

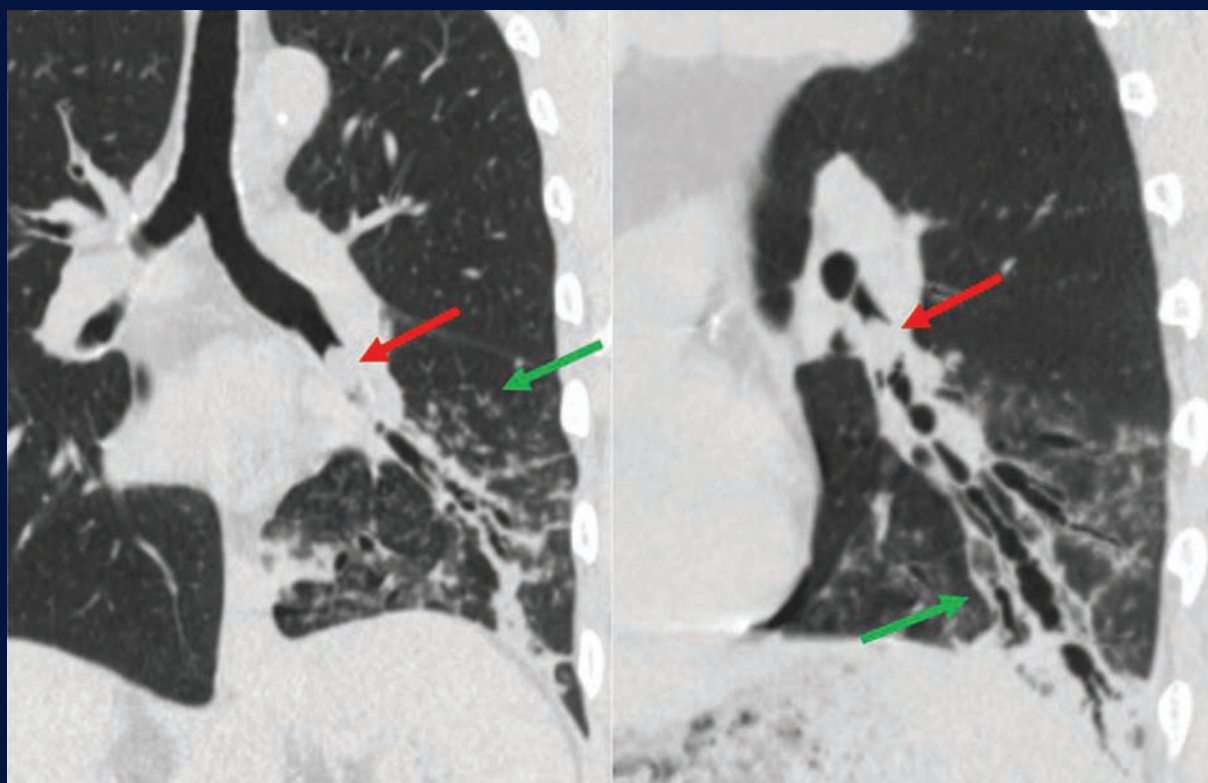
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF
DISEASE IN
CHILDHOOD

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Controle a asma^{1,2}

sem confundir os papéis.³



MAIOR CONTROLO NUMA ÚNICA TOMA.^{1,2}



LABA | ICS



1 INALAÇÃO



1 VEZ AO DIA

Revinty
furoato de fluticasona + vilanterol ELLIPTA
ELE CONTROLA

O perfil de segurança de Revinty foi validado em ensaios clínicos de grande escala, como o SUMMIT⁴ (n=4121) e SLS na Asma (n=2114)¹

1) Woodcock A et al. Lancet 2017; 390:2247–2255. 2) Bateman ED et al. Thorax 2014; 69:312–319. 3) GINA. Global strategy for asthma management and prevention, 2021. Available at: <https://ginasthma.org/gina-reports/> (Acedido: dezembro 2021). 4) Vestbo J et al. Lancet 2016;387:1817-1826. ICS: Corticosteroide inalador; LABA: Agonista β2 de longa duração de ação.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM. NOME DO MEDICAMENTO Revinty Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Revinty Ellipta 92/22 mcg: Cada inalação disponibiliza uma dose administrada de 92 mcg de furoato de fluticasona e 22 mcg de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 100 mcg de furoato de fluticasona e 25 mcg de vilanterol (como trifrenatato). Revinty Ellipta 184/22 mcg: Cada inalação disponibiliza uma dose administrada de 184 mcg de furoato de fluticasona e 22 mcg de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 200 mcg de furoato de fluticasona e 25 mcg de vilanterol (como trifrenatato). Cada dose administrada contém aproximadamente 25 mg de lactose mono-hidratada **FORMA FARMACÉUTICA** Pó para inalação em recipiente unidose **INDICAÇÕES TERAPÉUTICAS Asma:** Revinty Ellipta 92/22 mcg e 184/22 mcg está indicado para o tratamento regular da asma em adultos e adolescentes com idade ≥ 12 anos em que a utilização de um medicamento contendo uma associação (agonista beta₂ de ação prolongada e corticosteroides para inalação) é adequada; doentes que não estão adequadamente controlados com corticosteroides para inalação e com agonistas beta₂ de curta duração de ação 'conforme o necessário'; doentes que estão já adequadamente controlados com corticosteroides para inalação e com agonistas beta₂ de ação prolongada. **DPOC:** Revinty Ellipta 92/22 mcg está indicado para o tratamento sintomático de adultos com DPOC com um FEV₁ previsível normal <70% (após o broncodilatador) com antecedentes de exacerbação apesar da terapêutica regular com um broncodilatador. **POSOLOGIA E MODO DE ADMINISTRAÇÃO Asma (92/22 mcg e 184/22 mcg)** Adultos e adolescentes ≥ 12 anos Deve considerar-se uma dose inicial de uma inalação de 92/22 mcg uma vez por dia para adultos e adolescentes ≥ 12 anos que requeiram uma dose baixa a média de corticosteroides para inalação em associação com um agonista beta₂ de ação prolongada. Se os doentes não estiverem corretamente controlados com 92/22 mcg, a dose pode ser aumentada para 184/22 mcg. Os doentes devem ser regularmente reavaliados. A dose deve ser titulada para a dose mais baixa com a qual é mantido um controlo efetivo dos sintomas. Revinty Ellipta 184/22 mcg deve ser considerado para adultos e adolescentes ≥ 12 anos que requeiram uma dose mais elevada de corticosteroides para inalação em associação com um agonista beta₂ de ação prolongada. Os doentes normalmente verificam uma melhoria na função pulmonar 15 minutos após a inalação. É necessário o uso diário regular para manter o controlo dos sintomas de asma e o uso deve ser continuado mesmo quando esta é assintomática. Se os sintomas surgirem no período entre as doses, deve ser utilizado um agonista beta₂ de curta duração de ação, por inalação, para o alívio imediato. A dose máxima recomendada é 184/22 mcg 1x/dia. Crianças <12 anos A segurança e a eficácia ainda não foram estabelecidas na indicação para a asma. **DPOC (92/22 mcg)** Adultos ≥ 18 anos Uma inalação 1x/dia. Os doentes normalmente verificam uma melhoria na função pulmonar 16-17 minutos após a inalação. **População pediátrica** Não existe utilização relevante na população pediátrica para a indicação de DPOC. **Populações especiais Idosos (> 65 anos)** e **Compromisso renal** Não é necessário ajustar a posologia. **Compromisso hepático** Estudos revelaram um aumento na exposição sistémica ao FF. Devem tomar-se precauções na definição da posologia em doentes com compromisso hepático que possam estar em risco mais elevado de reações adversas sistémicas associadas a corticosteroides. Para os doentes com compromisso hepático moderado ou grave a dose máxima é de 92/22 mcg. **Modo de administração** Via inalatória. Deve ser administrado à mesma hora do dia, todos os dias. Se uma dose for omitida, deve tomar-se a próxima dose à hora habitual no dia seguinte. Após inalação, os doentes devem enxaguar a boca com água sem a engolir. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas foram cefaleia e nasofaringite. Com a exceção de pneumonia e fraturas, o perfil de segurança foi semelhante em doentes com asma e DPOC. Durante os estudos clínicos, pneumonia e fraturas foram mais frequentemente observadas em doentes com DPOC. **Infeções e infestações** Frequentes Pneumonia, infeção do trato respiratório superior, bronquite, gripe, candidíase da boca e da garganta **Doenças do sistema imunitário** Raras Reações de hipersensibilidade incluindo anafilaxia, angioedema, erupção cutânea e urticária **Doenças do metabolismo e da nutrição** Pouco Frequentes Hiperglicémia **Perturbações do foro psiquiátrico** Raras Ansiedade **Doenças do sistema nervoso** Muito frequentes Cefaleia **Raras Tremor** **Afeções oculares** Pouco frequentes Visão turva **Doenças cardíacas** Pouco frequentes Extra-sístoles **Raras** Palpitações, taquicardia **Doenças respiratórias, torácicas e do mediastino** Muito frequentes Nasofaringite **Frequentes** Dor orofaríngea, sinusite, faringite, rinite, tosse, disfonia **Raras** Broncospasmo paradoxal **Doenças gastrointestinais** Frequentes Dor abdominal **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes Artralgia, dorsalgia, fraturas, espasmos musculares **Perturbações gerais e alterações no local de administração** Frequentes Pirexia. **TITULAR DA AIM** GlaxoSmithKline (Ireland) Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** outubro 2021. **APRESENTAÇÃO:** Revinty Ellipta 92 mcg+22 mcg, 30 doses; Revinty Ellipta 184 mcg+22 mcg, 30 doses. **Regime de comparticipação:** Escalão B. Regime Geral 69%; Regime Especial 84%. **Medicamento Sujeito a Receita Médica.** Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial-Portela & C^ª, S.A., -à Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. As Marcas Registradas são propriedade ou licenças das empresas do grupo GSK. ©2022 empresas do grupo GSK ou sob licença.DMgMA_PT211117

