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Horizon Scanning Technology Prioritising Summary

Hypertonic saline therapy for cystic fibrosis

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PRIORITISING SUMMARY

REGISTER ID: **000282**

NAME OF TECHNOLOGY: **HYPERTONIC SALINE THERAPY FOR CYSTIC FIBROSIS**

PURPOSE AND TARGET GROUP: **CYSTIC FIBROSIS PATIENTS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☒	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☒	No	
☐	Not applicable	

A number of nebulisers are registered by the TGA, however hypertonic saline is not required to be registered.

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
USA	✓		
Canada	✓		

IMPACT SUMMARY:

Hypertonic saline would be prescribed by medical practitioners for cystic fibrosis (CF) patients. The hypertonic saline would be administered to CF patients in their own home using commercially available nebulisers. This additive treatment may improve quality of life, lower lung exacerbations and lower need for antibiotic treatments among CF patients.

BACKGROUND

Cystic fibrosis is a genetic condition caused by defects in the Cystic Fibrosis Transmembrane Regulator (CTFR) gene. The disorder is recessive, thus both parents must be carriers of copies of the defective gene. CF affects the function of several organs including the lungs, pancreas, intestines, and liver. The CTFR gene is

responsible for salt transport across cell membranes; as a consequence of the genetic defect, the mucus of people with CF is thick and viscous. This leads to problems with several organs. For example, in the lungs it leads to poor clearance of mucus and consequent repeated infections and blockages eventually resulting in loss of lung function. This degradation of organ function can lead to a shorter life expectancy, in Australia the life expectancy of a CF patient is mid to late thirties (Cystic Fibrosis Australia 2009a).

Although it is not fully understood, CF is thought to affect the liquid layer that lines the air exposed lung tissues. The defective CFTR gene may lead to an excessive reduction in this liquid layer, reducing the clearance of mucus. This can then block airways and acts as a promoter for lung infections, both of which lead to decreased lung function over time and eventual lung failure resulting in death. Hypertonic saline (concentrations may range from 4-6%) is thought to increase the volume of this liquid layer and hence undo the effects of the faulty CFTR gene, although this is currently speculation. Pharmaceutical hypertonic saline is administered using widely available commercial nebulisers in the patient's home or clinical settings (Enderby & Doull 2007).

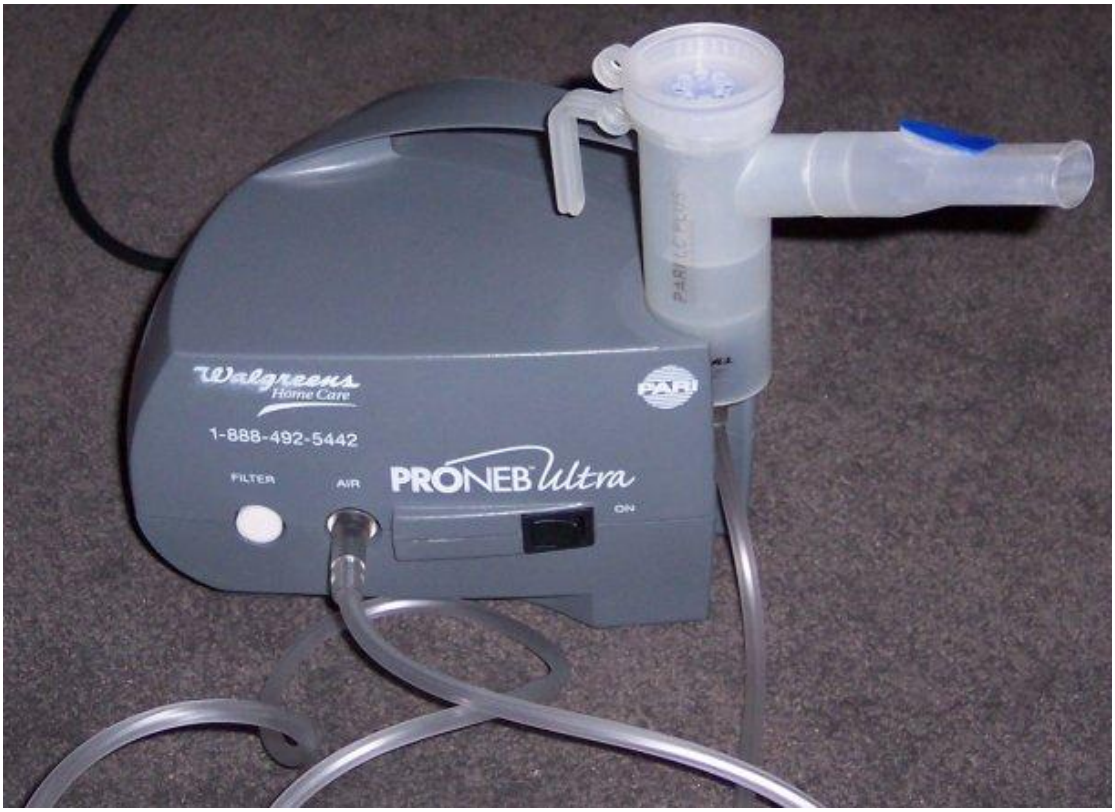

Figure 1 **A commercially available compressor and nebuliser**

CLINICAL NEED AND BURDEN OF DISEASE

One in twenty five Australians are carriers of CF. As the disease is recessive, if both parents are carriers, there is a 25% chance of their child having CF, i.e. two copies of the defective gene. Australia has approximately 2,500 people with CF. There are 80

