

CME Review

Management of asthma in children with long QT syndrome

Samuel Collins^{1,*}, John Widger¹, Andrew Davis^{2,3,4}, John Massie^{1,3,4}¹ Department Respiratory Paediatrics, Royal Children's Hospital, 50 Flemington Road, Melbourne, Victoria, 3052, Australia² Department of Cardiology, Royal Children's Hospital, 50 Flemington Road, Melbourne, Victoria, 3052, Australia³ Murdoch Childrens Research Institute⁴ Department of Paediatrics, University of Melbourne

EDUCATIONAL AIMS

The reader will be able to:

- Understand the pathophysiology of long QT syndrome and the relevance of different sub-types.
- Understand the role adrenergic beta receptor stimulation plays in cardiac events in long QT syndrome
- Consider the actions of commonly used asthma medications on the heart and their potential role in triggering cardiac events in patients with long QT syndrome.
- Be able to apply these principles when constructing an asthma management plan for patients with asthma and long QT syndrome.

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SUMMARY

The Long QT syndrome (LQTS) is a rare disorder in which patients are prone to life threatening ventricular arrhythmia and is a leading cause of sudden death in childhood. Asthma is common and its management in those with LQTS presents a number of potential difficulties. The mainstay of therapy in LQTS is beta-blockade, which may worsen symptoms of asthma. Conversely, beta-agonist therapy is the mainstay of asthma management; which, in those with LQTS, may provoke ventricular arrhythmias. We review available data regarding the management of coexistent LQTS and asthma, and provide a summary of the necessary considerations in managing these patients.

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INTRODUCTION

Asthma is a common problem in children for which there are well established management guidelines.¹ Some patients, however, may also have long QT syndrome (LQTS), see Figure 1, which is being increasingly recognised and may be as common as 1 in 2500.² The difficulty for patients with both conditions is that some standard asthma therapies, in particular those that stimulate β -adrenergic receptors, may provoke cardiac arrhythmia; conversely, the mainstay of treatment of long QT syndrome is β -receptor

blockade that may worsen asthma symptoms. We performed a literature search on asthma in LQTS (Pubmed – MESH terms [Long QT syndrome] [Jervell-Lange Nielsen Syndrome] [Romano-Ward syndrome] [Asthma] [Asthma, Exercise-induced]), which revealed only three papers. One of these was a short case series³ and two were data from the International Long QT registry.^{4,5} None of the papers provided a satisfactory strategy for managing these patients with apparently incompatible treatment needs. In addition, lists of drugs to be avoided in LQTS include beta-agonists such as salbutamol (also known as albuterol), terbutaline and salmeterol.⁶

Given the lack of published information on the management of asthma for patients with long QT syndrome, we have aimed to provide a theoretical framework and practical approach to management of this uncommon but difficult clinical problem.

LONG QT SYNDROME

Long QT syndrome is an important cause of syncope and sudden death in childhood. The individual is prone to 'Torsades de Pointes',

* Corresponding author at: Department of Respiratory Medicine, Royal Children's Hospital, Melbourne, 50 Flemington Road, Parkville, Melbourne, Victoria 3052, Australia. Tel.: +61 44 898 7188; fax: +61 03 9349 1289.

E-mail address: samacollins@gmail.com (S. Collins).

Abbreviations: LQTS, Long QT syndrome; RWS, Romano-Ward syndrome; JLNS, Jervell-Lange-Nielsen syndrome; AS, Anderson-Tawil Syndrome; TS, Timothy syndrome; ICD, Implantable Cardiac Defibrillator; VT, Ventricular tachycardia; EADs, Early after-depolarisations; TDR, Transmural dispersion of repolarisation; HR, Hazard Ratio.

Table 1

Classification of Long QT syndromes according to gene mutation and affected ion channel.

