NEUROLOGY

NEWER INTERVENTIONS IN EPILEPSY MANAGEMENT

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Abstract: *Epilepsy is a global issue affecting about 70 million people among the world population. Nearly 80% of them live in low and middle-income countries with limited resources. Although highly advanced treatment is available in some countries, up to 90% of people with epilepsy are not adequately treated or are not treated with conventional antiepileptic therapy in resource limited countries.*

This review will highlight a few of the newer advances in management of epilepsy in children. They include pharmacological interventions, ketogenic diet, early genetic diagnosis and newer model multi-disciplinary team management of children with epilepsy.

Keywords: *Epilepsy, Treatment, Advances.*

Epilepsy is a global issue affecting about 70 million people worldwide. Nearly 80% of them live in low and middle-income countries with limited resources. An estimated 2.4 million people are diagnosed with epilepsy each year.[1] Although highly advanced treatment is available in some countries and parts of Asia, most of the people with epilepsy are not managed appropriately in developing countries.

Epilepsy in children differs from epilepsy in adults both in seizure type and epilepsy syndrome. The decision to treat is based on a careful evaluation of the balance between the likelihood of further seizures and the risk of adverse effect of the treatment. The aim of the treatment is to abolish seizures completely and at the same time keeping the side effects of the treatment to a minimum. It is generally reported that between 20-40% will have refractory epilepsy.[2] Refractory epilepsy increases the risk of cognitive deterioration, psychosocial dysfunction and

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sudden unexpected death. The treatment goal should be focused on preservation of social, vocational and cognitive performance and minimising complications.

This review will highlight newer advances in the management of epilepsy in children. They include pharmacological interventions (Perampanel, cannabinoids), ketogenic diet (KD), early genetic diagnosis and newer model multidisciplinary. Team management of patients with epilepsy. Epilepsy surgery has an important role in the management of refractory epilepsy but is beyond the scope of this article.

Good practice principles in medical management of epilepsy

Medical management of epilepsy is complex and has to be tailored to the individual patient. The management is variable in different parts of the world based on local availability of resources. Drug therapy remains the mainstay of management of epilepsy in children. Monotherapy is generally preferred to minimize the risk of adverse effects. If the treatment fails, it is preferable to try alternative monotherapy before moving on to combination treatment. Children who continue to have seizures on monotherapy are sometimes prescribed a long term second drug in addition.

Combining anti-epileptic drugs (AEDs) requires an understanding of their pharmacology, particularly their mechanisms of action. Other issues that must be considered in planning a treatment regimen for the individual patient include spectrum of efficacy, side-effect profile and propensity for adverse interactions. In the United Kingdom, National Institute of Health and Care Excellence (NICE) has formulated guidance for medical management of epilepsy.[3] Tables I and II summarize the guidelines for clinicians to choose an appropriate anti-epileptic medication based on the epilepsy syndrome and type of seizures.

Newer pharmacological interventions

Perampanel: Perampanel is a highly selective, non-competitive AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist. The mechanism of action is that it reduces neuronal

Table I. NICE guidelines on AEDs based on seizure types

Seizure type	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (that may worsen seizures)
Generalised tonic–clonic	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate Topiramate	Clobazam Lamotrigine Levetiracetam Sodium valproate		(If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy suspected) Carbamazepine Gabapentin Oxcarbazepine Phenytoin, Pregabalin, Tiagabine, Vigabatrin
Tonic or atonic	Sodium valproate	Lamotrigine	Rufinamide Topiramate	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine, Vigabatrin
Absence	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Clobazam, Clonazepam, Levetiracetam Topiramate Zonisamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin, Pregabalin Tiagabine, Vigabatrin
Myoclonic	Levetiracetam Sodium valproate Topiramate	Levetiracetam Sodium valproate Topiramate	Clobazam, Clonazepam, Piracetam Zonisamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin, Pregabalin Tiagabine, Vigabatrin
Focal	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate Lacosamide, Phenobarbital Phenytoin, Pregabali Tiagabine, Vigabatrin, Zonisamide	
Prolonged or repeated seizures and convulsive status epilepticus in the community	Buccalmidazolam Rectaldiazepam Intravenous lorazepam			
Convulsive status epilepticus in hospital **Refractory convulsive status epilepticus**	Intravenous lorazepam diazepam Buccal midazolam Intravenous midazolam Propofol (not in children) Thiopentalsodium	Intravenous phenobarbital Phenytoin		