babies born with CF every year in Australia equating to an incidence of 1 in 2500 births. Australia has a nationwide neonatal screening program that identifies approximately 95% of CF babies. Additionally, antenatal screening exists for subjects who have a CF family history or for partners of known CF patients.

Currently there is no cure for CF and as such therapy is aimed at slowing the progression of the disease. CF patients often require intensive lifelong treatment such as physiotherapy, antibiotic treatment, dietary control, digestive enzyme capsules and other therapies. Additionally, it is believed that loss of lung function begins in infancy and continues throughout the patient's life. The cause of death for CF patients is most predominantly loss of lung function (Cystic Fibrosis Australia 2009b).

DIFFUSION

While there is some evidence of usage in Australia there is not a wide spread use of this therapy. In particular there is little evidence of usage in young children and infants.

COMPARATORS

There are several techniques available for maintaining/preventing loss of lung function in CF patients. These are often used in combination to improve results. It is likely that hypertonic saline would be used in conjunction with these treatments rather than as a replacement for them. The main treatments for maintaining lung function aim to remove mucus secretions from the lungs and to unblock airways.

Physiotherapy is an integral part of CF treatment with most CF patients undergoing 2-4 sessions per day. Techniques such as chest percussion, vibrations and other physical manipulations are performed with the patient required to be in specific postures to facilitate mucus expulsion. Specific breathing techniques also play an important part in CF therapy. Controlled breathing with or without specific devices[1] is also used to maintain lung function (Cystic Fibrosis Australia 2009a).

SAFETY AND EFFECTIVENESS ISSUES

Several studies have investigated hypertonic saline in different populations of CF patients.

A study of 164 CF patients in 16 adult or paediatric centres across Australia investigated the effect of hypertonic saline on lung function during a 48 week treatment period. The study was conducted as a parallel, double-blinded trial in which subjects (6 years of age or older) were randomised to the experimental group, inhaling 4 ml of 7 per-cent hypertonic saline, or the control group, inhaling 4 ml of 0.9 percent saline, twice daily for 48 weeks. Both groups were treated with a bronchodilator before inhalation. Subjects continued their normal course of treatment in addition to

[1] Such as a handheld oscillating positive pressure device or a positive expiration pressure device. These devices provide enhanced clearance of secretions using air pressure and controlled breathing techniques.

the hypertonic saline, the randomisation algorithm attempted to correct for differences in treatment between the experimental and control groups. The primary outcome was change in lung function. This was measured as a function of three variables; forced vital capacity[2] [FVC], forced expiratory volume in one second[3] [FEV_1], and forced expiratory flow at 25 to 75 percent of FVC[4] [FEF_{25-75}]. There was no significant improvement in the primary outcome between the experimental and control arms. However, there were several significant improvements in hypertonic saline arm subjects as measured by secondary outcomes such as decreases in the frequency of pulmonary exacerbations, reduced antibiotic use for exacerbations, and reduced absenteeism from work or school (Table 1). Although the primary outcome was not met, there was an absolute difference between the hypertonic saline and control arms but due to variability in both arms the difference did not reach significance. In light of the safety, low cost of hypertonic saline treatment the authors conclude that it is an effective additional therapy (Elkins et al 2006) (Level II intervention evidence).

Table 1 Comparison between hypertonic saline and control treatments

	Significant improvement (p <0.05) with hypertonic saline treatment vs control treatment	**No significant difference (p >0.05) between hypertonic saline vs control treatment**
Primary outcome		Total lung function (FVC, FEV_1, FEF_{25-75})
Secondary outcomes	FVC alone	
	Frequency of pulmonary exacerbations	
	Reduced antibiotic use for exacerbations	
	Number of days free of exacerbations	
	Reduced absenteeism from work or school	
		Weight and body mass index
		Unscheduled hospital visits
		Pseudomonas aeruginosa in sputum
		Staphylococcus aureus in sputum
		Concentrations of interleukin-6, interleukin-8, interleukin-10, or TNF-α