Classification of LQTS by genotype						
Name	Syndrome	Gene	Chromosome	Function	Triggers	Prevalence in LQTS patients
LQT1	RWS, JLNS	KCNQ1	11p	a-subunit IKs	Exercise, swimming, emotion	40–55%
LQT2	RWS	KCNH2	7q	a-subunit IKr	Sound/emotion	35–45%
LQT3	RWS	SCN5A	3p	a-subunit INa	Sleep, emotion	2–8%
LQT4	RWS	ANK2	4q	Adaptor	Exercise	<1%
LQT5	RWS, JLNS	KCNE1	21p	B subunit IKs	Exercise/emotion	<1%
LQT6	RWS	KCNE2	21p	B subunit IKr	Exercise	<1%
LQT7	AS	KCNJ2	17q	a subunit IK1	Exercise/rest	<1%
LQT8	TS	CACNA1C	12p	a subunit ICa	No specific	<1%
LQT9	RWS	CAV3	3p	Adaptor INa	Rest and sleep	<1%
LQT10	RWS	SCN2B	11q	B subunit INa	Exercise	<0.1%
LQT11	RWS	AKAP9	7q	Adaptor IKs	Exercise	<0.1%
LQT12	RWS	SNTA1	20q	Scaffold protein	Rest	<0.1%

**Fig. 1.** ECG (lead II) showing QT prolongation.

a form of polymorphic ventricular tachycardia which may deteriorate to ventricular fibrillation. Most long QT syndromes are caused by mutations in genes that encode the ion channels of the myocyte.⁷ There are at least 500 mutations amongst 12 different genes associated with LQTS⁸ (Table 1) of which LQTS type 1 and 2 are the most common. The QT interval is corrected (QTc) for heart rate, most commonly using Bazett's formula: $QTc = QT / \text{square root of previous RR interval (both in seconds)}$.^{9,10} The QTc is normally distributed in those unaffected by LQTS and this distribution overlaps substantially with the QTc values of the affected population⁹.

Syncopal during physical activity is an important symptom that requires cardiac assessment, although within LQTS symptoms may vary according to genotype. Swimming and physical activity are important triggers of LQTS type 1, whereas loud noises and emotional stress are important triggers of LQTS type 2.¹¹ In LQTS type 3, events are more common at rest or in sleep in association with QT prolongation at slower heart rates.¹²

Long QT syndrome can be congenital or acquired, with the latter usually caused by medications⁶, including some that are commonly used in paediatric practice such as clarithromycin, erythromycin, and domperidone. Some individuals may be predisposed to drug-acquired LQTS through polymorphisms or minor mutations in the genes associated with inherited LQTS.^{13,14}

Inherited LQTS was first described in 1957 by Jervell and Lange-Nielsen.¹⁵ Single gene mutations cause autosomal dominant LQTS (Romano Ward syndrome)^{14,16} whilst Jervell and Lange-Nielsen had described the occurrence of two of these mutations in a single patient. Jervell and Lange-Nielsen syndrome and Romano-Ward are, therefore, one disease that is autosomal recessive for deafness and autosomal dominant for LQTS. Other, rarer, associated syndromes include Andersen-Tawil syndrome (LQT7), which is associated with periodic paralysis, and Timothy Syndrome (LQT8) which is an association of LQTS, syndactyly, facial malformations and neurodevelopmental delay.

The physiological response to beta-adrenergic stimulation or blockade will differ according to genotype as different LQTS genotypes are associated with different triggers (Table 1) and controversy exists as to whether beta-blockade is efficacious for

some genotypes such as LQT3. Additionally, animal models show differential response to beta-agonists according to genotype and one could speculate that in humans, the same may be true.¹⁷

PATHOPHYSIOLOGY OF LQTS

A decrease in repolarising outward potassium channels or an increase in the depolarizing inward sodium and calcium channels will lead to prolongation of the QT interval. Repolarising potassium channels also appear to function as protectors from prolongation of QT interval with increasing heart rates. QT prolongation leads to an increase in early-after-depolarisations (EADs), which may trigger arrhythmias.¹⁸ This is worsened by differential dispersion of ion channels throughout the heart, known as transmural dispersion of repolarisation (TDR), which may lead to EADs occurring more frequently in certain parts of the myocardium and potentially triggering ventricular ectopy.¹⁹ TDR is increased by β -adrenergic activity in LQTS, particularly LQT1.²⁰ This may explain the relatively poor response to β -blockers in variants of LQTS other than LQT1/2 and perhaps the reason LQT1 cardiac events are particularly associated with exercise.^{17,21} It is these genotypes that are likely to be more sensitive to the adrenergic effects of asthma medications (Table 1).

LQT1 mutations affect slowly repolarising outward potassium channels (IKs) whilst LQT2 mutations affect fast repolarising channels (IKr). These IKr channels are also the site of action of almost all drugs that induce LQTS and are modified by serum potassium. The presence of hypokalaemia will worsen the effects of channel dysfunction in those with these mutations.²² This is particularly important in the setting of acute asthma where repeated β -2-agonist administration may induce hypokalaemia.