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Índice Volume 6 Número 4

Thorax com artigos do Archives of Disease in Childhood

julho / agosto 2022

Edição Portuguesa N.º 4 julho / agosto 2022 - Volume 6

145 Editorial

147 Artigo original

147 Pneumonia pediátrica: derivação de um modelo para identificar doença grave

152 Fatores associados a doença respiratória grave do vírus

sincicial respiratório em crianças hospitalizadas: uma análise retrospectiva

156 Epidemiologia, características clínicas e resultados de tuberculose incidental em crianças no Canadá em 2013-2016: resultados de um estudo de vigilância nacional

161 Epidemiologia respiratória

161 Risco e impacto da tosse crônica em indivíduos obesos da população em geral

167 Melhoria da qualidade

167 Intervenções BReATHE (*Beating Regional Asthma Trough Health Education*) – uma abordagem inovadora no cuidado da asma infantil no Nordeste e Norte da Cúmbria, Reino Unido: um estudo intervencional

171 Declaração clínica da BTS

171 Declaração clínica da BTS sobre viagens aéreas para passageiros com doença respiratória



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Editorial

Este número da Edição de artigos das Revistas *Thorax* e *Archives of Disease in Childhood*, dedicados aos Sócios das Sociedades Científicas de Pneumologia, Alergologia e Imunologia Clínica, Medicina Geral e Familiar e Pediatria, apresenta uma série de artigos muito interessantes em que a criança é o alvo. No entanto, as outras vertentes do complexo poliedro que com acuidade crescente reconhecemos influenciar a saúde da criança e de todos, particularmente a respiratória, é muito diversificado. Neste número têm particular ênfase as infeções, com grande prevalência e ainda expressão de morbilidade e mortalidade em idade pediátrica, pneumonia aguda da comunidade, infeções por vírus sincicial respiratório e tuberculose.

Mas a importância e relevância destas infeções e as suas expressões clínicas é por todos reconhecida. Por isso nada de novo poderia ser antecipado. No entanto, estes três artigos procuram olhar para esta problemática a partir de um diferente ângulo: o da previsão de evolução com gravidade baseada em indicadores objetivos e o reconhecimento crescente de fatores individuais e demográficos para esta gravidade. Em tempos de registo clínicos rigorosos e utilização crescente de algoritmos é importante conhecer os indicadores relevantes das equações que nos permitem andar mais depressa, de forma mais prudente e consciente...

Imersos num Verão escaldante e numa grande instabilidade do Mundo o 4º artigo diz-nos que o futuro da saúde deverá contemplar alternativas aos motores de combustão. Mais uma evidência que nos chega de Pequim... Quem lá esteve ou teve algum doente que tenha lá residido não precisa ler o artigo para saber os resultados...

Mas queria aproveitar esta oportunidade para dar a conhecer o estudo de vigilância epidemiológica que está a decorrer numa parceria entre o INSA e a Sociedade Portuguesa de Pediatria com pontos focais em Hospitais com Pediatria, a nível nacional. Estes dados serão informativos para a epidemiologia viral mas permitirão também, no nosso País, conhecer os fatores de risco e gravidade e ainda vislumbrar a heterogeneidade das práticas.

Do Reino Unido chega-nos um excelente estudo de impacto de um programa educacional multifacetado na asma. E os resultados são naturalmente positivos e ...sustentados! Inspirador! E não ficamos por aqui. Temos finalmente uma orientação para as viagens de avião nos doentes pulmonares crónicos...

Boas leituras! Bom Verão! Boas Férias!

Que este tempo possa ser aproveitado para reflexões e reconstruções e possa vir a ser, individual e coletivamente, um alicerce de esperança num Mundo melhor.

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Pneumonia pediátrica: derivação de um modelo para identificar doença grave

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RESUMO

Contexto A pneumonia adquirida na comunidade (PAC) é uma das principais causas de internamento hospitalar de crianças. Existem dados limitados sobre os fatores preditivos de doença grave sem ferramentas preditivas pediátricas específicas.

Métodos Coorte retrospectiva (2011-2016) de casos de internamento por PAC. Analisámos variáveis clínicas recolhidas na apresentação hospitalar face aos resultados. Os resultados estratificados foram ligeiros (com hospitalização), moderados (procedimento de drenagem invasivo, cuidados intensivos) ou graves (ventilação mecânica, vasopressores, morte).

Resultados Reportámos 3300 casos de PAC, idade mediana de 2,0 anos (IQR 1-5 anos), com 2950 resultados ligeiros (88,5%), 305 (9,2%) moderados e 75 (2,3%) graves. Os resultados moderados-graves estiveram associados a hipoxia ($\text{SaO}_2 < 90\%$; OR 6,6, 95% IC 5,1 a 8,5), ao aumento do trabalho respiratório (grave vs. normal OR 5,8, 95% IC 4,2 a 8,0), a comorbilidades (+4 comorbilidades vs. nenhuma; OR 8,8, 95% IC 5,5 a 14) e a ser autóctone (OR 4,7, 95% IC 2,6 a 8,4). As crianças com febre apresentaram menos probabilidade de resultados moderados-graves do que as crianças sem febre (OR 0,57 95% IC 0,44 a 0,74). A área sob a curva (AUC) da característica de operação do recetor (ROC) do modelo completo foi de 0,78. As análises de sensibilidade demonstraram resultados semelhantes com as definições clínicas e radiológicas de PAC. Derivámos uma ferramenta técnica para estratificar a probabilidade reduzida, média ou elevada de doença grave (AUC 0,72). As pontuações elevadas (≥ 5) apresentaram uma probabilidade quase oito vezes superior de doença moderada-grave relativamente às pontuações reduzidas (≤ 1) (OR 7,7 95% IC 5,6 a 10,5).

Conclusões É necessária uma ferramenta preditiva de risco para a previsão de PAC infantil. Identificámos fatores de risco e derivámos uma ferramenta clínica simples que utiliza variáveis clínicas na apresentação hospitalar para determinar o risco de uma criança necessitar de tratamento invasivo ou de cuidados intensivos com um AUC ROC comparável com ferramentas para pneumonia em adultos.

INTRODUCTION

Worldwide, community-acquired pneumonia (CAP) accounts for 15% of all childhood deaths.¹ In high-income countries (HICs), CAP is a leading cause of hospital admission among children 0-4 years,² although mortality among hospitalised cases is low 0.1%-2.8%.^{3,4}

There is no singular definition of severe CAP. The WHO case definition of severe pneumonia (cough or breathing difficulty and tachypnoea with increased work of breathing and any general danger signs)⁵ has high sensitivity, to alert healthcare workers to identify a child needing hospitalisation, although poorly discriminates between CAP and other conditions.⁶ HICs benefit from high rates of pneumococcal, *Haemophilus influenzae* and measles immunisation, easier access to expert healthcare, lower rates of malnutrition, indoor air pollution and HIV infection. Expert guidelines, derived mostly from consensus rather than evidence, are preferred to guide CAP diagnosis and management in HICs.⁷ Severe CAP in HICs has been defined by morbidity outcomes such as treatment with mechanical ventilation, vasopressors or death.³

What is already known on this topic?

- Hospitalisation for paediatric pneumonia is common in high-income settings, although mortality is low.
- There is a need for a paediatric clinical tool to identify cases at increased risk of severe disease.

What this study adds?

- From a cohort of 3330 hospital admissions for community-acquired pneumonia, we have made considerable progress to developing a clinical risk tool.
- We detail objective variables, collected at presentation, associated with intensive care or invasive drainage treatments.