Table II. NICE guidelines on AEDs based on epilepsy syndromes

Epilepsy syndrome	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiarycare	Do not offer AEDs (may worsen seizures)
Childhood absence epilepsy or other absence syndromes	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Clobazam, Clonazepam Levetiracetam Topiramate Zonisamide Vigabatrin	Carbamazepine Gabapentin Oxcarbazepine, Phenytoin Pregabalin, Tiagabine
Juvenile absence epilepsy or other absence syndromes	Ethosuximide Lamotrigine Sodium valproate	Ethosuximide Lamotrigine Sodium valproate	Clobazam, Clonazepam Levetiracetam Topiramate, Zonisamide	Carbamazepine Gabapentin Oxcarbazepine, Phenytoin Pregabalin, Tiagabine Vigabatrin
Juvenile myoclonic epilepsy	Lamotrigine Levetiracetam Sodium valproate Topiramate	Lamotrigine Levetiracetam Sodium valproate Topiramate	Clobazam, Clonazepam Zonisamide	Carbamazepine Gabapentin Oxcarbazepine Phenytoin, Pregabalin Tiagabine Vigabatrin
Epilepsy with generalised tonic -clonic seizures only	Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate	Clobazam Lamotrigine Levetiracetam Sodium valproate Topiramate		
Idiopathic generalised epilepsy	Lamotrigine Sodium valproate Topiramate	Lamotrigine Levetiracetam Sodium valproate Topiramate	Clobazam, Clonazepam Zonisamide	Carbamazepine Gabapentin Oxcarbazepine, Phenytoin Pregabalin, Tiagabine Vigabatrin
Infantile spasms not due to tuberous sclerosis	Discuss with, or refer to, a tertiary paediatric epilepsy specialist Steroid (prednisolone or tetracosactide) or vigabatrin			
Infantile spasms due to tuberous sclerosis	Discuss with, or refer to, a tertiary paediatric epilepsy specialist Vigabatrin or steroid (prednisolone or tetracosactide)			

Epilepsy syndrome	First-line AEDs	Adjunctive AEDs	Other AEDs that may be considered on referral to tertiary care	Do not offer AEDs (may worsen seizures)
Benign epilepsy with centrotemp-oral spikes	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate Lacosamide Phenobarbital, Phenytoin Pregabalin, Tiagabine Vigabatrin, Zonisamide	
Panayiotopoulos syndrome	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepine acetate, Lacosamide Phenobarbital, Phenytoin, Pregabalin, Tiagabine, Vigabatrin, Zonisamide	
Late-onset childhood occipital epilepsy (Gastaut type)	Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate Topiramate	Eslicarbazepin acetate Lacosamide Phenobarbital, Phenytoin, Pregabalin, Tiagabine, Vigabatrin, Zonisamide	
Dravet syndrome	Discuss with, or refer to a tertiary paediatric epilepsy specialist Sodium valproate Topiramate	Clobazam Stiripentol		Carbamazepine Gabapentin, Lamotrigine Oxcarbazepine Phenytoin, Pregabalin Tiagabine, Vigabatrin
Continuous spike and wave during slow sleep	Refer to a tertiary paediatric epilepsy specialist			
Lennox-Gastaut syndrome	Discuss with, or refer to a tertiary paediatric epilepsy specialist Sodium valproate	Lamotrigine	Felbamate Rufinamide Topiramate	Carbamazepine Gabapentin Oxcarbazepine Pregabalin, Tiagabine Vigabatrin
Landau-Kleffner syndrome	Refer to a tertiary pediatric epilepsy specialist			
Myoclonic astatic epilepsy	Refer to a tertiary pediatric epilepsy specialist			

hyperexcitability by targeting glutamate activity at postsynaptic AMPA receptors. It is approved as an adjunct therapy for focal-onset seizures and primary generalized tonic-clonic seizures (GTCS) in patients aged 12 years and older.[4] A multicentre, randomized, double-blind, placebo-controlled study, has demonstrated a 23.3% to 27.2% reduction in focal-onset seizures when perampanel is used as adjunctive treatment.[5] In a placebo controlled study in 164 patients aged 12 years and older with GTCS, a reduction in seizure frequency was observed in the perampanel group. 30.9% of patients treated with perampanel were free of Primary generalized tonic-clonic seizures, compared to 12.3% in the placebo group during the 13-week maintenance period.[4]