Current evidence points to inherited LQTS as a disorder of ion channels leading to a failure in the mechanisms that protect cardiac conduction against depolarisation/repolarisation disturbances resulting from adrenergic stimulation and increases in heart rate. The likely chain of events in the myocardium is shown in Figure 2.

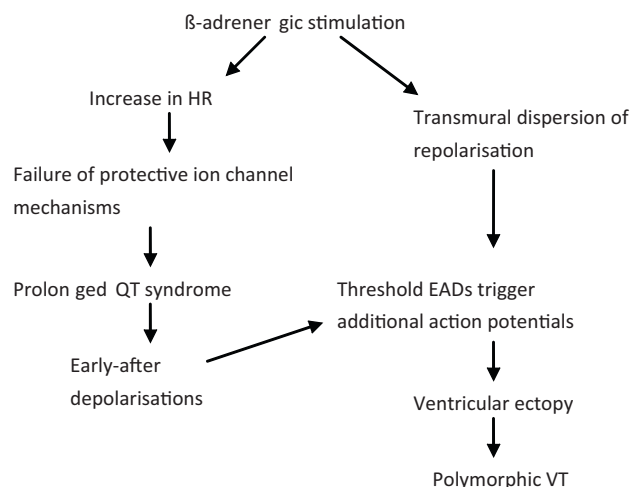


Fig. 2. Presumed mechanism of cardiac arrhythmia in LQTS.

PHYSIOLOGY OF β ADRENORECEPTORS

β adrenergic receptors can be subdivided into types 1, 2 and 3 and were initially ascribed to cardiac, respiratory and adipose tissue respectively. They are coded for by genes on chromosomes 10, 5 and 8.²³ β -2 receptors are found extensively throughout the lung, including airway smooth muscle tissue, where they regulate relaxation via cAMP activation²⁴. These receptors are the target of long and short acting β -agonists, which are mainstay treatments in asthma.

Cardiac myocytes express both β 1 and β 2 adrenoreceptors with a ratio of 70:30 in atria and 80:20 in ventricles. Although this ratio originally led to the belief that the positive inotropic and chronotropic effects of adrenergic stimulation were largely through β -1 receptors, *in vitro* and *vivo* studies have demonstrated a roughly equal effect from both β -1 and β -2 receptors.²⁵ Of interest to the clinician is the observation that intra-coronary injections of salbutamol cause an increase in heart rate, even in the face of β -1 blockade²⁶ and, given the relatively high β -2 receptor concentration in the sino-atrial node, may suggest that exercise related heart rate increase is at least partly β -2 mediated. Moreover, there are positive inotropic effects from β -2 agonist administration (salbutamol/terbutaline), with some attenuation following β -1 blockade. This implies that β -2 agonists are not completely selective in their action on the heart²⁶ and that β -agonist therapy exerts important effects on the myocardium. The long acting β -agonists, formoterol and salmeterol, are more selective for β -2 receptors however their lower affinity for the receptor means this difference is unlikely to be clinically significant.²⁷

As mentioned above, increasing heart rate – particularly exercise related – is a trigger for cardiac arrhythmias in patients with LQT1,2,4,5,6,10 and 11. Since it appears this increase in heart rate may be largely β -2 mediated, the potential danger of β -2 agonist administration in the treatment of asthma in those with LQTS becomes apparent.

CURRENT TREATMENT OF LQTS

The mainstays of preventative therapy in LQTS are β -blockade. Implantable cardiac defibrillators (ICD) and thoracoscopic selective cardiac sympathectomy, which is reserved for more difficult cases.^{7,28,29} β -blockers have been shown to be extremely effective, particularly in LQT1 patients³⁰ causing a 53% reduction in risk of cardiac events in children³¹ and a 64% reduction in adolescence³²,

Table 2

Examples of beta-blockers classed by beta-receptor subtype selectivity.

