Table 1 Prevention of respiratory exacerbations in cystic fibrosis

Approach	Agents	Evidence/study type*	Summary of results	Notes
Mucolytic agents	N-Acetylcysteine	Systematic review[28]	Exacerbation reduction not directly measured in trials	
	rhDNase	Three RCTs[29–32]	Reduction in exacerbations seen in several trials involving different patient groups	
	Hypertonic saline	One long-term RCT[36]	Reduction in exacerbations	
Physiotherapy and exercise	PEP	One study examining postural drainage/ percussion and the forced expiratory technique with the effect of forced expiratory technique alone[39]	No difference in rate of hospital admissions	
	Flutter	Flutter device compared with physiotherapy with PEP mask in 40 children with CF over a 12 month period[40]	A significant increase in rate of hospital admissions in flutter treated group	
	Exercise	One trial aerobic training[41]	No effect on exacerbation rate from aerobic training	
		One trial anaerobic training[42]	Exacerbation rate not analysed in anaerobic trial	
Antibiotics	Antistaphylococcal treatment	Cochrane review[23]	No difference in proportion of patients admitted to hospital	Respiratory exacerbations not defined
				Possible increase in rates of PsA infection
	Initial treatment of *P aeruginosa*	Cochrane review[26]	Studies have not reported effect on respiratory exacerbations	Ongoing studies will address whether early treatment of initial isolates of PsA will reduce respiratory exacerbations
	Nebulised antibiotics	Cochrane review[22]	Limited pooling possible to examine effect of respiratory exacerbations	
			Proportion requiring IV antibiotics reduced	
			Proportion requiring hospital admission reduced	
			Reduced days on IV antibiotics	
		RCT (n = 520) of tobramycin for inhalation (300 mg twice daily); 3 cycles of 1 month on, 1 month off treatment[60]	Reduced in hospital days.	Generally well tolerated treatment
				Long-term effect on tobramycin susceptibility uncertain
	Macrolides	Cochrane review[24]	Clear evidence from RCTs of a small but significant improvement in respiratory function following treatment with azithromycin	Study by Clement not included in meta-analysis
		Four RCTs (total n = 369) of azithromycin; trial 3–12 months (3 parallel group, 1 crossover design)[63–65 67]	Proportion requiring IV antibiotics reduced[64 66]	Hospitalisation examined in different time scales (3 and 6 months); it was not possible to combine these data in a meta-analysis
			Proportion requiring hospital admission reduced[64 66]	Modest increase in azithromycin groups of primary trial end point (FEV_1)[62–64]
			Reduced days on IV antibiotics†[64–67]	Not all patients had chronic PsA infection[62 64 66]
			Reduced in-hospital days[64 66]	No evidence during trial of increased antibiotic resistance or dispropionate acquisition of ''new'' infections[62–64 66]
			Reduced exacerbation episodes[65 67]	
			Longer time to first exacerbation[67]	
			Reduced oral courses[63 67]	
	Timing of antibiotic therapy	One published RCT (n = 60): patients randomised to two treatment arms (elective or symptomatic) and followed clinically at yearly reviews[125]	No difference in exacerbation rates	Study design resulted in more IV antibiotics being administered to patients receiving elective than symptom-directed antibiotics
Nutritional support	Enteral supplementation	No RCTs	Studies have not reported effect on respiratory exacerbations	Enteral feeding may lead to increased weight and possibly reduced rate of decline of lung function
	Oral high energy supplementation	One published RCT[82]	Study did not report effect on respiratory exacerbations	
Neonatal screening	Newborn diagnostic screening	RCT on newborn screening[83]	Longitudinal study has not demonstrated lung function advantage or reduction in respiratory exacerbations	Nutritional and growth advantage in patients diagnosed by newborn screening
Anti-inflammatory treatment	Oral corticosteroids	Cochrane review[17]	Studies have not reported effect on respiratory exacerbations	Increased side effects in oral steroid group

Table 1 Continued

Approach	Agents	Evidence/study type*	Summary of results	Notes
		One published RCT (n = 285); prednisone 2 mg/kg or prednisone 1 mg/kg or placebo on alternate days (maximum dose 60 mg); primary analysis planned for after 4 years of study[86]	No difference in rates of hospitalisation in high-dose steroid, low-dose steroid or placebo groups	An excess of adverse events resulted in the high-dose prednisolone (2 mg/kg on alternate days) being discontinued prematurely 3 years after accrual of participants commenced and the low dose was also discontinued 1 year later
	Inhaled corticosteroids	Cochrane review[14]	No evidence of effect on respiratory exacerbation rates	
		Subsequent RCT (n = 171): inhaled fluticasone withdrawal trial, 6 months duration[88]	Time to exacerbation not different between ICS withdrawal group vs ICS ongoing group	
			IV and oral antibiotic days and courses (treatment episodes) equivalent	Patients with asthma and recent oral steroids excluded from recruitment
	NSAIDs	Cochrane review[19]	Details on effects of respiratory exacerbations not provided	Post hoc subgroup analysis, effect on rate of decline of lung function confined to children aged 5–13 years
		RCT (n = 85) ibuprofen (20–30 mg/kg/day) twice daily; study duration 4 years[89]	Proportion of patients requiring hospitalisation in 12 months prior to study greater in ibuprofen group (27%) and this was stable in the final 12 months of the study (29%). Increase in placebo group in final 12 months of study (from 14% to 37%)	Low rates of prescription possibly related to gastrointestinal complications or need for ongoing drug level monitoring
			No difference in number of hospitalisation episodes or days spent in hospital	
	Leucotriene antagonists	Study published in abstract form[93]	Increased respiratory exacerbations (adults)	Safety monitoring committee prematurely terminated trial (420 of 600 recruited).
			Increased proportion of patients admitted to hospital with respiratory exacerbations (adults)	Adverse effects not seen in paediatric patients
Treatment of specific pathogens		No RCTs	No data available	Many RCTs exclude patients with multiresistant bacterial infection (eg, BCC infection).
Vaccinations	Influenza vaccination	Cochrane review[15]	No trials directly comparing vaccine with placebo	
	Pneumococcal vaccination	No RCTs	No data available	
	Pseudomonas vaccination	One unpublished RCT (see citation in body of text)	No effect on decreasing *Pseudomonas* colonisation	

RCT, randomised controlled trial; PEP, positive expiratory pressure; PsA, Pseudomonas aeruginosa; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; BCC, *Burkholderia cepacia* complex.
*Specific RCTs highlighted in the table which have addressed aspects of respiratory exacerbations (including hospital episodes and treatment with intravenous antibiotics).
†Clement study: reduction in intravenous antibiotics for patients with PsA infection.