**Drug-interactions**	**Contraindications**
Malignancy: B-cell lymphoma associated with EBV (↑azathioprine, tacrolimus and ciclosporin)	Antacids (↓bioavailability)	Pregnancy and breast feeding
Lymphoproliferative disease or unexplained anaemia, thrombocytopenia or neutropenia	Cholestyramine (↓bioavailability)	Localised and systemic infection
Gastrointestinal disturbance	Probenecid (↑concentration)	
Urogenital irritation/ infection	Aciclovir (↑concentration of both drugs)	
Bone marrow failure: bruising and sore throat. (Severe sepsis in 0.5%)		

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Rituximab

CONSENT
Common AE
- Infusion reaction
- Bone marrow suppression
- Infection
- Mild hypersensitivity reactions
- SLE-like syndrome

Rare/ SAE:
- PML (with concomitant immunosuppressant)
- Hypogammaglobulinaemia (with repeat treatments)
- Severe skin reaction:SJS*, TEN**

Dose	1g IVI x2 (2 weeks apart)	Further 1g IVI at 4 weeks post second dose if no CD19 depletion
REQUIRED PRE-MEDICATIONS: 100 mg IVMP + 10 mg IV chlorphenamine + 1g PO paracetamol		

Adverse events	Incidence	Contraindications
Infusion reactions	25% during first infusion; usually mild to moderate in severity; reduced incidence on subsequent infusions	Hypersensitivity to Rituximab or other murine proteins
Hypogammaglobulinaemia	Low serum IgM (22.4%), IgG (3.5%), or IgA (1.1%) levels for more than 4 months; serious infections more common in those with low IgG levels	Severe heart failure
Serious infection	3.94/100 patient-years (as per MTX in RCT); infection rate static over 5 years of treatment; serious opportunistic infection rare (0.06/100 patient-years)	Active infection
	Zoster reactivation: 9/1,000 patient-years (as per MTX)	*Pregnancy/ breastfeeding*
	TB: 2/3,194 cases (0.06%)	
	PML: Rare (2.3/100,000 patient-years)	

Pre-treatment assessment	FBC, CD19, U&E, LFTs, HIV, HBV, HCV, HBs Ag, anti-HbcIgG, Ig, BhCG. VZV, TB screening (Vaccination recommended >4 weeks prior to treatment)
Monitoring	Ig x6monthly
	C19 x4 weeks-4 months post-dose to check response

Event	Action
HBsAg –ve anti-HBc IgG+ve	Check HBV DNA titre: if undetectable monitor: if ↑ with treatment refer to hepatology for anti-virals
HBsAg –ve anti-HBc IgG -ve	Pre-treatment vaccination
HBsAG +ve and/or anti-HBc IgG +ve	Pre-treatment prophylaxis (consider alternative to Rituximab/ with hepatology)
HCV +ve	Discuss with hepatology

***SJS: Stevens Johnson syndrome**
****TEN: Toxic epidermal necrolysis**

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CYCLOPHOSPHAMIDE

CONSENT: Adverse reactions	PREVENTION
Bladder toxicity	1L prehydration with normal saline or orally over 1 hour prior to pulsed cyclophosphamide 3L/day oral fluid intake for 3 days Mesna 200mg IV in 100ml sodium chloride 0.9% infusion over 30 minutes before pulsed cyclophosphamide Mesna 400mg PO stat at 2 hours post- cyclophosphamide Mesna 400mg PO stat at 6 hours post cyclophosphamide
PJP	Co-trimoxazole 480mg three times per week (care with allergy)
GI disturbance	Cyclizine 50mg slow IV bolus or ondansetron 8mg slow IV bolus 15 minutes before pulsed cyclophosphamide Domperidone 10-20mg PO TDS for 3-5 days
CIN	Annual smear x3years Follow up as per national guidelines
Vaccination	Influenza/ pneumococcus (if possible) Avoid live vaccination
Fungal infection	Consider prophylaxis
Staph. Aureus	Consider treatment in Wegner's granulomatosis
Infertility	Counsel; consider cryopreservation if clinically permitted
Osteoporosis	Bisphosphonate + calcium + vit. D (given co-prescription of corticosteroids)
TB	Risk assessment
HBV, HCV, HIV, VZV	Screen pre-treatment. Treat if indication (specialist discussion)

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CYCLOPHOSPHAMIDE

Prednisolone*:
- 60mg OD x1week
- 45mg OD x1week
- 30mg OD x1week
- 20mg OD x2weeks
- 15mg OD x2weeks
- 12.5mg OD x4weeks
- 10mg OD x8weeks
- 7.5mg OD x6months
- 5mg OD x3-6months