Perampanel is once-daily dosing and has a half-life of 106 hours. Enzyme-inducing antiepileptic drugs can reduce perampanel plasma concentrations and decrease its efficacy.[5]The most common adverse events are dizziness, fatigue, headache and somnolence. Specific adverse effects to monitor are neuropsychiatric events, including aggression, anger, homicidal ideation, hostility, and irritability. These side effects are dose-related and most often occur in the first 6 weeks of therapy. The combination of alcohol and perampanel significantly worsened mood and increased anger and the product labelling recommends avoiding the use of alcohol while on therapy with perampanel.[6]

Cannabidiol (CBD): Cannabinoids have been recognized to have a role in treatment of resistant epilepsy. The history of cannabis being used in treatment of various medical conditions dates back to perhaps as early as 4000 BC. In 1843 O'Shaughnessy W.B reported successful treatment of a 40days old infant with seizures. In 1937 following the marijuana act, scientific community lost interest in exploring cannabis as an anti-epileptic drug. In the 1970s and 80s there were reports of reduction in seizure frequency after smoking cannabis. Mechoulam and Carlini, in 1978 conducted the first human epilepsy trial.

Widespread community interest in cannabinoid products for epilepsy has grown as a consequence of social media reports of successful treatment in individual children. While the precise mechanisms by which CBD exerts its anticonvulsant properties in humans remain unknown, growing evidence suggests CBD reduces neuronal hyperexcitability through a unique multimodal mechanism of action. It antagonizes G protein-coupled receptor 55 (GPR55) at excitatory synapses. The inhibition of intracellular calcium release decreases excitatory currents and seizure activity. CBD desensitizes transient receptor potential vanilloid type 1 (TRPV1) channels. The resultant decrease in extracellular calcium influx decreases neurotransmission. CBD inhibits equilibrative nucleoside transporters (ENT1), reducing adenosine reuptake. The increase in extracellular adenosine reduces hyper excitability and neurotransmission.[7] CBD is metabolized in the liver by CYP2C19 and CYP3A4 enzymes and UDP glucuronosyltransferase 1 family, UGT1A7 and UGT2B7 isoforms. Peak plasma concentration (Tmax) is 2.5 to 5 hours. It is excreted in stools with minor renal clearance. Co-administration of CBD with clobazam, produce a 3-fold increase in plasma concentration of N-desmethylclobazam. Concomitant use of CBD and valproate increases the incidence of elevation of liver enzymes.

Open label study of Devinsky, et al (2016) included children and adolescents with refractory epilepsy.[8] Overall 36.5% reduction in seizures was reported. There was significant variability in daily dosage (up to 25 mg/kg/day). This study reported adverse events including somnolence, diarrhea and fatigue. Rosenberg (2016) performed a post study analysis of Quality of Life in Childhood Epilepsy (QOLCE) surveys in 20 patients.[9] Significant improvements in global scores and several sub scores were reported.

Thiele, et al (2018) enrolled 171 patients with Lennox-Gastaut syndrome (LGS) who were randomized to receive CBD or placebo.[10] A 2 weeks dose escalation of CBD to 20 mg/kg/day over two weeks and 12 weeks maintenance was used in this study. There was a monthly reduction in atonic seizures frequency by 43.9% in CBD group compared to 21.8% in placebo group (p=0.0096). There was also a monthly reduction in all seizure types by 41/2% in CBD group compared to 13.7% in placebo group (p=0.0004).

