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Cover picture

EHRLICH: CHEMOTHERAPY IS LAUNCHED

In a crowded laboratory at Frankfurt's Institute of Experimental Therapy, German research scientist Paul Ehrlich (1854-1915) habitually scrawled work orders to associates with stubby colored pencils on "blocks" of note paper. Dr. Ehrlich and his Japanese assistant, Dr. Sahachiro Hata, announced Salvarsan (606) to the world in 1910 as a "chemical bullet" for treatment of syphilis. Dr. Ehrlich's success with chemical synthesis gave impetus to a new medical science, chemotherapy. Though his greatest achievements were in this field, Dr. Ehrlich contributed to many branches of medicine and shared in a 1908 Nobel Prize for his work on immunology.

 Robert A. Thom, Artist

Pharmacological management of common childhood psychiatric disorders

Introduction

Psychiatric disorders affect 10-20% of children and adolescents worldwide and the onset of 50% of these is prior to the age of 14 years. Perception of, and preferred modalities of treatment of psychiatric disorders are influenced by cultural values more than in other fields of medical practice. This is reflected in prescribing practices as well as in use of non-pharmacological interventions.

Pharmacological management of child psychiatric conditions is complicated by several factors.

a. Difficulties in arriving at a diagnosis
   Child psychiatric conditions are difficult to diagnose, as only a minority of children have clear symptoms restricted to a single domain. Thus, management is often aimed at symptoms rather than diagnoses.
b. Higher rates of co-morbidity
   The rate of co-morbidity of mental illnesses among children is reported to be approximately 40% [1].
c. Requirement for prescription of multiple medications
   Co-pharmacy, the use of multiple medications to manage different conditions, is commonly practiced in child psychiatry due to high rates of co-morbidity. Poly-pharmacy, the use of more than one medication to treat a single disorder, is used in severe cases which are resistant to treatment and where children have intolerance/sensitivity to adverse effects.
d. Lack of robust evidence for pharmacological management due to ethical and methodological challenges in carrying out research in this age group and uncertainty of long-term benefits.
e. Widespread use of medication for off-label indications and use of unlicensed medications.
f. Unease among parents, teachers and medical professionals regarding the use of medication to alter behaviours and emotions of children. This is further complicated by inaccurate and unhelpful media portrayals and social media posts.
g. Differences in pharmacokinetics and pharmacodynamics in children
   Absorption, distribution, metabolism and excretion of medications are all affected by developmental changes. Children's bodies comprise of relatively more water than fat and plasma albumin levels are lower, both of which affect the volume of distribution of medications. The relative mass of liver and kidney tissue in children is greater than in adults when compared to their body weight and this results in higher levels of first-pass metabolism and higher rates of elimination. Hence, simply adjusting drug doses based on body weight will not lead to optimal dosing in children.

   Pharmacodynamic differences also complicate medication use. Majority of psychotropic medications act on neurotransmitter systems (dopaminergic, serotonergic etc). Receptor densities of these systems undergo significant changes during development and this affects the efficacy as well as safety of medications when used in children.

Furthermore, increasing rates of prescribing have raised concerns of over diagnosis and inappropriate use of medication in child psychiatric practice. In this context, high quality assessment and prescribing practices to enhance outcomes for children are being advocated [2].

Steps in prescribing medication for a child with a psychiatric condition

1. Psychiatric assessment
   A comprehensive psychiatric assessment by a trained clinician is an essential prerequisite to diagnosis and planning of management. This helps to determine the symptoms best addressed pharmacologically and by using non-pharmacological methods. Perusal of previous records reduce the use of medications which have previously been ineffective.
2. Medical evaluation
   Prior to initiating medication, a past medical history needs to be obtained and further medical evaluation arranged as appropriate. This will help exclude medical problems causing psychiatric symptoms and ensure that the child is physically suitable for a trial of medication.
3. Development of a management plan
   The management plan should be based on the bio-psycho-social formulation of the child's condition, whilst taking in to consideration the available evidence. This includes pharmacological and non-pharmacological interventions targeting specific symptoms. The child and parents must be offered adequate information to give their consent/assent to the proposed management plan. It must take in to account the bio-psychosocial factors impacting on suitability and practical application of the interventions.

4. Follow up

   Frequency of follow up will depend on severity of symptoms, type of medication prescribed and necessity for dose titration as well as level of psychosocial support required for the child and family. Response to treatment, tolerance of adverse effects, adherence and ongoing psychosocial stressors are monitored.