Non-selective (β 1 and β 2) blockers		Selective (β 1) blockers	
Cartelolol	Penbutolol	Acebutolol	Metoprolol
Carvedilol	Pindolol	Atenolol	Nebivolol
Labetalol	Propranolol	Betaxolol	
Nadolol	Sotalol	Bisoprolol	
Timolol		Esmolol	

and are usually initiated at diagnosis. Those at a higher risk of cardiac events include males, those with QTc greater than 0.50 and those with prior syncopal episodes.^{31,33}

Selection of β -blockers tends to be country and institution specific. Nadolol is commonly used in Europe and atenolol in Australia (where nadolol is not available). Compliance is a critical issue for all long QT patients.³⁴

Table 2 shows examples of non-selective and selective β -blockers. Bronchospasm is particularly associated with the use of non-selective β -blockers which act on both β 1 and β 2 receptors.

CURRENT EVIDENCE IN ASTHMA AND LONG QT

Asthma affects around 300 million people worldwide.³⁵ In the International Long QT syndrome registry, 3287 patients with QTc >450ms were identified and 101 these had received treatment for asthma. Treatment with β -agonist therapy for asthma was associated with a two-fold increase (hazard ratio [HR] = 2.0, 95% CI 1.26–3.15) in the risk of cardiac events (syncope, arrhythmia, aborted cardiac arrest), an effect that was more pronounced in the first year after commencing β agonist treatment (HR = 3.53, 95% CI 1.44 to 8.64) than in later years (HR = 1.77, 95% CI 1.06 to 2.95). This is potentially due to down-regulation of β -receptors with prolonged β -agonist therapy. The increase in cardiac events was worsened by the concomitant use of a steroid preventer (HR = 3.66, 95% CI 1.37 to 9.81), possibly due to the up-regulation of β receptors by corticosteroids.^{36,37} The increased risk associated with β -2 agonist administration was attenuated by concurrent β -blocker treatment (HR = 0.14, 95% CI 0.02 to 1.04, $p = 0.05$).⁴ Unfortunately medication dosing and disease severity were not measured and there is no mention of the genotype of LQTS, as these effects may differ between LQT1/2 and LQT3 groups. This study also includes all age groups, therefore the particular effects in children are not known.

In their 2002 case series, Khoudary and McGeady describe three patients with asthma who were subsequently diagnosed with LQTS. The three patients were commenced on β -blockers and remained well for long periods, before subsequently presenting in status asthmaticus. All three were treated with standard acute asthma treatment including inhaled β -2 agonists, intravenous steroids and one patient who received intravenous theophylline. No abnormal cardiac rhythms were seen.³ Whether β -blocker therapy was a contributing factor in the development of status asthmaticus in these cases is not clear. It is also unclear whether β -blocker therapy was protective against a cardiac arrhythmia in these patients who received significant β -2 receptor stimulation.

ALTERNATIVES TO β -AGONIST THERAPY IN ASTHMA

Inhaled anti-cholinergic medications such as ipratropium bromide are recommended in acute asthma management.³⁸ A 2005 systematic review showed inhaled anti-cholinergics were an effective addition to β -agonist therapy in moderate to severe asthma exacerbations.³⁹ Although the onset of maximal effect can

take 20–30 minutes, ipratropium bromide has been shown not to increase heart rate, even at relatively high doses.⁴⁰

Corticosteroids also form an essential part of acute management and, despite the suggestion that inhaled corticosteroids may potentiate the cardiac effects of β -agonists; there is no published evidence that short course oral steroids have this effect.

Intravenous magnesium sulphate has no deleterious effect on QT interval and is an established treatment for Torsades des Points.⁴¹ These combined effects on bronchospasm^{42,43} and cardiac conduction make intravenous magnesium sulphate an attractive therapeutic option in LQTS with asthma.

Intravenous aminophylline is known to cause a dose-dependent increase in heart rate⁴⁴ and is best avoided in LQTS. There is some evidence that a combination of β -agonists and aminophylline together are more harmful than either alone.⁴⁵

Long acting β -agonists such as salmeterol or formoterol should never be used alone in the management of asthma in children, and clearly pose some threat to those who also have LQTS. Some preventative medications include the combination of inhaled corticosteroids and long-acting β -agonists. These preparations are often recommended as step-up therapy for those with poorly controlled asthma using an inhaled corticosteroid alone. While this is the best approach to step-up therapy, a three-way randomised controlled trial showed that either a higher dose of inhaled corticosteroid or addition of a leukotriene receptor antagonist (montelukast) was beneficial in most cases.⁴⁶ Neither the three way step up trial nor other controlled trials of long acting β agonists include children less than six years so it would seem sensible to avoid them in under-sixes with asthma and LQTS.