Recent data from a large cohort reported the strongest associations between CAP and intensive care admission to be a history of preterm birth, congenital heart disease and dyspnoea.⁸ The study did not detail intensive care treatments, and while these findings are useful, they are lacking quantitative measures such as vital signs and included cases with bronchiolitis. A prospective multicentre model derived from the EPIC data in the USA reported $\text{PaO}_2/\text{FiO}_2$ ratio, heart rate and respiratory rate centiles on presentation as the strongest predictors of severity. The model is difficult to apply in clinical practice, not yet validated and surprisingly reported no association between comorbidities and disease severity.⁹

Identifying objective clinical variables associated with CAP requiring intensive care treatments would inform key management decisions including transfer to tertiary care, empiric antibiotic selection and the need for additional investigations. The site of care is an important management decision directly influenced by disease severity^{10,11} and the need for high acuity care only available in tertiary centres.¹²

Unlike adult CAP, there is no validated clinical tool to assess paediatric disease severity. To derive a paediatric model, agreement on CAP case (clinical vs radiological)^{10,13} and severity¹⁴ definitions are required. We hypothesised that children at risk of severe CAP could be identified at the time of presentation to hospital.

AIMS

This study aimed to identify objective clinical variables associated with severe CAP, among children hospitalised with a clinical diagnosis of CAP. From this analysis, we sought to develop a simple clinical score to identify children at increased risk of severe disease.

METHODS

A cohort of children hospitalised for CAP at the Children's Hospital at Westmead, Sydney, Australia, between 1 January 2011 and 31 December 2016. Patients were identified by diagnostic coding (International classification of diseases, ICD-10) of pneumonia and individually reviewed by SH. Included cases met all of the following conditions: acute respiratory and infective symptoms with lower respiratory signs (tachypnoea, hypoxia, focal chest findings) not better explained by another pathology. We excluded cases of bronchiolitis, immunodeficiency, chronic suppurative lung disease, tracheostomy, recent hospitalisation (<14 days) or admission for a non-respiratory complaint.

Variables were collected at the first assessment. Vital signs were recorded as ordinal variables using age-adjusted standardised charts (see online supplemental data). Work of breathing (mild, moderate, severe) was recorded, if disagreement between medical or nursing descriptions, the more severe was recorded. We recorded a comorbidity as a medical issue with continued specialist input. We collected chest radiograph results from radiology reports; chest radiographs were categorised as consolidation with or without other infiltrate, normal or uninterpretable.¹⁵ We defined radiographic CAP for subgroup analysis as the presence of consolidation with or without other infiltrate.

Disease severity was stratified as mild (hospital admission), moderate (intensive care admission or invasive drainage procedure) or severe (mechanical ventilation, vasopressors or death).

Mild cases were compared with moderate-severe cases combined, due to low numbers in the latter. Univariable and multivariable binary logistic regression models were used to explore predictors of the outcome of moderate-severe CAP. Models were developed from multivariable regression beginning with a list of risk factors deemed to be clinically important (age, weight, indigenous background, number of comorbidities, prior antibiotics, immunisation status, respiratory rate, work of breathing, oxygen saturation and heart rate). Categories within risk factors where 95% CIs for the beta coefficients overlapped were collapsed together, and risk factors where 95% CIs for the only level contained the value 1 were dropped from the model, with the aim of creating a final model containing only risk factors with levels whose CIs do not overlap. Beta coefficients for individual risk factors from the final model were divided by the coefficient with the lowest absolute value and rounded to integers and summed across all risk factors, then compared with severity outcome proportions. We defined thresholds for low, intermediate and high risk based on observed severity outcomes: low risk <4%, moderate 4%–8% and high >8% proportion of moderate-severe CAP. Records with missing data were included in the model only if the missing variable could not alter the risk tier (low, intermediate or high). All analyses were performed in SAS V.9.4 (SAS Institute). No adjustment was made for multiple statistical comparisons. Repeat admissions in the same patient were assumed to be independent of each other (<1% total admissions).

RESULTS

We identified 4833 CAP admissions during the period 2011–2016; 3330 admissions (3305 patients) were included in the analysis. Excluded cases are as follows: non-respiratory presentation (n=529), immunocompromise (n=342), record duplication (n=208), recent hospitalisation (n=192), incomplete observations (n=88), respiratory symptoms with alternate diagnosis (n=90) and age >16 years (n=54).

The median age was 2.0 years (IQR 1–5 years), 52% were male, most were previously healthy (65% no comorbidities) and up to date with immunisations (91%). There were 2950 (89%) mild, 305 (9%) moderate and 75 (2%) severe CAP outcome classifications. Table 1 presents patient characteristics and outcomes.

In the mild cohort, 945 out of 2950 (32%) received supplemental oxygen and 262 out of 2950 (9%) received high-flow nasal cannula. Non-invasive was required in 146 out of 380 (49%) of the moderate-severe cohort. Complicated pneumonia requiring drainage procedures occurred in 107 out of 3330 (3%) cases, the

outcomes and microbiological findings of this dataset have been reported.^{16 17}

Figure 1 provides ORs and 95% CIs for factors associated with moderate-severe outcomes in univariable models. Cases with mild outcomes were younger than those with moderate-severe outcomes (OR=1.05 per year, 95% CI 1.02 to 1.08, p=0.001). Multiple comorbid medical conditions (two comorbidities vs nil; OR 3.6, 95% CI 2.6 to 5.1, 4 comorbidities vs nil; OR 8.8, 95% CI 5.5 to 14, both p<0.001), indigenous background (OR 4.7, 95% CI 2.6 to 8.4, p<0.001), abnormal weight centile (>97th vs normal OR 1.6, 95% CI 1.1 to 2.5, p<0.001 and <3rd centile vs normal, OR 2.8, 95% CI 2.0 to 3.9, p<0.001) were associated with moderate-severe outcomes. Having 48 hours of oral antibiotics prior to presentation (OR 0.55 95% CI 0.35 to 0.85, p<0.001) and being up to date with routine immunisations (OR 0.64, 95% CI 0.49 to 0.85, p<0.001) were both associated with milder outcomes.

The examination findings associated with moderate-severe outcomes were as follows: tachypnoea (severe tachypnoea; OR 2.2, 95% CI 1.6 to 3.0, both p<0.001); and apnoea on presentation (OR 91.8, 95% CI 33 to 254, p<0.0001), work of breathing (severely increased OR 5.8, 95% CI 4.2 to 8.0, p<0.001) and hypoxaemia (SaO₂ ≤90% vs ≥95%; OR 6.6, 95% CI 8.5 to 5.1, p<0.001).

Multivariable analysis of the effects of heart rate, respiratory rate and temperature allowing two-way interaction between variables, with moderate-severe outcomes, showed no evidence of interaction (all p>0.05). A temperature >38.5°C was associated with lower OR of moderate-severe outcome (OR 0.57 95% CI 0.44 to 0.74, p<0.001).

Bacteraemia (OR 3.0, 95% CI 1.8 to 4.7, p<0.001) was associated with a moderate-severe outcome. Neither an elevated C reactive protein (CRP) nor radiograph abnormality was associated with moderate-severe outcomes. Table 2 presents the multivariable regression of factors associated with moderate-severe outcomes.

Table 3 details the scoring tool for risk stratification, presenting the strongest variables and their weighting. Compared with cases with a low score, moderate or severe CAP was more likely for those with an intermediate (OR 2.2, 95% CI 1.5 to 3.1, p<0.001) or high score (OR 7.7, 95% CI 5.6 to 10.5, p<0.001). The ROC curves present the sensitivity and specificity of the models with an area under the curve (AUC) of 0.78 initial and 0.72 final (online supplemental material).

A subgroup analysis of cases meeting a radiographic definition of pneumonia reported a greater proportion of cases with moderate-severe outcomes than the entire cohort (radiographic diagnosis 263/1871, 14% vs clinical diagnosis 380/3330, 11%). All variables included in the clinical tool were associated with moderate-severe outcomes in the radiographic-confirmed subgroup.

DISCUSSION

We describe a large cohort of paediatric CAP from a high-income healthcare setting. The mortality rate in our cohort was low (<1%), with 9% requiring intensive care unit (ICU) admission. We have made considerable progress towards developing a severity score for paediatric pneumonia by describing objective variables, determined at presentation, and easily collected. We derived a simple clinical risk score associated with disease severity.

We stratified disease severity by ICU admission or invasive drainage procedure, a definition of clinical utility. From the model of best performing variables, we have derived a clinical scoring tool, which, if validated in another cohort, would support clinicians to stratify a patient's risk of severe disease at the time of hospital admission.

Children admitted with CAP and malnutrition (underweight or overweight), multiple comorbidities, increased work of breathing, hypoxia and age-adjusted tachypnoea or tachycardia had more severe outcomes. Children with prior antibiotic treatment and up-to-date immunisations were less likely to have severe disease.