   Pharmacological management consists of three phases; an initiation phase, maintenance phase and discontinuation phase. Initiation of medication and dose titration to obtain response occurs during the initiation phase and remission or recovery occurs during the maintenance phase. If indicated, medication is tapered off and the child is monitored for recurrence of symptoms during the discontinuation phase. Frequency and monitoring during follow up will be affected by the phase of treatment.

Common child psychiatric disorders

Child psychiatric conditions are divided broadly in to emotional disorders, externalizing disorders and developmental disorders [3] (Table 1).

Pharmacological management

Anxiety disorders

Medications are indicated for moderate to severe symptoms of anxiety disorders in children including obsessive compulsive disorder, social anxiety disorder and generalized anxiety disorder. Non-pharmacological interventions are generally used prior to medication and studies have demonstrated greater efficacy for the combination of specific serotonin reuptake inhibitors (SSRIs) and cognitive behaviour therapy than either treatment alone [3,4].

Sertraline (for children 6 years and above), fluoxetine and fluvoxamine are approved by the US Food and Drug Administration (FDA) for obsessive compulsive disorder (OCD) in children. The efficacy of clomipramine for paediatric OCD is widely debated. Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI) has FDA approval for generalized anxiety disorder in children. However, due to the adverse effects, this is considered third-line after two failed trials of different SSRIs. Benzodiazepines have no evidence from controlled trials for childhood anxiety disorders and are known to cause paradoxical disinhibition in some children.

Adverse effects of SSRIs include worsening anxiety, agitation and disinhibition as well as gastrointestinal adverse effects, headache, insomnia and increased motor activity. These are usually mild and transient. Doses similar to those in adults are used due to faster metabolism in children. Therapeutic effects can take up to 6 to 8 weeks to manifest. SSRIs may be cautiously withdrawn during a period of minimal stress after a maintenance period of 1 year following improvement of symptoms.

Depression

Pharmacological treatment is recommended for moderate to severe depression in children and adolescents along with psychosocial interventions [4]. SSRIs are widely used.

Fluoxetine has been the medication most widely studied, and is licensed for use in children with depression from the age of 8 years by the FDA. However, this comes with a black box warning by the FDA for increased risk of suicidal thinking and behaviour in children and adolescents commenced on fluoxetine, in short-term studies. Fluoxetine is started at a dose of 10 mg daily and increased to a minimum effective dose of 20 mg daily after 1 week. Beneficial effects are seen after 2 weeks and up to 6 weeks. Fluoxetine should be continued for 6-9 months after recovery following the first episode. For multiple episodes, maintenance treatment for at least 2 years is recommended. Escitalopram is the only other FDA approved SSRI for depression in adolescents aged 12 years and above. Sertraline and citalopram have also been studied in children with depression and are recommended as second-line

Table 1. Common child psychiatric disorders

Emotional disorders	Externalizing disorders	Developmental disorders
Anxiety disorders	Attention deficit hyperactivity disorder (ADHD)	Intellectual disability
Depression	Conduct disorder	Specific reading disorder
Somatoform disorders		Autism spectrum disorders
		Nocturnal enuresis

agents [4]. Tricyclic antidepressants are ineffective in pre-pubertal children due to differences in pharmacodynamic properties.

Attention deficit hyperactivity disorder (ADHD)

Medications are indicated when there is moderate to severe ADHD and when behavioural methods have failed or are difficult to implement [1,3,4].

Methylphenidate, a central nervous system stimulant, is the first line medication and is used in children 6 years and above. Its safety in younger children is not established. Only the immediate release form, which has a duration of action of 2-4 hours due to its short half-life, is available in Sri Lanka. It is started at a dose of 5 to 10 mg per day and most children require multiple doses per day. Maximum dose is 2.1 mg/kg/day in divided doses, up to 60 mg daily. Caution is needed in children with cardiac problems, seizures, tic disorders and poor weight gain. Common adverse effects are anorexia, insomnia, jitteriness, raised blood pressure and growth deceleration. Hence monitoring of height, weight, pulse rate and blood pressure is required.

Dexamphetamine is another stimulant medication used in ADHD, but there is less evidence regarding its safety and efficacy. Lisdexamphetamine, a prodrug, is increasingly being used and there is growing evidence that it can be considered as an alternative to extended-release methylphenidate.

Atomoxetine, a norepinephrine reuptake inhibitor, is a first-line alternative in children who respond poorly to stimulant medications and who are intolerant of their dopaminergic adverse effects (anxiety, tics etc). Maintenance dose is 1.2 mg/kg/day and atomoxetine takes up to 4-6 weeks to exhibit beneficial effects. Common adverse effects include sleep disturbances, nausea, abdominal pain and anorexia. Severe liver damage occurs in about 1 in 50,000 patients treated and atomoxetine carries a black box warning for increase in suicidal thinking.