+/-12.5% in first 2 months
+/-25% after that

Induction
- **Cyclophosphamide**
  - 15mg/kg x10 cycles (Max: 1.5g)
  - Titrate to age/GFR/WCC
  - **AND**
  - Oral prednisolone*
  - **OR**
  - IVMP/ PLEX (life threatening or organ threatening disease)

Remission
- Taper steroids as per CYCLOPS regimen*
- Commence maintenance therapy as appropriate 3 weeks following end of cyclo
  - Azathioprine
  - Methotrexate
  - Mycophenolate mofetil

Maintenance
- Taper at 2years if clinically stable

Dosing in obese patients: use ABW25, using the equation IBW + 0.25 x (TBW - IBW)

Age (years)	Creatinine 150-300 mol/L	Creatinine 300-500 mol/L
<60	15 mg/kg/pulse	12.5 mg/kg/pulse
>60 and <70	12.5 mg/kg/pulse	10 mg/kg/pulse
>70	10 mg/kg/pulse	7.5 mg/kg/pulse

Pre-dose FBC:	
WBC< 4 x10^9/L or NE<2 x10^9/L prior to dose	Postpone dose and check weekly until WBC> 4 x10^9/L and NE>2 x10^9/L
After pulse 1 monitor FBC on day 7, 10 and 14: After each dose change monitor FBC on day 10:	
If Leucocyte **nadir** 1-2 x10^9/L or neutrophil nadir 0.5-1.0 x10^9/L (after 1st 2 doses or at day 10 after dose change)	Reduce pulse by 40% of previous dose
If Leucocyte **nadir** 2-3 x10^9/L or neutrophil nadir 1.0-1.5 x10^9/L (after 1st 2 doses or at day 10 after dose change)	Reduce pulse by 20% of previous dose

Monitoring:	
FBC	As above
Cr clearance	Pre-dose
Urinalysis	3 monthly. x1 year / 6 monthly x2-5 years. If haematuria: MSSU ,;if no infection: cystoscopy Annual cytology: on going.
Clinical	Monthly x 3/12; then 3-6 months x1yr; then 6-12 monthly x2-5 year
Cervical smear	Annually for first 3 years, then according to national guidelines

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* De Groot et al. Ann Intern Med. 2009 May 19;150(10):670-80.

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IV Immunoglobulin

Calculate ideal body weight (IBW) (kg):
IBW for males = 50 + [2.3 x (height in inches - 60)]
IBW for female = 45.5 + [2.3 x (height in inches - 60)]

Calculate dose-determining weight (DDW) (kg):
DDW = IBW + 0.4 [actual body weight (kg) – IBW]

Use DDW for calculating the IVIg dose required

Induction	Starting dose	
2 doses of IVIg 4-6 weeks apart	Dose: 2g/kg (1mg/kg in myasthenia) If BMI ≥30 kg/m2 or if actual weight >20% more than IBW, consider adjusted-bodyweight	Rate :0.4g/kg/day over 5 days Max. rate: 100ml/hr Max. volume: 1mg/kg/day
MAINTENANCE: SEE ALGORITHM		

Consent/ Adverse reactions
10-15%:infusion related headaches, higher risk in migraineurs (Can be managed with pre-medication, rate and dose reduction/ dose fractionation and migraine prophylaxis)
Elevated thromboembolic risk: Hold IVIg during active infection. Review procoagulant medication, risk of hyperviscosity, DVT risk. ↑TEE risk by 50%/year if IVIg and HTN and T2DM; ↑53%/yr if IVIg and T2DM; ↑15%/yr if IVIg and HTN: **Proactively manage HTN and T2DM in IVIg patients.**
Anaphylaxis/ transmission of infective agent : very rare i(>1:10,000).
Haemolytic anaemia: Very rare (>1:100,000 infusions). Lymphopenia/ thrombocytopenia: transient / rarely clinically significant. Check FBC IF clinically indicated (not routinely)

MONITORING

Pre-treatment assessment	**Hepatitis screen , HIV, IgA** **FBC, U&E, PPE, immunofixation** **Consider testing Ig levels, plasma viscosity**
Before each infusion	Blood pressure, oxygen saturation, pulse, respiratory rate and temperature
	Check FBC (differential), urea and electrolytes **ONLY if clinically indicated**
	Review for evidence of infection
	Check for evidence of VTE
Annual clinical assessment (consultant or CNS)	Pre and post-treatment assessment using at least 3 validated disability measures

ACTIONS

Event	Action
Mild infusion related reactions	Slow or stop infusion. Give paracetamol for fever/headaches. Restart infusion as per protocol when symptoms have resolved. If symptoms persist, stop the infusion and seek medical advice
MODERATE/ SEVERE reaction	Stop infusion. Call for medical help. If necessary, administer supportive drugs: Hydrocortisone iv,Chlorphenamine iv, Salbutamol. Anaphylaxis/Crash box should be available
IgM / IgG paraprotein	Consider possibility of mixed cryoglobulinaemia. Seek immunological advice Consider measuring serum viscosity
Serum viscosity > 3 mPas	Exercise caution; use slower rate of infusion and lower dose. Before and after infusion check viscosity.