The British Thoracic Society (BTS) and the Pediatric Infectious Disease Society CAP guidelines include consensus-based definitions of severe pneumonia.^{11 18} Our study provides an evidence

Table 1 Community-acquired pneumonia patient characteristics by severity

Patient characteristics	Total n=3330	Mild outcome n=2950	Moderate/severe outcome n=380
Median age in years (IQR)	2.0 (1.0–5.0)	2.0 (1.0–5.0)	2.0 (1.0–6.0)
Male (n, %)	1739 (52)	1528 (52)	211 (56)
Indigenous (n, %)	49 (1)	31 (1)	18 (5)
Weight centile 3rd–97th (n, %)*	2892 (87)	2600 (88)	292 (77)
Number of comorbidities (n, %)			
0	2213 (65)	2029 (68)	184 (48)
1	671 (20)	601 (20)	70 (18)
2	227 (7)	171 (6)	56 (15)
3	140 (4)	105 (4)	35 (9)
4+	79 (2)	44 (1)	35 (9)
Category of comorbidity			
Congenital heart disease	248	198	50
Neurological disease	179	121	58
Preterm birth	273	228	45
Pulmonary disease	338	307	31
Other	79	74	5
Immunisations up to date (n, %)	3020 (91)	2692 (89)	328 (86)
Prior antibiotics treatment (n, %)	817 (25)	749 (25)	68 (18)
Examination findings			
Respiratory rate† (n, %)			
Normal	2254 (68)	2048 (69)	206 (54)
Moderately increased	695 (21)	591 (20)	104 (27)
Severely increased	380 (11)	311 (11)	69 (18)
Work of breathing (n, %)			
Apnoea	26 (1)	5 (<1)	21 (6)
Normal	1051 (32)	1005 (34)	46 (12)
Mild increased	1206 (36)	1113 (38)	93 (24)
Moderately/severely increased	1044 (31)	825 (28)	219 (58)
Abnormal pulse oximetry (n, %)			
91%–94%	669 (20)	604 (20)	65 (17)
≤90%	478 (15)	320 (11)	158 (42)
Heart rate† (n, %)			
Normal	1878 (56)	1720 (58)	158 (42)
Tachycardia moderate	932 (28)	815 (28)	117 (31)
Tachycardia severe	518 (16)	415 (14)	103 (27)
Temperature (n, %)			
35.6°C–38.4°C	2293 (69)	2015 (68)	278 (73)
≥38.5°C	1025 (31)	930 (32)	95 (25)
Investigation results			
Positive blood culture (n, %)	88 (3)	62 (2)	26 (7)
Abnormal white cell count‡ (n, %)			
Leucopenia	179 (6)	147 (6)	32 (9)
Leucocytosis	927 (32)	774 (31)	153 (41)
C reactive protein >10 mg/L‡ (n, %)	1771 (85)	1533 (85)	238 (89)
Treatment characteristics			
Medical retrieval to CHW (n, %)	160 (5)	68 (2)	92 (24)
Direct to intensive care (n, %)	201 (6)	0	201 (53)
From ward to intensive care (n, %)	100 (3)	0	100 (26)
Mechanical ventilation (n, %)	68 (2)	0	68 (18)
Median days hospitalised (IQR)	2 (1–4)	2 (1–3)	8 (5–13)
Vasoactive agents (n, %)	17 (<1)	0	17 (5)
No vasoactive or ventilator support (n, %)		2906 (99%)	161 (42%)
Death (n, %)	9 (<1)	0	9 (2)

*WHO growth chart centile.

†According to age-adjusted New South Wales Health 'Between the flags' criteria.

‡According to Children's Hospital at Westmead (CHW) laboratory reference ranges.

base to support some *existing* consensus criteria while offering new insights, additional precision and objectivity to CAP assessment. We support the inclusion of increased work of breathing, hypoxia and tachypnoea as criteria for severe CAP. However, the BTS threshold of 50 breaths/min for all children >12 months may lack sensitivity in older children. Our age-adjusted thresholds for moderate tachypnoea were 50 (1–4 years), 35 (5–11 years) and 30 (children >12 years).¹⁹

The inclusion of fever >38.5°C in the severe CAP definitions is derived from consensus²⁰ and sepsis recognition guidelines.²¹ A systematic review of factors associated with pneumonia severity reported that a fever was not associated with more severe disease.²² Analysis of severity outcomes using heart rate, respiratory rate and the presence of fever, allowing for interaction, demonstrated higher rates of moderate-severe outcomes in children presenting without fever. We postulate that tachypnoea and tachycardia in febrile cases

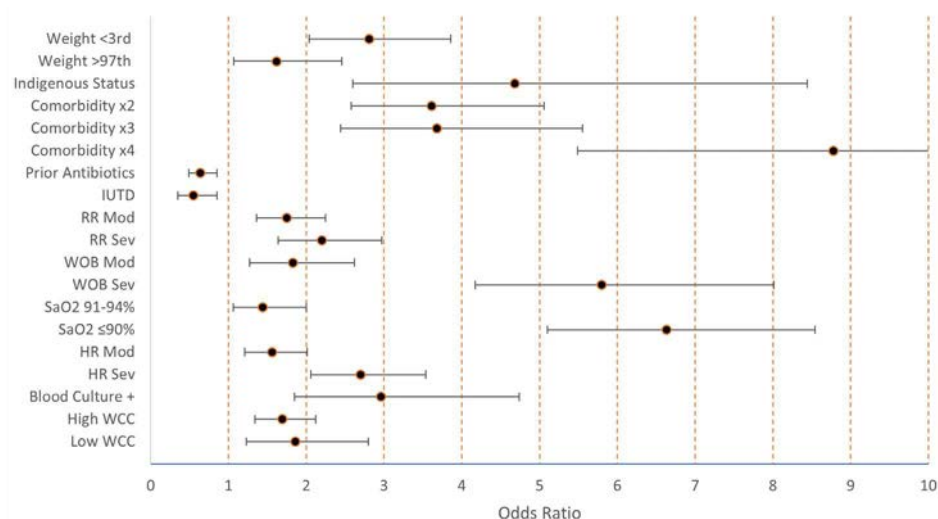


Figure 1 Forest plot displaying OR and 95% CIs of variables associated with moderate-severe outcome of children admitted with community-acquired pneumonia, 2011–2016. HR, heart rate; IUTD, immunisations up to date; RR, respiratory rate; SaO₂, arterial oxygen saturation; WCC, white cell count; WOB, work of breathing. Created by the authors.

reflect an increased metabolic rate, while in afebrile cases, these responses are driven by hypoxic compensatory mechanisms.²³ Our data suggest that the presence of fever on presentation is not useful in determining CAP severity and clinicians should be particularly wary of tachycardia and tachypnoea when the child is afebrile.

In low-income countries, malnutrition is a well-recognised association with more serious illness and death in pneumonia.^{1,24} Our study appears to be the first to report this association in a HIC and is consistent with intensive care studies reporting malnourished children having longer hospital stays and higher mortality.²⁵ The RISC and PIRO scores are clinical tools that share several variables described in our cohort. The RISC model included chest indrawing and both scores included hypoxia (SaO₂ <90%) and malnutrition. These tools are validated in areas with lower Pneumococcal conjugate vaccine (PCV) coverage and higher rates of malnutrition, HIV infection and mortality (6.5%–7.1%).^{26,27}

The stratification of mild, moderate and severe outcomes used in this study is consistent with other research⁹ and we observed a correlation between length of hospital stay and disease severity, another surrogate for disease severity, with moderate-severe cases staying an average of 6 days longer than mild. The delineation of moderate CAP as requiring treatment in a paediatric ICU marks is

of pragmatic value. Within our large dataset, 26%–28% of moderate and severe cases, respectively, were not identified as requiring intensive care treatment at presentation. Similarly, 43% of those retrieved to tertiary care were never admitted to intensive care and may have been able to be managed at the referring site. The use of a clinical risk prediction tool is needed and may improve precision around transfer decisions, allowing clinicians to be specific and proactive rather than reacting to clinical deterioration.

The multivariable model demonstrated reasonable discriminatory ability for identifying patients with more severe disease outcomes with an AUC of 0.78. The final AUC of the scoring tool was 0.72, comparable to adult CAP tools CURB-65, PSI and SMART COP (AUC 0.67–0.87)²⁸ which identify patients at risk of severe disease and tailor management to hospital admission, early consideration of ICU and the use of broad-spectrum antibiotics.²⁹

Case definitions are a major challenge in CAP research.³⁰ A subgroup analysis of our cohort including cases meeting a clinical and radiographic criteria reported the same clinical variables included in the model. Radiographic requirements are limited by availability, radiation exposure, poor inter-rater agreement³¹ and discordance between radiographic changes and disease severity^{22,32}; our data support a continued emphasis on clinical risk stratification.

Table 2 Multivariable regression of variables associated with moderate-severe outcome for CAP

Variable	Comparator	OR (95% CI)	P value
Weight <3rd centile	3rd–97th centile	1.64 (1.09 to 2.48)	0.018
Weight >97th centile	3rd–97th centile	1.73 (1.06 to 2.81)	0.028
Indigenous background	Not indigenous	3.32 (1.60 to 6.91)	<0.001
2 comorbidities	None	1.70 (1.10 to 2.60)	0.02
4+ comorbidities	None	4.43 (2.52 to 7.79)	<0.001
SaO ₂ ≤90%	SaO ₂ ≥95%	2.40 (1.75 to 3.30)	<0.001
Severe tachycardia*	Normal HR	1.71 (1.20 to 2.40)	0.002
Mild increased work of breathing	Normal	1.15 (1.02 to 2.25)	0.04
Moderate-severe increased work of breathing	Normal	5.80 (4.17 to 8.08)	<0.001
Temperature >38.5°C	35.6°C–38.4°C	0.69 (0.52 to 0.93)	0.01
Positive blood cultures	Negative	3.05 (1.80 to 5.20)	<0.001
High WCC†	Normal WCC	1.62 (1.24 to 2.10)	<0.001
Low WCC†	Normal WCC	2.02 (1.23 to 3.33)	0.006

*According to age-adjusted New South Wales Health 'Between the flags' criteria,

†According to Children's Hospital at Westmead laboratory reference ranges.