Alpha2-agonists, clonidine and guanfacine are third-line medications for ADHD. There is no evidence for the use of second-generation antipsychotics.

Autism spectrum disorder

Children with autism have high rates of psychiatric comorbidity (up to 70% in some studies) and evidence for pharmacological agents is mainly available for management of these conditions rather than the core features of autism [3,4]. Children with autism are more likely to experience adverse effects than normally developing individuals.

Second-generation antipsychotics have evidence for efficacy in management of irritability (including aggression and self-injurious behaviours) in children with autism. However, these should be employed after adequate environmental and behavioural approaches have failed. Both risperidone and aripiprazole have FDA approval for treatment of irritability associated with autism. Risperidone dose range is 0.25 mg to 1 mg/day and for aripiprazole it is 5 to 15 mg/day for short-term use (6-12 months). Risperidone causes metabolic adverse effects and hyperprolactinaemia and these need to be monitored. Evidence for improved long-term outcomes are lacking. There is evidence from controlled trials for the use of lithium and sodium valproate for management of irritability, but these are less efficacious than second-generation antipsychotics. Benzodiazepines are not recommended.

Melatonin in doses of 1-10 mg at night has shown beneficial effects in the management of sleep disturbances of children with autism. Methylphenidate and SSRIs are used in children with autism for the management of ADHD symptoms and anxiety, respectively.

Nocturnal enuresis

Medications are used in children 7 years and above with nocturnal enuresis, who do not respond to behavioural methods [3].

Desmopressin, a synthetic antidiuretic hormone analogue, is the first line medication and is given orally in doses of 0.2 to 0.6 mg at night. However, relapse usually occurs upon discontinuation of desmopressin. Low doses of tricyclic antidepressants (imipramine 25 to 75 mg) are also efficacious, but due to their adverse effect profile, desmopressin is preferred.

Tic disorders

Pharamacological management is indicated in tic disorders where the tics cause significant distress or functional impairment [1,3,4].

Clonidine, an alpha2-agonist is used as the first-line medication in doses of 3 to 5 micrograms/kg/day in divided doses. Clonidine causes sedation and postural hypotension and dose is build up gradually due to this. Both first and second-generation antipsychotics have shown efficacy in the treatment of tics, but due to their advrse effect profile, a clonidine trial is given prior to antipsychotics. Risperidone and aripiprazole both have evidence for the treatment of tics.

Bipolar affective disorder

Although bipolar illness is rare in children, it is an area of controversy and intense research interest in recent years. Second-generation antipsychotics appear to show higher short-term efficacy compared to mood stabilizers in management of manic symptoms. There is evidence for use of lithium and sodium valproate in maintenance treatment, but adherence to lithum and blood monitoring can be difficult especially in adolescents.

Summary

Childhood psychiatric disorders are difficult to diagnose and have high rates of co-morbidity.

Most available medications have been studied among adults and evidence for efficacy and safety in children, especially in relation to long-term use is inadequate.

In childhood psychiatric disorders, pharmacological agents are always offered as part of a comprehensive management plan which includes psychological and social interventions.

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Self-assessment questions on common childhood psychiatric disorders

1. Regarding pharmacological management of child psychiatric disorders

A. Management is often aimed at symptoms rather than diagnoses
B. Polypharmacy is commonly practiced in child psychiatry due to high rates of co-morbidity
C. There is widespread use of medication for off-label indications
D. Adjusting drug doses based only on body weight leads to optimal dosing in children
E. It is always used in conjunction with psychosocial measures

2. Methylphenidate

A. is a central nervous system stimulant
B. improves attention span
C. is recommended for a 4-year-old child
D. maximum dose of the immediate release form is 2.1 mg/kg/day in divided doses
E. increases the seizure threshold

3. Regarding use of psychotropic medication in autism spectrum disorder

A. Fluoxetine improves socio-emotional reciprocity
B. They are less likely to experience adverse effects of psychotropic medications
C. Aripiprazole is effective for aggressive behaviour
D. Melatonin is used for associated self-injurious behaviours
E. Methylphenidate is used to treat comorbid anxiety disorders

4. A nine-year-old girl is brought due to severe self-injurious behaviour associated with aggressive outbursts. She has a diagnosis of autism spectrum disorder. Her parents and therapists report minimal improvement with psychosocial interventions.

Which of the following is the most appropriate pharmacological management for this girl?