Leukotriene receptor antagonists such as montelukast and zafirlukast act on the cysteinyl leukotriene (Cys LT₁) receptor, which is activated by leukotriene C₄, D₄ and E₄. CysLT₁ receptors are located in spleen, leucocytes and lung but not in heart⁴⁷, therefore they should be safe to use in LQTS. Current evidence does not support the use of leukotriene antagonists in the management of acute exacerbations of asthma⁴⁸; although there is some evidence for a positive effect in viral-wheeze.⁴⁹ Leukotriene receptor antagonists may be used for mild persistent asthma or exercise induced asthma and although competitive sports are discouraged in LQTS, recreational exercise is relatively well tolerated.⁵⁰

RECOMMENDATIONS

Patients with a confirmed diagnosis of LQTS are at high risk of cardiac events and current best practice is to commence β -blockers at diagnosis,⁷ as this reduces mortality in untreated children and adolescents^{31,32} and a diagnosis of asthma should not prevent this. While the effects of β -agonists on cardiac events may be attenuated by β -blockers it would be wise to minimise the pro-arrhythmogenic effects of asthma medication whilst maintaining adequate asthma control. It is also important to emphasise the need for close liaison with Cardiologists in planning the management of these patients. This is particularly important in high risk groups such as certain genotypes, boys, patients with previous syncope and those with QTc greater than 0.50³¹, where further treatment with surgery or ICD may be considered.^{28,29} There are three main situations to consider –

- Confirmed LQTS patient with a new diagnosis of asthma (or worsening asthma)
- Known asthma patients who are subsequently diagnosed with LQTS
- LQTS patients on β -blockers presenting with acute, severe asthma

Patients with a diagnosis of LQTS, in whom asthma is suspected, should be referred to a paediatric respiratory physician or asthma clinic for proper assessment of symptoms and medication needs.

LQTS PATIENT WITH A DIAGNOSIS OF ASTHMA

Once a diagnosis of asthma has been made in these patients, careful assessment of the severity of symptoms should be made. These patients should already be on a β -blocker as part of their LQTS treatment.

- Consideration should be given to use of ipratropium bromide as a reliever medication. If this is ineffective, beta-agonist reliever should be added.
- If symptoms are severe enough to require a preventer medication then consider starting a leukotriene antagonist as first line. The aim here would be to avoid the potential corticosteroid related increase in cardiac event risk.
- Failure to achieve control on a leukotriene antagonist could lead to addition of low-dose inhaled corticosteroids.

Patients who still require regular doses of an inhaled β -agonist and/or those who have frequent exacerbations should be managed in liaison with a Cardiologist in order to consider further prophylactic treatment such as left sympathetic denervation or implantable cardiac defibrillator (ICD).

This approach can also be modified according to LQTS genotype as β -agonists are likely to be relatively safe in LQT3, and it may be more appropriate to take a more standard approach to asthma management in these patients.

ASTHMA PATIENTS WHO RECEIVE A DIAGNOSIS OF LQTS

A difficulty may arise if a patient with well controlled asthma is diagnosed with LQTS. LQT3 patients are unlikely to need any change to their β -agonist therapy; however the current recommendations are for all LQTS patients to be started on β -blockers regardless of genotype.⁷ An assessment by a respiratory physician is advisable, as this would be an excellent opportunity to rationalise the patient's asthma medications. An approach similar to that in new diagnosis of asthma, as described above, could then be adopted. The addition of ipratropium bromide as a reliever could help to reduce the need for β -agonist therapy. Close monitoring of symptoms following commencement of β -blockers is suggested.

FAMILY MEMBERS OF THOSE WITH LQTS

In family members of those who have LQTS, all potentially afflicted members are screened with ECG and potentially exercise testing and genotyping prior to genetic counselling. This process should allow clinicians to differentiate those who should be treated as having LQTS and those who can follow standard asthma management guidelines.

ACUTE, SEVERE EXACERBATIONS OF ASTHMA IN LQTS PATIENTS

Management of these situations involves a balance of risks. The effects of a cardiac event in LQTS are potentially serious and treatment should aim to minimise this risk, however, this must be balanced against the need to appropriately treat a severe asthma exacerbation. It is important to consider that an acute exacerbation of asthma may cause a significant tachycardia and that successful treatment of the exacerbation may actually lead to a decrease in heart rate despite β -agonist therapy.