CAP, community-acquired pneumonia; HR, heart rate; RR, respiratory rate; SaO₂, arterial oxygen saturation; WCC, white cell count; WOB, work of breathing.

Table 3 Scoring tool for likelihood of moderate-severe CAP derived from CAP hospitalisations at the Children's Hospital at Westmead, 2011–2016

Variable	Score
Number of comorbid conditions ≥ 4	6
Number of comorbid conditions 2–3	3
Moderate-severe work of breathing	4
Mildly increased work of breathing	1
SaO ₂ <91%	4
Indigenous background	4
Weight for age <3rd or >97th centile	2
Moderate-severe tachycardia	1

Classification	Total score	Moderate-severe outcome (n, %)
Low risk (n=1336)	0–1	51 (3.8%)
Intermediate risk (n=852)	2–4	67 (7.9%)
High risk (n=1112)	≥ 5	259 (23%)

CAP, community-acquired pneumonia.

The study was limited by retrospective design with data being subject to omission, specifically, environmental tobacco exposure and blood pressure were poorly reported. The lack of standardised admission criteria to intensive care and broadening the pneumococcal vaccine in mid-2011 from 7-valent to 13-valent may be confounding factors. There was no standardised criteria in deciding admission to intensive care. The clinical variables were collected at the first medical encounter, the time from presentation to assessment was not included in this study. Health department performance reports during the study period report the study hospital median time to assessment for the lowest acuity CAP triage was 33–41 min.³³ Ethnicity data beyond indigenous status was not included though is important, patients identifying indigenous status were three times more likely to have a moderate-severe outcome. More severe outcomes may be related to lower socioeconomic levels, access to healthcare, increased smoking and different host susceptibility and response to causative organisms, as has been described in CAP studies from other countries.³⁴ We did not find an association between outcomes and CRP in the model. Guidelines for CAP do not recommend routine measurement of biomarkers and so sampling was inconsistent. Other data have shown an association with hypoalbuminaemia at presentation and complicated pneumonia³⁴; this is an important consideration for future research.

It is unclear if the findings from our data would be applicable in low-middle income countries, where factors such as overcrowding, low vaccination rates, poor home ventilation and alternate remedies are important concerns.³⁵

CONCLUSION

A clinical risk prediction tool for CAP in children is needed. We have defined risk factors to derive a simple clinically applicable tool for validation in other settings. CAP managed with invasive drainage or intensive care treatment was associated with multiple comorbidities, increased work of breathing, hypoxia, malnutrition, tachycardia and indigenous background. Our model identified children at risk of severe disease with an AUC 0.72–0.78. These findings provide an evidence base to current consensus definitions; however, the tool requires prospective validation.

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Contributors SH conceptualised, designed the study, collected the data, carried out the initial analyses with EHB, drafted the initial manuscript and revised the manuscript and is responsible for the overall content. HS, HG and DAF assisted in data analysis and critically reviewed and revised the manuscript. MS Barnes performed the statistical analysis and revised the Methods and Results sections. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Fatores associados a doença respiratória grave do vírus sincicial respiratório em crianças hospitalizadas: uma análise retrospectiva

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RESUMO

Contexto O reconhecimento precoce de crianças sob risco de infecção do trato respiratório inferior por vírus sincicial respiratório grave (RSV) é importante, uma vez que apoia as decisões de tratamento. Procuramos avaliar fatores associados a doenças graves entre jovens crianças hospitalizadas com infecção por RSV.

Métodos Realizamos um estudo de coorte retrospectivo para todas as crianças com idade < 2 anos hospitalizadas com infecção por RSV no trato respiratório inferior num único hospital pediátrico terciário ao longo de três estações de RSV (janeiro 2017 a dezembro 2019). Classificamos as crianças como tendo doença "moderada" ou "grave" com base no nível de intervenção respiratória e utilizamos modelos de regressão linear univariáveis e multivariáveis para determinar fatores associados à doença grave.

Resultados Entre 970 crianças hospitalizadas, 386 (40%) foram classificadas como tendo doença RSV "grave" e 584 (60%) como tendo doença RSV "moderada". As análises multivariáveis, a idade < 2 meses (OR: 2,3, 95% IC 1,6 a 3,3, p<0,0001), prematuros (OR: 1,6, 95% IC 1,1 a 2,4, p=0,02) e a co-deteção de RSV-vírus de parainfluenza tipo 3 (PIV 3) (OR: 2,6, 95% IC 1,05 a 6,5, p=0,04) estiveram independentemente associados à doença grave.

Conclusão A idade mais jovem, a prematuridade e a co-deteção de PIV3 estiveram associados a uma doença por RSV grave em crianças com idade < 2 anos hospitalizadas por infecção por RSV grave. A associação entre PIV3 e doença por RSV grave constitui um novo achado e exige mais investigação.

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infections (ALRIs) in infants and children.¹ Globally, RSV leads to approximately 33.1 million infections and 59 600 in-hospital deaths each year, with the largest burden in low-income and middle-income countries.¹ While mortality in high-income countries such as Australia is low, severe RSV disease represents a major burden on healthcare systems, particularly during winter.² While there are conflicting data, associations between severe RSV and later onset of asthma and recurrent wheeze have been shown,^{3,4} highlighting the importance of further characterising this group.

Several studies have identified risk factors for severe ALRI related to RSV. Younger age (particularly infants < 2 months of age) has been shown to be the strongest independent factor associated with severe RSV disease in a recent Australian study.⁵ Other risk factors include male sex, prematurity, maternal smoking, atopy, and chronic cardiac or pulmonary disease.^{6–10} However, most studies have been birth cohort or case-control studies with hospitalisation as the major outcome to define severe disease. Few studies have evaluated risk factors among hospitalised children with RSV ALRI; therefore, little is known about the contribution of other factors such as viral codetection. Further, there is often a lack of consistency in the definitions of severity used between studies.^{11,12}

Our objective was to evaluate the clinical, demographic and laboratory characteristics of children < 2 years of age hospitalised with laboratory-confirmed RSV disease to identify factors associated with severe disease.

What is already known on this topic?

- Respiratory syncytial virus (RSV) disease represents a large burden on healthcare systems.
- Early recognition of children at risk of severe RSV disease is important to inform management decisions.

What this study adds?

- Our study's findings support previous studies linking younger age and prematurity with increased RSV disease severity.
- The association between parainfluenza virus type 3/RSV codetection and severe disease is a novel finding that warrants further investigation.

METHODS

Study design

Children < 2 years hospitalised at The Royal Children's Hospital (RCH), Melbourne, Australia, between May 2017 and December 2019 with RSV infection were prospectively identified via laboratory notification of all positive cases. RSV status was determined using an in-house-developed and validated reverse transcription PCR from nasopharyngeal aspirates/swabs. Our standard respiratory viral panel also includes influenza A and B viruses, parainfluenza viruses 1, 2 and 3, and human metapneumovirus. RSV subgroup and the cycle threshold (Ct) value were provided by the RCH clinical laboratory.

Children presenting to the emergency department not requiring admission and those deemed to have nosocomial RSV infection (ie, symptoms developed > 48 hours after admission) were excluded from the study. Children could only be included in the study once and hence readmissions were excluded.

Clinical data collection

Patient data were extracted retrospectively from the electronic medical records to obtain relevant study data. This included demographics, clinical signs and symptoms, treatments, laboratory results, and outcomes. Data from full blood examinations was obtained on a subset of children as per individual clinician's discretion. Study data were collected and managed using REDCap electronic data capture tools hosted at Murdoch Children's Research Institute (MCRI). Guidelines for high-quality retrospective data collection by Kaji *et al*¹³ were followed. This included predetermining which data were to be collected using an organised collection form through REDCap, training data extractors and auditing their work.

Table 1 Definition of moderate and severe RSV disease based on the highest level of oxygen support received

	Frequency
Moderate	n=584
No oxygen support*	465 (80)
Low-flow oxygen support*	119 (20)
Severe	n=386
HHFNC*†	258 (67)
CPAP*†	82 (21)
BiPAP*†	2 (0.5)
Mechanical ventilation*†	44 (11.5)

*Data presented as n (%).

†Highest level of oxygen support.

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; HHFNC, humidified high-flow nasal cannula therapy; RSV, respiratory syncytial virus.

RSV genotyping and phylogenetics

To identify the circulating RSV genotypes, leftover airway samples were retrieved from the clinical laboratory of RCH and transported to MCRI for random processing of RSV glycoprotein gene sequencing and phylogenetic analysis (online supplemental methods 1). All sequences were uploaded to GenBank with accession numbers MW620481-MW620637 and MW620638-MW620806.