A. Sertraline 25 mg mane
B. Risperidone 0.5 mg nocte
C. Diazepam 5 mg nocte
D. Methylphenidate 5 mg mane
E. Lithium carbonate 250 mg nocte

(Answers on page 11)

Recent advances in the management of systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a prototypic multisystem autoimmune disorder with protean disease manifestations, involving almost all organs and tissues [1]. Due to its heterogeneity and the potential to cause fatal organ involvement, management of SLE often requires an intensive multipronged approach by specialists in rheumatology and other relevant specialities based on organ involvement. Over the last few years, there have been several advances in the management of SLE. The classification has also been revised. This article aims to discuss these recent developments.

2019 EULAR/ACR classification criteria

The 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for SLE includes a positive ANA at a titre of ≥1:80 on HEp-2 cells (by immunofluorescence) or an equivalent test as an obligatory entry criterion with additive criteria grouped into seven clinical and three immunological categories (Figure 1) [2]. Each additive criterion is weighted from 2 to 10. Patients with a score of 10 or more points are classified as having SLE.

Compared to the Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria which has a specificity of 84% and a sensitivity of 97%, the new criteria have been found to have higher specificity of 93% with similar sensitivity [3]. However, it is important to recognise that these classification criteria are primarily to identify a relatively homogeneous group of patients for research studies, and that SLE is essentially a clinical diagnosis in the presence of characteristic serological abnormalities with the exclusion of competing diagnoses.

Recommendations for management of SLE

Since the publication of the first EULAR recommendation for management of SLE in 2008, and the subsequent publications on neuropsychiatric manifestations (2010) and lupus nephritis (LN) (2012), new data have emerged on treatment targets and strategies, for example the use of calcineurin inhibitors as 'multitargeted' therapy in lupus nephritis [4]. Belimumab, a monoclonal antibody directed against soluble B lymphocyte stimulator (BLyS) was approved by the US Food and Drug Administration (FDA) as the first biological therapy for SLE in 2011 [5]. Based on such developments, an update on the EULAR recommendations for management of SLE was published in 2019 [6]. Summary of the main recommendations in this publication is given in Figure 1.

Overarching principles

The 2019 update emphasises on four key principles, which are listed in Box 1. The use of validated disease activity and chronicity indices, such as physician global assessment (PGA) is recommended to monitor patients with SLE.

Box 1: Overarching principles

1. SLE is diagnosed on clinical grounds in the presence of characteristic serological abnormalities.
2. SLE care is multidisciplinary. It is based on a shared patient-physician decision while taking individual, medical and societal costs into consideration.
3. Treatment of organ-threatening/life-threatening SLE includes an initial period of high-intensity immunosuppressive therapy, followed by a longer period of less intensive therapy to consolidate response and prevent relapses.
4. Treatment goals in SLE include long-term patient survival, prevention of organ damage and optimisation of health-related quality of life.

Goals of treatment

It is recommended that management of SLE should aim at achieving disease remission and prevent accumulation of organ damage while minimising adverse effects of therapy to improve long-term patient outcomes. However, in the disease course of SLE, complete remission (i.e. absence of clinical activity with no glucocorticoids and immunosuppressant medications) is rare [7]. Hence, a new low disease activity state has been defined, which has shown similar rates of averting damage accumulation and preventing disease flares compared to disease remission. If disease remission cannot be achieved, low disease activity in all organ systems should be targeted.

Low disease activity is defined as either;

- SLEDAI score ≤ 3 while on antimalarials
- SLEDAI ≤4, PGA≤1 while on ≤7.5 mg of prednisolone and well tolerated immunosuppressant agents

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥ 10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total scores.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR Anti-Smith antibody	6

Total score:

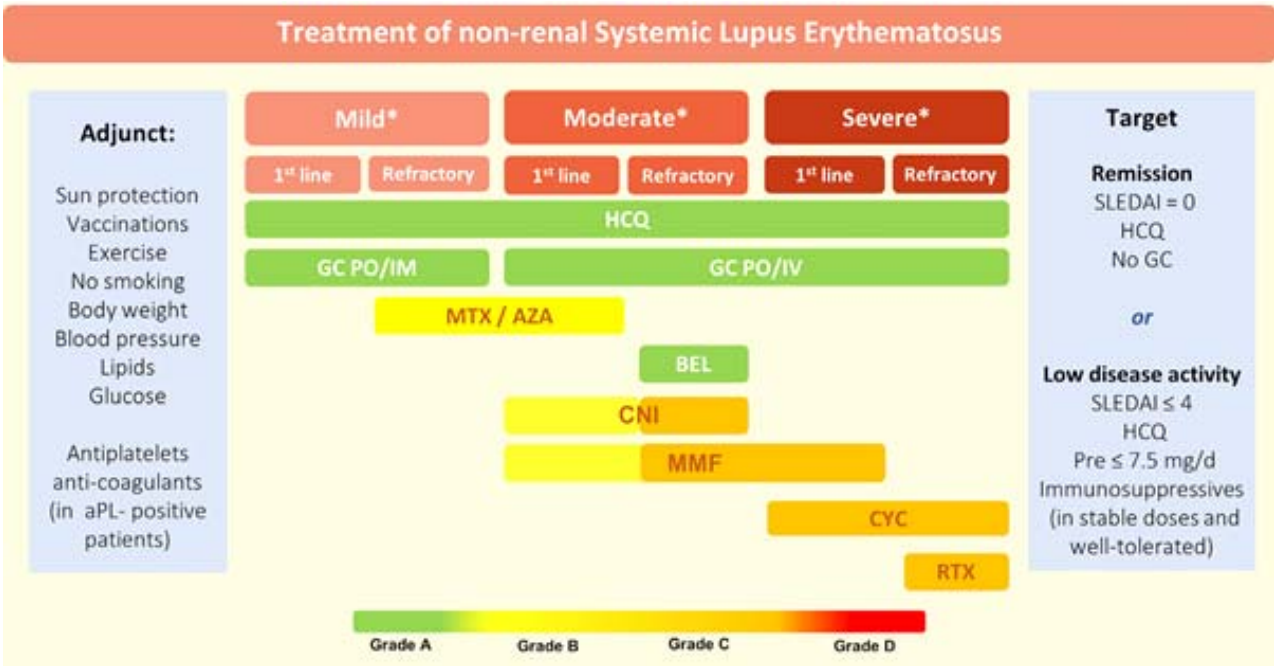
↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fufilled.

Figure 1. Classification criteria for systemic lupus erythematosus – 2019

Principles of management of SLE

Management of SLE depends on the type and severity of organ involvement. Patients with SLE are treated with hydroxychloroquine, unless contra-indicated and glucocorticoids to achieve a rapid response with or without other immunosuppressant agents. B cell-targeting biological agents are used in patients who have persistently active disease despite standard therapy or have frequent relapses. Figure 2 summarises the treatment of SLE according to disease severity stratification [6].



Mild: constitutional symptoms/mild arthritis/rash ≤9% BSA/ platelets 50-100x10^3/mm^3; SLEDAI ≤6; BILAG C or BILAG B manifestations

Moderate: RA-like arthritis/ rash 9-18% BSA /cutaneous vasculitis ≤18% BSA platelets 20-50x10^3 mm^3 /serositis; SLEDAI 7-12; ≥2 BILAG B manifestations

Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets <20x10^3/mm^3; TTP like disease or acute hemophagocytic syndrome; SLEDAI >12; ≥2 BILAG B manifestations

Figure 2. Treatment of non-renal SLE-recommended drugs with respective grading of recommendation

aPL, antiphospholipid antibodies; AZA, azathioprine; BEL, belimumab; BILAG: British Isles Lupus Assessment Group disease activity index; CNIs, calcineurin inhibitors; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; IM, intramuscular; MMF, mycophenolate mofetil; MTX, methotrexate; Pre, prednisolone; PO, per os; RTX, rituximab; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Medicines used in the management of SLE

1. Hydroxychloroquine

All patients with SLE regardless of the degree and type of disease should be treated with hydroxychloroquine (HCQ), unless contra-indicated. HCQ has multiple benefits including relief of constitutional symptoms, muco-cutaneous manifestations, musculoskeletal manifestations and some studies suggest that it may reduce disease flares, organ damage accrual and mortality.

Retinal toxicity, which is a main concern with long-term HCQ therapy is duration and serum concentration dependent. Other major risk factors include chronic kidney disease and pre-existing retinal or macular disease [8]. In the absence of such risk factors, it is recommended that ophthalmological screening by visual fields examination with or without spectral domain-optical coherence tomography be performed at baseline, then at 5 years, and annually thereafter. It is recommended that the daily dose of HCQ should not exceed 5 mg/kg real body weight as the

risk of retinal toxicity is very low below this threshold. However, one must bear in mind that a dose of 6.5 mg/kg/day was prescribed in studies which established the efficacy of HCQ in SLE, and the therapeutic effects of this low dose it is yet to be established.