NICE guidelines published in December 2019 states that cannabidiol with clobazam is recommended as an option for treating seizures associated with Dravet syndrome and LGS in patients aged 2 years and older, only if the frequency of convulsive seizures is checked every 6 months. Cannabidiol is stopped if the frequency has not fallen by at least 30% compared with 6 months before starting treatment.[11,12,13]

Non-pharmacological intervention

Ketogenic diet (KD)**:** It is a high fat, low carbohydrate and adequate protein diet well-established as treatment option for drug resistant childhood epilepsies. KD was first described in the medical literature in 1921 as a treatment for epilepsy in children, following other reports of the beneficial effects of fasting on seizure control. The diet

was designed to mimic the metabolic changes that occur in the body during starvation, i.e. adaption to spare muscle protein breakdown and draw on energy reserves of body fat. Muscles and other tissues progressively switch energy source from glucose to free fatty acids which are converted to ketone bodies (acetoacetate and beta-hydroxybutyrate); these become the primary energy substrate for brain and other metabolically active tissues in the absence of adequate glucose supply. This state of ketosis is characterized by the rising levels of ketone bodies which can be measured in the blood or urine. This diet was known as the 'ketogenic diet' and is the basis of the classical ketogenic diet still used today.

This classical diet is based on a ratio of ketone producing foods in the diet (fat) to foods that reduce ketone production (carbohydrate and protein). A 'ketogenic' ratio of at least 3:1 is usually needed for maintenance of a good state of ketosis and optimal seizure control, although this varies between individuals and some will need a lower (2:1) or a higher (4:1) ratio. In a 3:1 diet, 87% of the energy is provided by fat, in a 4:1 diet this increases to 90%. Protein intake is based on minimum requirements for growth and is generally provided by a high-biological value source at each meal. Carbohydrate is very much restricted; the main sources being a limited portion of vegetables or fruit.

The medium chain triglyceride (MCT) ketogenic diet was developed in the 1970s as an alternative to the classical diet. MCT is absorbed and transported more efficiently in the body than other types of fat and will yield more ketones per unit of dietary energy. Therefore less total fat is needed on the MCT diet allowing more protein and carbohydrate food sources to be included. The traditional MCT diet which provided a higher amount of energy from MCT however led to reports of gastro-intestinal problems in some children and a modified version with less MCT was suggested.

The first RCT of the KD to demonstrate effectiveness in children aged 2-16 years was published in 2008.[14] In this trial, 145 children aged 2-16 years, who had failed at least two AEDs and had at least seven seizures weekly, were randomized to receive a KD, either immediately or after a 3-month delay with no additional treatment changes (the latter being the control group). After 3 months, the mean percentage of baseline seizures (on an intention-to-treat analysis) was significantly lower in the diet group (62%) than in controls (13.7%, p<0.0001). Twenty-eight (38%) of the diet group had greater than 50% seizure reduction, compared to four (6%) in control group (p<0.0001). A randomized controlled trial of both classical and MCT ketogenic diets did not find either type of diet to be significantly better in terms of efficacy or tolerability, concluding both diets have their place in the treatment of childhood epilepsy. The efficacy of the classical ketogenic diet for children with refractory epilepsy has been strongly supported by 2 randomized controlledtrials.[14, 15] For children with glucose transporter type 1(GLUT1) deficiency or pyruvate dehydrogenase complex deficiency, ketogenic diet is the treatment of first choice.[16]

Constipation was the most commonly reported adverse event of the ketogenic diet. One of the long-term concerns of the classical ketogenic diet is its negative effect on physical growth due to its limited protein content.[17] The ketogenic diet variant with medium chain triglycerides has the advantage of allowing a higher amount of protein and carbohydrates compared to the classical ketogenic diet. Still, no significant differences in growth were found between the classical and medium-chain triglycerides diet groups after 12 months, despite the significantly higher protein intake in the medium-chain triglyceridesdiet.[17]

In the past, neonates and infants were infrequently treated with the KD. However in a study by Dressler, et al the advantages of early use of the KD before 1.5 years of age and after 1.5 years of age was studied.[18] There were no significant differences between groups with respect to responder rates (63.8% vs 57.9 at 3 months), but more infants became seizure free (34.5% vs 19% at 3 months; 32.7% vs 17.5% at 6 and 12 months respectively. A significantly higher number of infants remained seizure free in the long term (p= 0.001). The study concluded that in infants with infantile spasms, LGS, myoclonic astatic epilepsy (MAE) and focal epilepsy, efficacy of KD has been shown high. The study recommended early use of KD in infancy as seizure freedom is essential for good developmental outcome.