Definitions

'Severe disease' was defined as requirement for high-flow nasal prong oxygen support, continuous positive airway pressure, bilevel positive airway pressure or invasive mechanical ventilation. 'Moderate disease' was defined as requiring low-flow oxygen support or no oxygen support. This classification was in keeping with that used by Freire *et al*¹² in a recent publication on bronchiolitis. A decision to initiate high-flow nasal prong oxygen support was based on the RCH clinical practice guidelines.¹⁴ 'Prematurity' was defined by a gestational age <37 weeks. 'Socio-Economic Indexes for Areas (SEIFA)' determines the socioeconomic advantage or disadvantage based on postal codes in Australia, with larger numbers indicative of increased advantage. 'Family atopic history' included eczema, asthma or allergic rhinitis in a first-degree relative. 'Smoke exposure' was defined as smoking within the household. 'Ill-contact' included any contact with respiratory illness within the household. 'Allergies' included food and drug allergies. 'Breastfed' was defined as being breast fed at the time of admission. 'Immunisation up to date' required vaccination according to the Australian National Immunisation Program schedule for their respective age group.

Statistical analyses

Binary variables were coded using 0='no' and 1='yes' for analyses. These were summarised using frequencies and proportions. Continuous variables were presented as mean and SD (or median and IQR for non-normal data). Logistic regression was used to compare categorical variables across groups. For comparison of continuous variables across groups, Mann-Whitney U test or t-test was used based on normality of data. A Spearman's correlation was used to correlate Ct values with age and onset of illness. Backwards step logistic regression was used to identify factors associated with severe disease. The multivariable model included variables selected a priori and those identified empirically based on $p < 0.05$ on univariable analyses. Variables identified a priori were young age <2 months, prematurity, poor feeding and apnoea, which was guided by the literature.^{11 12 15} Variables reported with large amounts of missing data (>30% missing values) were excluded from multivariable analysis. Results of univariable and multivariable logistic regression models are presented as ORs, 95% CIs and corresponding p values. Statistical analyses were performed using STATA V.15.1.

RESULTS

Characteristics of the study population

During the study period, 1250 children under the age of 2 years were diagnosed with RSV infection at RCH, with 970 (78%) of these patients being admitted to hospital. Of these, 232 (24%) were admitted in 2017, 355 (37%) in 2018 and 383 in 2019 (39%). In our

study, 386 children were classified as severe disease (40%) and 584 (60%) as moderate disease (table 1). The median age at admission was 3.9 months (IQR: 1.5–11.2) and the median duration of hospitalisation was 2.2 days (IQR: 1.1–4.2). Most infections occurred in winter (June–August), which corresponds to the usual peak season of RSV infections in Australia (online supplemental figure 1).

Male children were over-represented (n=547/970, 56%) and a minority (n=15/970, 1.5%) identified as Aboriginal or Torres Strait Islander. One-fifth of the children (n=204/970, 21%) were born prematurely, with a median gestational age of 35 weeks (IQR: 31–36). The mean SEIFA decile was 6.7, with an SD of 2.6, showing most of our cohort were above the 50th percentile (more advantaged).

Children admitted with RSV often had siblings under the age of 5 years (n=435/752, 58%) and an ill household contact was present in approximately two-thirds (n=593/895, 66%). The mode of delivery was primarily vaginal delivery (n=523/878, 60%) and the majority were up-to-date with immunisations (n=765/886, 86%). Approximately one-fifth (n=201/970, 21%) had comorbidities, with most comorbidities being respiratory (n=55/201, 27%), cardiac (n=45/201, 22%), congenital abnormalities (n=22/201, 11%) or neurological (n=18/201, 9%) (table 2).

Table 2 Characteristics of children with severe and moderate RSV disease*

Characteristics	Whole cohort N=970	Severe n=386	Moderate n=584	P value
Age, months†‡	4 (1.5–11.2)	2.5 (1.2–8.5)	5.1 (1.9–13)	<0.0001
Male sex§	547/970 (56)	213/386 (55)	334/584 (57)	0.5
Indigenous descent§	15/970 (2)	6/386 (2)	9/584 (2)	0.99
Prematurity§	204/970 (21)	108/386 (28)	96/584 (16)	<0.0001
Gestational age, weeks†	35 (31–36)	35 (32–36)	34 (29–36)	0.4
<30 wGA¶	40 (20)	16 (16)	24 (25)	0.1
30–34 wGA¶	60 (29)	36 (33)	24 (25)	0.2
35–36 wGA¶	104 (51)	56 (51)	48 (50)	0.8
Birth weight, g**	2934±867	2868±912	2985±827	0.1
SEIFA score***††	6.7±2.6	6.4±2.7	7±2.6	0.001
Family atopic history§	220/671 (33)	78/272 (29)	142/399 (36)	0.1
Eczema§	105/953 (11)	29/379 (8)	76/574 (13)	0.01
Allergies§	72/966 (7)	18/384 (5)	54/582 (9)	0.01
Smoke exposure§	49/407 (12)	24/160 (15)	25/247 (10)	0.1
Breast fed§	506/964 (52)	209/381 (55)	297/583 (51)	0.2
Siblings <5 years§	435/752 (58)	188/306 (61)	247/446 (55)	0.1
Ill contact§	593/895 (66)	240/348 (69)	353/547 (64)	0.2
Immunisation up-to-date§	765/876 (87)	293/341 (86)	472/535 (88)	0.3
Vaginal birth§	523/878 (60)	201/345 (57)	322/533 (60)	0.4
Elective caesarean birth§	223/878 (25)	86/345 (25)	137/533 (26)	0.7
Emergency caesarean birth§	132/878 (15)	58/345 (17)	74/533 (14)	0.3
Comorbidity§	201/970 (21)	78/386 (20)	123/584 (21)	0.7
Cardiac‡‡	45 (22)	19 (24)	26 (21)	0.7
Respiratory‡‡	55 (27)	14 (18)	41 (33)	0.03
Neurological‡‡	18 (9)	6 (8)	12 (10)	0.8
Congenital abnormalities‡‡	22 (11)	11 (14)	11 (9)	0.3
Other‡‡§§	61 (30)	28 (36)	33 (27)	0.3

Significant p-values (<0.05) are in bold text.

*Logistic regression used for all analyses unless stated otherwise.

†Data presented as median (IQR).

‡Mann-Whitney U test performed.

§Data presented as n (%).

¶Data presented as n (%) of those born prematurely.

**Data presented as mean±SD.

††t-test performed.

‡‡Data presented as n (%) of those with comorbidity.

§§Other comorbidities include chronic liver/kidney disease, hypothyroidism and metabolic/genetic disorder.

RSV, respiratory syncytial virus; SEIFA, Socio-Economic Indexes for Areas; wGA, weeks gestational age.

Table 3 Clinical signs of children with severe or moderate RSV disease*

Characteristics	Severe n=386	Moderate n=584	P value
Increased work of breathing†‡	328/383 (86)	363/581 (62)	<0.0001
Tachypnoea†‡	177/386 (46)	222/584 (38)	0.02
Oxygen saturation‡§	96 (94–99)	98 (96–100)	<0.0001
Fever†‡	45/385 (12)	109/581 (19)	0.004
Wheezing†‡	188/383 (49)	216/582 (37)	<0.0001
Apnoea†¶	60/385 (16)	19/583 (3)	<0.0001
Poor feeding§¶	312/386 (81)	279/583 (48)	<0.0001

Significant p-values (<0.05) are in bold text.

*Logistic regression used for all analyses unless stated otherwise.

†Data presented as n (%).

‡Recorded at admission.

§Data presented as median (IQR).

¶Recorded at history or observed during admission.

RSV, respiratory syncytial virus.

Demographic and clinical factors associated with severe RSV disease

The severe group were significantly younger than the moderate group, with a median age of 2.5 months compared with 5.1 months ($p<0.0001$), respectively (table 2). Children in the severe group were more likely to have a history of prematurity ($p<0.0001$). Interestingly, the severe group were less likely to report eczema ($p=0.01$) and/or allergies ($p=0.01$); however, this may have been due to their younger age. Environmental factors such as tobacco smoke exposure, breast feeding, presence of siblings and ill contacts were similar between the groups. Additionally, immunisation status and mode of delivery at birth showed no relationship to severity of disease. Presence of comorbidities including cardiac, neurological and congenital abnormalities was similar between the groups, with the exception of respiratory comorbidities, which were more common in the moderate group ($p=0.03$; table 2). As expected, the severe group had a longer duration of hospitalisation (4.1 days compared with 1.2 days, $p<0.0001$; online supplemental figure 2).

Clinical signs of severity (eg, increased work of breathing, tachypnoea, poor feeding) were more likely to be present in the severe group, with the exception of fever, which was less common (table 3).