2. Glucocorticoids

Although glucocorticoids provide rapid resolution of symptoms, medium to long term target is to discontinue glucocorticoids or to minimise the daily dose to ≤7.5 mg/day prednisolone equivalent due to the many harmful effects of long-term therapy. Dose and route of administration of glucocorticoids depend on the type and severity of organ involvement. In severe, organ threatening disease, pulses of intravenous methylprednisolone at doses of 250-1000 mg per day, given for 1-3 days, provide a quick therapeutic effect. It also allows lower starting doses of oral glucocorticoids. Furthermore, prompt initiation of immunosuppressant agents along with glucocorticoids permits tapering off and subsequent discontinuation of glucocorticoids.

3. Immunosuppressive medications

The addition of an immunosuppressive agent is recommended in patients who do not respond to HCQ alone or in combination with glucocorticoids or in whom glucocorticoid dose cannot be tapered to a daily dose of ≤7.5 mg/day prednisolone equivalent. In cases of organ-threatening or life-threatening disease, immunosuppressive agents may be included in the initial therapy. The choice of immunosuppressive agent depends on several factors including predominant type of organ involvement, patient's age, childbearing potential and fertility wishes, other safety concerns and the cost.

Methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF) and cyclophosphamide (CYC) are all used as immunosuppressive agents in SLE. AZA can be given in women with childbearing potential and during pregnancy, but all others are known to be teratogenic. MMF has been shown to be effective in renal and non-renal lupus, except in neuropsychiatric disease, and evidence suggest it to be superior to AZA in achieving remission and preventing flares.

CYC should be considered in severe renal, cardio-pulmonary, neuropsychiatric or other organ-threatening disease. It can also be used as rescue therapy in refractory non-major organ manifestations. However, gonadotoxicity is a major concern with CYC and GnRH analogues to reduce depletion of ovarian reserve and ovarian cryopreservation prior to treatment should be offered to patients with childbearing potential.

4. Biological agents

Belimumab should be considered in patients with refractory extrarenal disease, in whom glucocorticoids cannot be tapered off or have frequent relapses. Rituximab is used in severe renal, or haematological and neuropsychiatric disease refractory to other immunosuppressive agents and/or belimumab, or in patients with contra-indications to these agents. Generally, more than one immunosuppressive agent should have failed prior to switching to rituximab, except in cases with severe thrombocytopaenia and haemolytic anaemia, in which rituximab can be considered earlier.

Management of specific disease manifestations

Renal disease

Clinically apparent renal involvement occurs in nearly 50% of patients with SLE and it contributes to significant morbidity and mortality [9]. Prevalence of renal involvement in Sri Lankans appear to be even higher, with rates as high as 69% being reported in some studies [10]. Evidence shows that males, those with juvenile onset, with serologically active disease and those with positive anti-C1q antibodies are at a higher risk of developing renal involvement. Such high risk patients should be monitored at least every 3 months to detect early signs of renal involvement. Tests used for screening include urinalysis, urinary protein excretion, serum creatinine and estimated glomerular filtration rate. A diagnostic renal biopsy is crucial to ensure optimal outcome if any signs of renal disease are detected. Treatment of LN comprises of an intensive induction phase followed by an extended maintenance phase. CYC and MMF are recommended for induction therapy as they have the most favourable efficacy to toxicity ratio. Low-dose CYC (Euro-Lupus regimen – intravenous CYC 500 mg every 2 weeks for 6 doses) is favoured over high-dose CYC for it has a comparable efficacy with lower risk of gonadotoxicity. Reduced glomerular filtration rate, presence of fibrous crescents or fibrinoid necrosis or tubular atrophy/interstitial fibrosis in renal histology is associated with increased risk of progression into end-stage kidney disease. In such cases, high-dose CYC may be considered. In podocytopathy, membranous LN or in proliferative LN refractory to standard therapy within 3-6 months, calcineurin inhibitors (CNIs) may be considered as second-line agents for induction or maintenance therapy. Combination of tacrolimus with MMF has been shown to be effective in such cases. Primary immunosuppressive agents used for maintenance therapy include MMF and AZA, chosen based on the agent used for induction, patient factors, including age, race and pregnancy wishes. MMF is associated with fewer relapses. Rituximab may be considered in relapsing or refractory disease.

Recommendations for management of non-renal disease manifestations are summarised in Table 1.

Table 1. Summary of management of non-renal disease manifestations of SLE

Skin disease

- Broad-spectrum sunscreens and smoking cessation are strongly recommended.
- If the skin manifestations are atypical or refractory, a diagnostic skin biopsy should be considered.
- First-line treatment includes topical glucocorticoids and calcineurin inhibitors, antimalarials with or without systemic glucocorticoids.
- In those who do not respond to first-line therapy, high-dose glucocorticoids, MTX, retinoids, dapsone or MMF can be added.
- Thalidomide is considered only as "rescue" therapy in those who fail to respond to multiple other therapies.