Diagnostic intervention: Genetic testing

Targeted genetic testing plays an integral part of management of early onset infantile and refractory epilepsies in children. Identification of the causative mutation affects treatment as well as prognostic and genetic counselling. A number of studies have found a risk of 2%-4.6% for individuals with an affected first-degree relative.[19] Although this represents a doubling of risk, over 75% of individuals with a positive family history have only one affected relative and few families follow Mendelian patterns ofinheritance.[20]

Many types of epilepsy have a genetic component; this includes those that are largely genetic such as the genetic generalized epilepsies (GGE, previously called the

idiopathic generalized epilepsies). In contrast to the common self-limited generalized and focal epilepsies, there are many severe monogenic epilepsy syndromes where molecular testing has a key role in clinical practice today. Important examples include SCN1A (voltage-gated neuronal sodium channel) mutations associated with Dravet syndrome.

Advances in genomic technologies such as microarray-based comparative genomic hybridization (CGH) and DNA sequencing have revealed hundreds of heterogeneous pathogenic variants in patients with neuro developmental disorders, including epilepsy. In recent years, the importance of copy number variation (CNV), where variable numbers of genes exist, such as deleted or duplicated genes, has come to be recognized as part of normal human variation. CNVs are more likely to be pathogenic if they are larger. CNV testing by single nucleotide polymorphism (SNP) microarray or array comparative genomic hybridization (CGH) is also known as molecular karyotyping.

Early infantile epileptic encephalopathy (EIEE) is a devastating epilepsy syndrome with onset in the first months of life. Different countries are offering gene panel testing of varying numbersof genes tested and whole exome sequencing.

In a study by Ostrander, et al they applied whole-genome analysis (WGA) consisting of whole-genome sequencing and comprehensive variant discovery approaches to a cohort of 14 EIEE subjects for whom prior genetic tests had not yielded a diagnosis.[18] The study identified both de novo point and INDEL mutations and de novo structural rearrangements in known EIEE genes, as well as mutations in genes not previously associated with EIEE. The detection of a pathogenic or likely pathogenic mutation in all 14 subjects demonstrated the utility of WGA to reduce the time and costs of clinical diagnosis of EIEE. While exome sequencing may have detected 12 of the 14 causal mutations, 3 of the 12 patients received non-diagnostic exome panel tests prior to genome sequencing. Thus, given the continued decline of sequencing costs, their results supported the use of WGA as an efficient strategy for the clinical diagnosis of EIEE and other genetic conditions.[21]

Multidisciplinary care model

Nurse practitioners (NP) / Epilepsy Nurse Specialist(ENS): Epilepsy centers are increasingly employing multidisciplinary teams as a means to extend the availability of neurologic outpatient services.[22]

Nurse practitioners (NPs) offer a particular skillset of clinical expertise and counseling that is pertinent to epilepsy care, however, the result of their addition has not yet been well-characterized. Although epilepsy nurse specialists are used in the United Kingdom, a systematic review did not find strong evidence of benefit in clinical outcomes or patient satisfaction.[23] A 2016 Cochrane review concluded that epilepsy specialist NPs may improve the knowledge, compliance and quality of life of patients with epilepsy.[24] A study comparing physician only care model and NP/ENS - physician care team, found that both care models exceeded 90% adherence for the objective quality measures of documentation of seizure frequency, offering an intervention to reduce seizures and documenting or ordering testing for seizure etiology. With a longer follow-up period, the improved safety counseling provided by the NP-physician team care model may decrease mortality and morbidity. Furthermore, greater recognition of behavioral and psychiatric comorbidities may improve quality of life. There is evidence that epilepsy specialist nurses provide less costly consultation than physicians and that epilepsy specialist NPs can considerably reduce the primarycare costs associated with patients with epilepsy.[23, 24] This study suggests that employment of a NP–physician team can increase availability of care without compromising quality of care.