CF caused lung damage is thought to begin in infancy and hence investigation of hypertonic saline as a treatment for infants is highly important. A pilot study to assess the tolerability of hypertonic saline in infants and young children enrolled 13 CF subjects. This short term study assessed if there were any negative outcomes to a hypertonic saline treatment. The subjects were all given a sequential treatment regimen consisting of a throat swab for microbiologic assessment, a baseline

[2] Forced vital capacity is a measure of the maximum rate of exhalation starting from a position of full inspiration, with no limit to duration of expiration
[3] Forced expiratory volume in one second measures the amount of air exhaled in one second
[4] Forced expiratory flow at 25 to 75 percent of FVC This is the average flow (or speed) of air coming out of the lung during the middle portion of the expiration

assessment of pulmonary function, administration of a bronchodilator, a second assessment of pulmonary function, hypertonic saline administration, and a third assessment of pulmonary function. There was no significant difference in the markers of tolerability assessed before or after hypertonic saline treatment. These markers included lung function, respiratory symptoms, respiration rate, heart rate, oxygen saturation, and microbiologic yield from the throat swab. The only side effect was coughing in 3 infants during hypertonic saline inhalation, which resolved within five minutes (Subbarao et al 2007) (Level IV intervention evidence).

A second assessment of hypertonic saline in CF children and infants was carried out by Dellon *et al*. Two populations were assessed in this study; eight infants (4 months to 3 years old) and seven preschoolers (4 years to 7 years). The treatment protocol assessed involved the administration of a bronchodilator, baseline pulmonary function assessment, treatment with normal saline, a second pulmonary function assessment, treatment with hypertonic saline, then a third pulmonary function assessment. There was no change to lung function during the protocol except in one preschool aged child who had a transient >20% drop in $FEV_{1.}$ This was treated with a second dose of bronchodilator. The authors concluded that there were no significant issues with administering hypertonic saline to this population (Dellon et al 2008)(Level IV intervention evidence).

The administration of hypertonic saline to CF patients seems to be a useful additional therapy that may reduce exacerbations of the lungs and may improve the quality of life of CF patients. Hypertonic saline seems to be safe to administer to infants and children.

COST IMPACT

The hypertonic saline is delivered by a nebuliser. This requires both the nebuliser and compressor. These are widely available on the internet and cost from $AU 90 to 270. The cost of the hypertonic saline is expected to be minimal and this would be available from pharmacists.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

No issues were identified/raised in the sources examined.

SUMMARY OF FINDINGS

The studies assessed here show that hypertonic saline has minimal side effects in CF patients and appears to be safe for usage in infants and children. A long term, blinded trial showed that while there was no difference in lung function over the study period there were improvements in several important secondary outcomes, such as lung exacerbations and increased quality of life. Further studies are needed to assess the

potential hypertonic saline induced changes to lung function that may either be beneficial or detrimental and whether this has an impact on quality of life and survival. Given the low cost and safety of hypertonic saline treatment it seems to be a moderately effective additional therapy for CF patients.

HEALTHPACT ACTION:

The use of hypertonic saline for the treatment of cystic fibrosis patients appears to be routine in a number of Australian jurisdictions, including Queensland and Western Australia, therefore HealthPACT has recommended that further assessment of this technology is no longer warranted.

NUMBER OF INCLUDED STUDIES

Total number of studies	
Level II Intervention evidence	1
Level IV Intervention evidence	2

REFERENCES:

Cystic Fibrosis Australia (2009a). [Internet]. Available from: http://www.cysticfibrosis.org.au [Accessed 12th May].

Cystic Fibrosis Australia (2009b). *Understanding Cystic Fibrosis* [Internet]. Cystic Fibrosis Australia. Available from: http://www.cysticfibrosis.org.au/pdf/Understanding_CF.pdf [Accessed 12th May].

Dellon, E. P., Donaldson, S. H. et al (2008). 'Safety and tolerability of inhaled hypertonic saline in young children with cystic fibrosis', *Pediatr Pulmonol*, 43 (11), 1100-1106.

Elkins, M. R., Robinson, M. et al (2006). 'A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis', *N Engl J Med*, 354 (3), 229-240.

Enderby, B. & Doull, I. (2007). 'Hypertonic saline inhalation in cystic fibrosis--salt in the wound, or sweet success?' *Arch Dis Child*, 92 (3), 195-196.

Subbarao, P., Balkovec, S. et al (2007). 'Pilot study of safety and tolerability of inhaled hypertonic saline in infants with cystic fibrosis', *Pediatr Pulmonol*, 42 (5), 471-476.

SEARCH CRITERIA TO BE USED:

Administration, Inhalation

Bronchodilator Agents/administration & dosage

Child

Child, Preschool

Cystic Fibrosis/ drug therapy

Respiratory Function Tests

Saline Solution, Hypertonic/administration & dosage/ adverse effects

Surface-Active Agents/administration & dosage/ adverse effects