Laboratory factors associated with severe RSV disease

RSV genotyping was performed on a random subset of 263 of 970 (27%) patients (online supplemental figure 3) to observe whether specific viral genotypes were associated with disease severity. Similar proportions of RSV A and RSV B were observed between the moderate and severe groups (table 4). ON1 genotypes were identified for all RSV A sequences ($n=125$), and BA11 genotypes ($n=138$) were identified for all RSV B sequences (online supplemental figure 3). Ct values were positively correlated with age ($r_s=0.15$, $p<0.0001$) and onset of illness ($r_s=0.15$, $p<0.0001$). However, when adjusting for age and onset of illness, Ct values were still significantly lower in the severe disease group, suggesting higher viral load ($p<0.0001$; table 4).

All infants tested for RSV ($N=970$) underwent standard respiratory viral panel testing, enabling viral codetection. RSV was the sole detectable respiratory viral pathogen in the majority ($n=869/970$, 90%). Viral–viral codetection was similar across the two severity groups for a range of viruses except parainfluenza virus type 3 (PIV3). PIV3 was twice as likely to be present in the severe compared with the moderate disease group (OR: 2.2, 95% CI 1.2 to 4.3, $p=0.02$). PIV3 codetection was not associated with any differences in RSV Ct values between the moderate and severe groups. Full blood examinations revealed no differences between groups except for neutrophils, which were significantly lower in the severe group ($p=0.01$).

Multivariable analysis of factors associated with severe RSV disease

A multivariable model including clinical, laboratory and outcome data was employed. The

Table 4 Laboratory investigations of children with severe or moderate RSV disease*

Characteristics	Severe n=386	Moderate n=584	P value
RSV subgroup A†	155/313 (50)	266/486 (55)	0.1
Ct value‡§	20.6 (18.2–24.6)	22.7 (19.9–27.2)	<0.0001
RSV subgroup B†	158/313 (50)	220/486 (45)	0.3
Ct value‡¶	21.4 (19.1–24.9)	23.5 (20–27.9)	<0.0001
Codetection†	41/386 (11)	60/584 (10)	0.9
Parainfluenza 1 codetection¶	1 (2)	1 (2)	0.8
Parainfluenza 2 codetection¶	3 (7)	5 (8)	0.9
Parainfluenza 3 codetection¶	23 (56)	16 (27)	0.02
Influenza A¶	8 (20)	18 (30)	0.3
Influenza B¶**	0 (0)	6 (10)	–
Metapneumovirus¶	6 (15)	14 (23)	0.4
Haemoglobin (g/L)††††	244/386 (63) 118±20	269/584 (46) 119±17	0.6
Platelets ($\times 10^9/L$)††††	240/386 (62) 405±141	267/584 (46) 401±158	0.8
Lymphocytes ($\times 10^9/L$)†§§§	235/386 (61) 4.3 (3.1–6.1)	264/584 (45) 4.8 (3.2–6.5)	0.1
Monocytes ($\times 10^9/L$)†§§§	234/386 (61) 1 (0.6–1.4)	264/584 (45) 0.9 (0.6–1.4)	0.2
Neutrophils ($\times 10^9/L$)†§§§	243/386 (63) 3.4 (1.9–5.6)	269/584 (46) 4.3 (2.2–6.3)	0.01
Eosinophils ($\times 10^9/L$)†§§§	102/386 (26) 0.2 (0.1–0.3)	126/584 (22) 0.2 (0.1–0.3)	0.6
C reactive protein (mg/L)†§§§	159/386 (41) 24 (9–60)	216/584 (37) 24 (9–52)	0.6

Significant p-values (<0.05) are in bold text.

*Logistic regression used for all analyses unless stated otherwise.

†Data presented as n (%).

‡Data presented as median (IQR) of those with RSV subtype A.

§Mann-Whitney U test performed.

¶Data presented as n (%) of those with codetection.

**No logistic regression calculated as the severe group had no cases of influenza B.

††Data presented as mean±SD.

†††-test performed.

§§Data presented as median (IQR).

¶¶Data presented as median (IQR) of those with RSV subtype B.

Ct, cycle threshold; RSV, respiratory syncytial virus.

variables included were age <2 months, sex, prematurity, work of breathing, tachypnoea, poor feeding, apnoea, PIV3 codetection and Ct value (table 5).

DISCUSSION

In this large Australian study of >900 children under 2 years of age hospitalised with RSV ALRI, we have systematically described their clinical and laboratory characteristics and compared those with moderate and severe disease. Consistent with other studies on this

Table 5 Multivariable analysis of factors strongly associated with development of severe RSV disease*

Characteristics	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age <2 months	2.3 (1.7 to 3.0)	<0.0001	2.3 (1.6 to 3.3)	<0.0001
Prematurity	2.0 (1.4 to 2.7)	<0.0001	1.6 (1.1 to 2.4)	0.02
Eczema	0.5 (0.3 to 0.9)	0.01	–	–
Allergies	0.5 (0.3 to 0.8)	0.01	–	–
Respiratory comorbidity	0.5 (0.3 to 0.9)	0.03	–	–
Increased work of breathing	3.6 (2.6 to 5.0)	<0.0001	3.2 (2.1 to 5.0)	<0.0001
Tachypnoea†	1.4 (1.1 to 1.8)	0.02	1.6 (1.2 to 2.2)	0.001
Fever†	0.6 (0.4 to 0.8)	0.004	–	–
Wheezing†	1.6 (1.3 to 2.1)	<0.0001	–	–
Apnoea†,‡	5.5 (3.2 to 9.3)	<0.0001	4.5 (3.1 to 6.5)	<0.0001
Poor feeding†,‡	4.6 (3.4 to 6.2)	<0.0001	4.5 (3.1 to 6.5)	<0.0001
Parainfluenza 3 codetection†	2.2 (1.2 to 4.3)	0.02	2.6 (1.05 to 6.5)	0.04
Ct value†	0.94 (0.91 to 0.96)	<0.0001	0.96 (0.93 to 0.99)	0.01

Significant p-values (<0.05) are in bold text.

*Backwards step logistic regression performed for multivariable analysis to generate adjusted OR, 95% CI and p values.

†Recorded at admission.

‡Recorded at history or observed during admission.

Ct, cycle threshold; RSV, respiratory syncytial virus.

topic, we have shown that age <2 months and history of prematurity were independently associated with severe disease.^{9 16 17} While RSV subgroup was unrelated to disease severity, a lower Ct value (and by inference higher viral load) was observed in children with severe disease. ON1 and BA11 have been reported as the predominant genotypes of RSV A and RSV B subgroups in many places including Australia.^{18 19} Furthermore, we observed that RSV-PIV3 codetection was associated with greater than twofold higher risk of severe disease compared with the absence of codetection, which was a novel finding.

Few studies have evaluated factors associated with disease severity in hospitalised infants with laboratory-proven RSV disease,^{11 12 20} and among these definitions of severe disease vary widely. Furthermore, many studies were undertaken prior to the widespread availability of high-flow nasal prong therapy. For example, Rodríguez *et al*²⁰ defined severe RSV disease by the need for intensive care unit admission, while Butler *et al*¹¹ developed a severity score based on oxygen therapy, intravenous/nasogastric fluids and hospitalisation duration, with 'severe' disease defined as need for mechanical ventilation or hospitalisation of >5 days.¹¹ If we had applied this classification system to our cohort, only 11% of children would have been considered in the severe group. We therefore aligned our definitions with those of Freire *et al*,¹² which differentiated moderate and severe disease on the basis of level of respiratory support.

Consistent with previous studies, we have shown that young age and prematurity are independently associated with severe RSV disease.^{9 16 17} We also showed that comorbidities such as cardiac and respiratory comorbidity were high in our cohort (22% and 27%). Interestingly, children with respiratory conditions were more likely to have moderate than severe disease. This may be explained by clinicians exercising a lower threshold for admission of children with these comorbidities as per the RCH clinical practice guidelines.^{21 22} The observation that fever was more common in the moderate disease group may simply reflect the younger age of the severe group (2.5 months compared with 5.1 months), as younger infants with RSV bronchiolitis are less likely to develop fever.²³

Laboratory findings were also of interest. As expected, we found significantly higher RSV viral load in the severe disease group compared with the moderate group. Higher viral load has been shown to be associated with increased disease severity, as seen in a previous study comparing inpatients with outpatients with RSV infection.²⁴ Moreover, in a human challenge model, higher viral load was also correlated with higher symptom and physical examination scores and coincided closely with the timing of peak disease severity.²⁵

Most parameters on blood examination were similar between moderate and severe disease groups except neutrophils. It is plausible that the degree of neutrophil depletion may be proportional to disease severity, although this remains speculative. While neutrophils have been implicated in severe disease,²⁶ the lower total neutrophil counts observed in the severe group could also be explained by the higher proportion of prematurity and the younger age of children in the severe group.^{27 28}

Interestingly, we found that PIV3 codetection was independently associated with severe disease in this study, suggestive of possible viral synergy. This finding is supported by a study by Yoshida *et al*,²⁹ in which RSV-PIV3 was associated with increased risk of pneumonia and lower respiratory tract infection; however, this was also seen with other viruses, for example, human metapneumovirus. Unlike the present study, multivariable analyses were not performed in Yoshida *et al*'s study.²⁹ Interestingly, both studies showed inverse association between RSV and influenza. The mechanisms underlying such viral interactions are not fully understood but may be related to modulation of underlying host innate immune responses.