Surgery in resistant epilepsy

Epilepsy surgery is an effective way to control seizures in patients with drug-resistant epilepsy, often leading to improvements in cognition, behaviour, and quality of life. The effectiveness of surgical treatment depends on epilepsy type, underlying pathology, and accurate localisation of the epileptogenic brain region by various clinical, neuroimaging, and neurophysiological investigations. The surgical options include resective surgery and palliative surgery. Few of the resective surgical procedures include temporal lobe resections, extra temporal lobe resections and hemispherectomy. Palliative epilepsy surgical procedures include corpus callasotomy and Multiple Subpial Transections (MST). Minimally invasive procedures include neurostimulation procedures including Deep brain stimulation, Vagal Nerve stimulation and Responsive neurostimulation. Vagus nerve stimulation is applicable for drug-resistant epilepsy patients where resection of the lesion is not possible and for drug-resistant epilepsy patients with a previous history of surgical treatment failure. Responsive neurostimulation is a new technology that can discover epilepsy seizure activities in the brain through monitoring electrocorticographic activity, and to give a direct focal electrical stimulation, so as to

reduce epilepsy seizure through the targeted way.[25] Other minimally invasive surgical interventions include Stereotactic Radiosurgery and Stereotactic Laser Ablation (SLA). In stereotactic Radiosurgery, by focusing on the ionizing radiation targeted to the deep lesions, this method can avoid the damage to the surrounding tissue. When the epileptogenic zone is located in the deep brain or the important structure of the brain, which is not suitable to do the surgery, the stereotactic laser ablation may be a good choice.[25]

Conclusion

Though pharmacotherapy is the main modality of treatment in most epilepsies, ketogenic diet should be considered early in specific epileptic syndromes. Recent technological advances have resulted in newer drugs which have helped to reduce the seizure burden in patients with refractory epilepsy and to improve quality of life. Genetic testing aids early diagnosis, targeted treatment and avoidance of abundance of investigations. Continuing research will be needed for further advances in targeted treatment of genetic epilepsies.

Points to Remember

- *Epilepsy in children can differ from epilepsy in adults both in seizure type and epilepsy syndrome.*

- *Medical management of epilepsy is complex and has to be tailored to the individual patient. Monotherapy is generally preferred.*

- *If the monotherapy fails, it is considered preferable to try alternative monotherapy.*

- *Children who continue to have seizures on monotherapy are prescribed a long term second drug in addition.*

- *Pharmacotherapy with newer drugs and nonpharmacological therapy like ketogenic diet useful in certain resistant epilepsy.*

- *Genetic testing aids in diagnosis.*

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A survey is reported of 113 systematic reviews of therapies in neonatology, based on 559 eligible randomized trials in total. These reviews were prepared by the CNRG and were published in the Cochrane Library, Issue 3,2001. The median number of included trials per review was 3 (range 0 to 32) and participants 207 (range 0 to 5460). Among 90 reviews with a categorical primary outcome, the median number of outcome events per review was 54 (range 1 to 1284). Among reviews finding a statistically significant benefit of treatment, the effect size was large (median relative risk 0.55, range 0.09 to 0.93). Reviews of surfactant for prevention and treatment of respiratory distress syndrome were able to detect moderate-sized treatment effects (median relative risk 0.85) because of the large number and size of trials in this field. Among many reviews finding no evidence of treatment effect, large and potentially important benefits or harms could not be excluded. Most CNRG reviews were current. There is a continuing need to prepare systematic review of therapies not yet covered and to keep an increasing number of reviews up-to-date.

Study of lung ultrasonography as a diagnostic tool in childhood pneumonia.

According to current guidelines, pneumonia is diagnosed by clinical history, respiratory rate, fever, respiratory signs, and symptoms. A cross-sectional study was undertaken to compare chest ultrasonogram with chest radiography (CXR) in the diagnosis of 60 children. with fever and signs of respiratory distress, and they were divided in two groups: group I with pneumonia, which included 45 patients who were finally diagnosed as having clinically evident pneumonia, and group II without pneumonia.

Lung ultrasonography could detect consolidation in more than one lobe than CXR ($P = 0.048$). Authors have conlcluded that chest ultrasonogram offers an important contribution to the diagnostic procedures of pleuropulmonary disorders in children, such as pneumonia and pleural effusion, with higher sensitivity, specificity, and positive predictive index compared with CXR.

Elmashad GM, Bahbah WA, Mousa WA, Shalaby MM. Study of lung ultrasonography as a diagnostic tool in childhood pneumonia. Menoufia Med J 2019; 32:1043-50.