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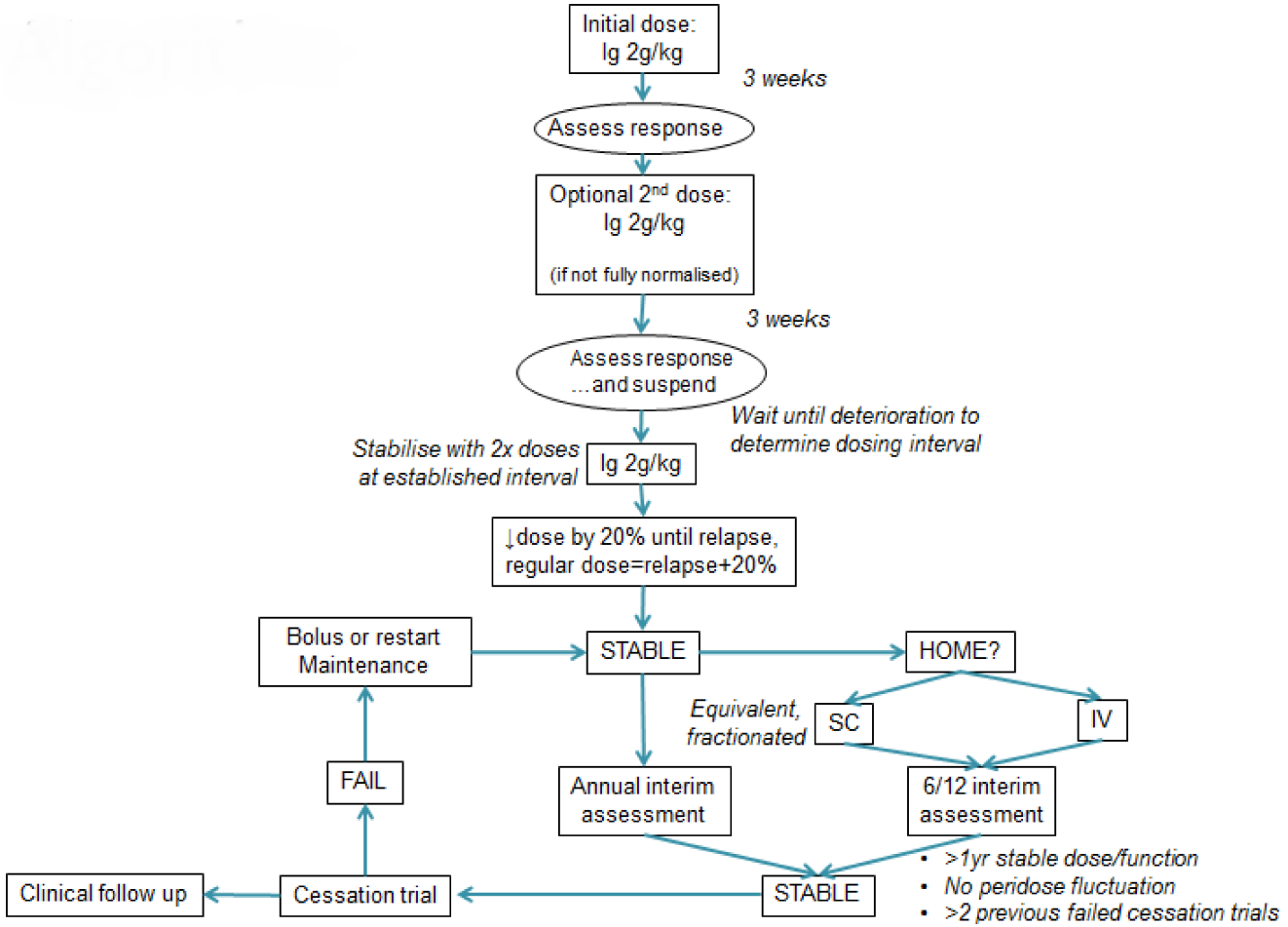
IVIg dosing algorithm

*** At least 3 pre-set, individualised outcome measures**



Lunn et al., J Peripher Nerv Syst. 2016 Mar;21(1):33-7.

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