Haematological disease

Immune thrombocytopenia

- Moderate to high-dose glucocorticoids including pulse of intravenous methylprednisolone, in combination with immunosuppressive agents are recommended as first-line therapy for significant lupus thrombocytopaenia (platelet count below 30000/mm3).
- AZA, MMF or cyclosporine can be used as immunosuppressive agents. Of these, cyclosporine has the least potential for myelotoxicity.
- In the acute phase, intravenous immunoglobulin (IVIG) may be considered if there is inadequately response to high-dose glucocorticoids.
- Refractory cases (i.e. failure to reach a platelet count >50 000/mm^3) are treated with rituximab or CYC.
- Thrombopoietin agonists or splenectomy are reserved as last options.

Autoimmune haemolytic anaemia (AIHA)

- Treatment of AIHA follows the same principles as thrombocytopenia with regards to use of glucocorticoids, immunosuppressive agents and rituximab.

Autoimmune leucopaenia

- Although it rarely requires treatment, a thorough work-up is recommended to exclude other causes, particularly drug-induced leucopaenia.

Neuropsychiatric disease (NPSLE)

- A comprehensive work-up to rule out mimics such as infections and malignancy is required prior to attributing neuropsychiatric manifestations to SLE.
- Treatment depends on whether the postulated pathophysiological mechanism is inflammatory or thrombotic/ embolic/ischaemic. In some cases, the two processes may co-exist.
- If the disease manifestations are due to an inflammatory process, glucocorticoids or immunosuppressive agents are recommended.
- Antiplatelet or anticoagulants are used in atherothrombotic or antiphospholipid syndrome related manifestations.

Conclusion

The objective of this article is to outline the principal recommendations for management of SLE. The management of associated comorbidities such as antiphospholipid syndrome is beyond the purview of this article. To summarize, all patients with SLE should be treated with HCQ, unless contra-indicated; glucocorticoids are used to achieve a rapid response and should be tapered to an acceptable daily dose or withdrawn completely where possible; immunosuppressive medications (i.e. MTX, AZA and MMF) are added as steroid sparing agents and belimumab is considered in refractory cases. The above description is a brief summation of complex management strategies of a heterogenous disease which requires specialised and multidisciplinary care.

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Self-assessment questions on systemic lupus erythematosus

1. A 26-year-old woman presents with fatigue and arthralgia for 2 weeks, fever for 3 days and reduced urine output over the last few days. The patient has a previous diagnosis of systemic lupus erythematosus made one year ago. On examination, she is febrile and looks ill. She has a pulse rate of 96 beats per minute with a blood pressure of 100/70 mmHg. She does not have any rashes or oral ulcers. Her general and system examination is otherwise unremarkable. Prior to this admission, the patient had low disease activity while being on HCQ 200 mg daily, azathioprine 75 mg daily and prednisolone 5 mg daily. The azathioprine dose has been increased from 50 mg to 75 mg 4 months ago to tail off steroids.

Her full blood count is given below

Total white cell count	-	2.9	10^9/L	(4-11 × 10^9/L)
Differentials				
Neutrophils	-	1.3	10^9/L	
Lymphocytes	-	1.6	10^9L	
Haemoglobin	-	9.5	g/dL	(11-14 g/dL)
MCV	-	96		(76 - 96)
Haematocrit	-	32	L/L%	
Platelets	-	148	10^9/L	(150-400 10^9/L)

What is the most appropriate immediate next step in management of this patient?

A. Increase HCQ dose to 200 mg twice daily.
B. Withhold azathioprine.
C. Increase prednisolone dose to 0.5 mg per kilogram per day.
D. Intravenous methylprednisolone 1000 mg pulse therapy.
E. Add mycophenolate mofetil.

2. Known adverse effects of mycophenolate mofetil include

A. Amenorrhoea
B. Increased liver enzymes
C. Myelosuppression
D. Persistent diarrhoea
E. Pneumocystis jirovecii pneumonia

3. A young woman who is diagnosed with systemic lupus erythematosus has got married recently and wishes to become pregnant. She has been in disease remission for the last 6 months while being on low dose prednisolone, hydroxychloroquine, and other immunosuppressant medicines.

Which of the following medicines are known to have minimal foetal or maternal risk?