Ipratropium bromide should be administered as first line therapy to all patients in an attempt to reduce the need for inhaled

β -agonists. The difficulty with this approach is that ipratropium bromide may not have the rapidity of onset required for a severe exacerbation and therefore concurrent administration with inhaled β -agonists is likely to be needed. If inhaled β -agonists are used, they should be administered with continuous cardiac monitoring and close monitoring of serum potassium levels (particularly in LQT2 patients whose mutation leaves them highly sensitive to hypokalaemia). Metered dose inhaler with a spacer should be used for administration given their improved ratio of inhaled drug to systemic absorption compared to nebulised β -agonists.⁵¹

There is evidence for short course oral steroids in acute exacerbations so it would be appropriate for LQTS patients to commence a standard three day course of oral prednisolone (1 mg/kg/day; max 50 mg) at the earliest opportunity.

Given the beneficial effects on both bronchoconstriction^{42,43} and cardiac conduction⁴¹, it would be appropriate for all LQTS patients presenting to hospital with a severe asthma exacerbation to receive a dose of intravenous magnesium sulphate (0.1 mmol/kg).

Intravenous aminophylline or salbutamol should be avoided if possible given their known effect on heart rate. If clinical need necessitates the use of these agents then this should be done with cardiac monitoring and access to defibrillation. In those patients who are at particularly high risk (LQT1, male, QTc>0.50 s) or those with previous aborted cardiac arrest, then early intervention with non-invasive ventilation should be considered.⁵²

It is essential that each patient is provided with a personalised asthma action plan, including plan of management in an emergency situation. This can be tailored to each patient's asthma severity and their particular LQTS phenotype.

CONCLUSION

Although inherited LQTS is a relatively rare disease, asthma is very common and the problem of managing it in LQTS will arise. Given the limited evidence to guide treatment in these patients and the known risks of cardiac events, even in those on β -blocker treatment, efforts should be made to minimise β -adrenergic stimulation in these patients. This theoretical framework should provide a sensible approach to asthma management in patients who also have LQTS.

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CME SECTION

This article has been accredited for CME learning by the European Board for Accreditation in Pneumology (EBAP). You can receive 1 CME credit by successfully answering these questions online.

TRUE/FALSE QUESTIONS

1. Regarding long QT syndrome, which of the following is true?
 - A amongst those with long QT syndrome, patients have similar cardiac responses to physiological triggers.
 - B beta 1 receptor stimulation is responsible for increase in heart rate and results in prolongation of the QT interval.
 - C **there is overlap between the QTc interval of those affected by long QT syndrome and those who are unaffected.**
 - D acquired and inherited long QT syndromes are genetically distinct entities
 - E there are sub-types of long QT syndrome - Romano-Ward and Jervell-Lange-Nielsen syndromes.
2. Regarding current evidence on asthma in long QT syndrome, which of the following are true with regard to those with long QT syndrome?
 - A **asthma treatment is associated with an increased risk of cardiac events.**
 - B use of inhaled corticosteroids for the treatment of asthma decreases the risk of cardiac events.
 - C the risk of a cardiac events continues to increase with time.
 - D **beta-blocker treatment greatly reduces the risk of a cardiac event in those treated for asthma.**
 - E there is good evidence that the risk of cardiac events in children treated for asthma is low.
3. Which of the following drugs are associated with potential prolongation of QTc.
 - A **salbutamol**
 - B montelukast
 - C **aminophylline**
 - D magnesium
 - E ipratropium bromide
4. Regarding treatment of asthma in patients with long QT syndrome, which of the following are false?
 - A all patients should be started on a beta-blocker regardless of long QT genotype.
 - B **beta-agonists should be withdrawn owing to the risk of cardiac events.**
 - C **family members of those with long QT syndrome should be considered to have long QT syndrome when planning their asthma management.**
 - D those with infrequent intermittent asthma should be considered for an ipratropium bromide reliever.
 - E those with difficult asthma should be considered for alternative treatments for long QT syndrome.
5. When a patient with long QT syndrome presents with an acute, severe exacerbation of asthma, which of the following can be used?
 - A **inhaled beta-agonists with cardiac monitoring and serum potassium monitoring.**
 - B intravenous aminophylline
 - C **nebulised ipratropium**
 - D intravenous magnesium sulphate
 - E intravenous salbutamol