A. Azathioprine
B. Cyclophosphamide
C. Hydroxychloroquine
D. Methotrexate
E. Mycophenolate mofetil

(Answers on page 12)

Answers for self-assessment questions on common childhood psychiatric disorders

1. TTTFT

Management of child psychiatric conditions is often aimed at symptoms rather than diagnoses due to difficulties in arriving at a diagnosis. High rates of co-morbidity leads to the practice of polypharmacy, where multiple medications are used to manage different conditions. Medications are commonly used for off-label indications due to lack of adequate evidence. Differences in pharmacokinetics and pharmacodynamics in children have to be considered along with their body weight when deciding on dosages. The management plan should be based on the bio-psycho-social formulation of the child's condition, and should always include suitable non-pharmacological measures.

2. TTFTF

Methylphenidate is a central nervous system stimulant effective for symptoms of Attention deficit hyperactivity disorders (ADHD) in children aged 6 years and above. Only the immediate release form is available in Sri Lanka and its maximum dose is 2.1 mg/kg/day in divided doses. It reduces seizure threshold.

3. FFTFF

There is no convincing evidence for pharmacological agents in the management of core features of autism. Children with autism are more likely to experience adverse effects due to psychotropic medications than children without neurodevelopmental disorders. Second-generation antipsychotics are used to manage aggression and self-injurious behaviours when environmental and behavioural approaches have failed. Melatonin is used in the management of sleep disturbances and methylphenidate is used in children with autism for the management of ADHD symptoms.

4. Answer: B

Second-generation antipsychotics are used in the management of irritability (including aggression and self-injurious behaviours) in children with autism and are recommended only after adequate environmental and behavioural approaches have failed. Recommended dose range for risperidone is 0.25 mg to 1 mg/day for short-term use (6-12 months). There is evidence from controlled trials for the use of lithium and sodium valproate but these are less efficacious than second-generation antipsychotics. Benzodiazepines are not recommended.

Answers for self-assessment questions on systemic lupus erythematosus

1. B – immediately withhold azathioprine

This patient's full blood count (FBC) done three days prior to admission shows that she is developing leukopenia. Her haemoglobin is low with a marginally elevated MCV and platelet count is also marginally low. Bone marrow suppression is known to occur with azathioprine and the earliest feature is leukopenia followed by a reduction in the platelet count. Although a flare of SLE may present with fever and pancytopenia, the absence of any other features of an SLE flare should alert the doctor that this may be drug induced leukopenia with a superadded infection. Dengue fever which may cause leukopenia and thrombocytopenia, is unlikely due to the prodrome of two weeks and it cannot account for the low haemoglobin level with a high MVC. Therefore, the most appropriate next step in the management would be to withhold azathioprine, and to commence intravenous empirical antibiotics after taking blood, urine and other appropriate samples for culture and ABST. The patient fluid status should be assessed, and fluid resuscitation should be started. In the meantime, urgent investigations to assess the SLE disease activity and organ involvement including urine analysis and renal functions should also be performed.

2. FTTTF

Gastrointestinal (GI) symptoms and dose-related bone marrow suppression are the most commonly observed adverse effects with MMF. Although there is evidence to suggest that MMF increases the risk of viral infections such as cytomegalovirus (CMV) infection and herpes zoster, there is some reason to believe that MMF exerts a protective effect against *P. jirovecii*. Other common adverse effects include hypertension, hyperglycemia, hypercholesterolemia and headache.

3. TFTFF

Pregnancy in patient with SLE should be pre-planned and it is desirable for the patient to be in disease remission when attempting conception to minimise the risks to the mother and the foetus.

Hydroxychloroquine can be continued in pregnancy, and it is compatible with breastfeeding. Continuing azathioprine during pregnancy does not appear to increase the risk of teratogenicity or other adverse pregnancy outcomes in when immunosuppression is necessary. It is also compatible with breastfeeding. Methotrexate, mycophenolate mofetil (MMF) and cyclophosphamide should be avoided in pregnancy and lactation. Methotrexate should be withheld for 3 menstrual cycles prior to attempting conception and MMF should be discontinued for 6 weeks before pregnancy.

In addition to the above, glucocorticoid therapy during pregnancy may increase adverse pregnancy outcomes such as premature rupture of the membranes (PROM), intrauterine growth restriction and, it may also increase the risk of pregnancy-induced hypertension, gestational diabetes, osteoporosis, and infection in the mother. Therefore, the lowest dose of glucocorticoids possible to control disease activity should be used during pregnancy. Furthermore, short-acting glucocorticoids such as prednisolone and methylprednisolone are preferred over longer acting agents (e.g. dexamethasone, betamethasone) because these are poorly metabolised by the placenta and reach higher concentrations in the foetus.