There are several notable strengths to this study. First is the systematic inclusion of clinical, laboratory and outcome data from all hospitalised children <2 years of age with RSV infection over a 3-year period. This has enabled detailed evaluation of multiple factors associated with disease severity. Second, the large size of the cohort has allowed for multivariable analyses to determine relative contributions of a range of variables. Third, the inclusion of data from a single institution allows for consistencies across laboratory testing and clinical management pathways. However, there are several limitations that warrant mention. First, this is a single-centre study, which may limit generalisability of findings to other settings. Second, due to the retrospective nature of data collection, there were missing variables for exposures, such as household cigarette smoking and

childcare attendance, precluding their inclusion in multivariable analyses. Lastly, we did not test for an extended panel of respiratory viruses (eg, human rhinoviruses), which may have modified the relationship between RSV-PIV3 codetection and severe disease.

CONCLUSION

Our study identifies several independently associated factors of severe RSV disease in hospitalised children <2 years with ALRIs, including younger age, prematurity, PIV3 codetection and higher viral load. These data may assist clinicians in assessing and managing infants with RSV infection to better identify those at greatest risk of needing higher levels of respiratory support. The potential synergy between PIV3 and RSV is a novel finding and warrants further research to understand the contribution of host immunity and viral-host interactions to disease severity.

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Contributors JA wrote the manuscript, performed the analyses and aided in the conception of the study. DW conceived the study and study protocol, and provided major input into manuscript revision, analysis and drafting. LAHD performed genotyping experiments and reviewed the laboratory data. MO collected patient data used for the analyses and critically revised the manuscript. LAHD, PVL, KM, KC, GW, A-MC, AD, FEB, NWC and TD contributed to interpretation of the data and critically revised the manuscript. CN contributed to data analysis and interpretation and critically revised the manuscript. LAHD and DW are equally contributed as last authors.

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Epidemiologia, características clínicas e resultados de tuberculose incidental em crianças no Canadá em 2013-2016: resultados de um estudo de vigilância nacional

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RESUMO

Objetivo A tuberculose infantil é difícil de diagnosticar e tratar, sendo uma causa de morbidade e mortalidade pouco reconhecida. Os dados reportados pelo Canadá não se focam na tuberculose infantil nem recolhem detalhes clínicos, epidemiológicos e microbiológicos essenciais. O objetivo deste estudo foi avaliar os dados demográficos, a apresentação e as características clínicas da tuberculose infantil no Canadá.

Métodos Realizámos um estudo de vigilância prospetivo entre 2013 a 2016 com mais de 2700 pediatras e programas verticais de tuberculose para a tuberculose incidental em crianças com menos de 15 anos no Canadá, usando o *Canadian Paediatric Surveillance Program* (CPSP).

Resultados No total, foram incluídos 200 casos neste estudo. A tuberculose foi intratorácica em 183 pacientes, dos quais 85% apresentaram exclusivamente envolvimento intratorácico. A tuberculose no sistema nervoso central ocorreu em 16 casos (8%). Cinquenta e um por cento dos casos foram hospitalizados e 11 (5,5%) foram admitidos numa unidade de cuidados intensivos. Foram reportadas reações adversas medicamentosas em 9% dos casos. O caso original, sendo, na maioria das vezes, um familiar de primeiro grau, foi conhecido em 73% dos casos. Cinquenta e oito por cento dos casos reportados foram de crianças autóctones nascidas no Canadá. As taxas estimadas do estudo relativas a casos reportados (por 100 mil crianças por ano) foi de 1,2 em termos globais, 8,6 em crianças autóctones e 54,3 em crianças Inuit.

Conclusão A tuberculose infantil poderá causar uma morbidade e uma utilização de recursos significativas. As principais geografias e grupos apresentam taxas de incidência muito elevadas. Erradicar a tuberculose infantil no Canadá irá requerer esforços elevados a nível comunitário, concentrando-se nestes grupos de risco elevado.

BACKGROUND

Globally, there were an estimated 10 million new cases and 1.4 million tuberculosis (TB)-related deaths in 2018.¹ In Canada, there are on average 1800 incident cases of TB disease per year with approximately 3% of disease occurring in children younger than 15 years.² In Canada, Indigenous peoples and foreign-born individuals are disproportionately affected by TB.³ Compared with adult TB, childhood TB disease is more difficult to diagnose, presents unique management challenges^{4,5} and is an under-recognised cause of morbidity.^{6,7}

TB is a reportable disease at the federal and provincial/territorial levels in Canada. However, available data do not capture important details including the type of disease, use and results of diagnostic tests, rates of culture confirmation and hospitalisation, follow-up data, rates of adverse drug reactions

What is already known on this topic?

- Childhood tuberculosis is under-reported and under-researched but, globally, is a major hidden cause of childhood mortality.
- According to the Public Health Agency of Canada, childhood tuberculosis accounts for about 3% of all cases in the country.
- National data lacked important clinical, treatment and epidemiological detail including methods of diagnosis that is needed to improve diagnosis, management and control.

What this study adds?

- This study prospectively surveyed clinicians and programs managing childhood tuberculosis and provides more epidemiologic and clinical detail than published Canadian data.
- There is substantial variation in regional incidence and remarkably high rates of tuberculosis in Indigenous Canadians who accounted for more than half of cases.
- This study demonstrated high rates of hospitalisation, central nervous system infection with intensive care unit admission and a substantial rate of adverse drug reactions.

(ADRs), rates in specific childhood populations and whether source cases were identified. To address these gaps, we conducted a multi-year prospective surveillance study of incident TB disease in children under the age of 15 in Canada using the Canadian Paediatric Surveillance Program (CPSP). Additional pertinent background information is given in the online supplemental appendix.

METHODS

The CPSP, a joint project of the Public Health Agency of Canada (PHAC) and the Canadian Paediatric Society, conducts active monthly national surveillance of over 2700 participant paediatricians and paediatric subspecialists for certain childhood disorders. For this study, we also included non-paediatricians from the TB programmes of Alberta, Saskatchewan, Nunavut, the Northwest Territories and British Columbia.

We aimed to identify incident cases of childhood TB between October 2013 and September 2016 and follow-up every 6 months until 6 months post-treatment completion. Pertinent data from the TB programme at Hôpital Sainte-Justine in Montréal, Québec, were retrospectively obtained in May 2017 outside of the CPSP platform. The protocol (<https://www.wcpspcpsca/uploads/studies/childhood-TB-protocol.pdf>) initially used existing international case definitions for the diagnosis of intrathoracic childhood TB,⁸ however, revised criteria for intrathoracic TB were published in 2015 so we reviewed and reclassified all cases as confirmed or unconfirmed by consensus adjudication by three authors (SKM, RJPG, IK) according to the new criteria.⁹

We calculated population-based age-specific rates of reported cases using 2016 population data¹⁰; for those <1 year of age we used number of live births. Due to potential under-reporting, rates presented here represent the lowest possible estimate of incidence of childhood TB for specific groups. Rates for Indigenous populations were calculated using denominators from Statistics Canada Aboriginal Population Profile.¹¹ Details of study's ethics approvals are provided in the online supplemental appendix.

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FINDINGS

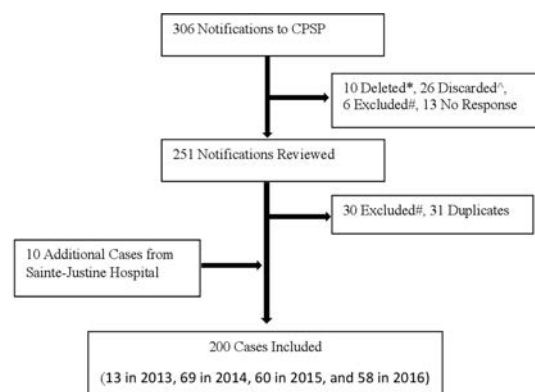
From October 2013 to September 2016, an average of 2536 monthly reporting forms were sent by CPSP and response rates averaged 81%. The number reported and reasons for exclusions are shown in figure 1 and 200 cases met the study case definition. Eighty cases (40%) were microbiologically confirmed and 116 (58%) were categorised as unconfirmed. The remaining 4 cases were categorised as presumed or difficult to classify. Sixty-six (36%) and 20 (53%) of intrathoracic and extrathoracic cases, respectively, were microbiologically confirmed.

The calculated minimum overall rate of reported cases of childhood TB during the study period was 1.2 per 100 000 per year compared with an approximate notification rate to PHAC of 1.6/100 000.¹¹ Comparisons with data reported by the PHAC are shown in the online supplemental appendix. Key demographics of cases reported to CPSP are shown in table 1. Reports by age group were 2.4 per 100 000 live births in children under 1 and 1.8, 0.6 and 0.9 per 100 000 population for the age groups 1–4, 5–9 and 10–14 years, respectively. Most cases (n=116, 58%) occurred in Canadian-born Indigenous children, the majority of whom were identified as First Nations (67%) or Inuit (30%). The reported case rate in all Indigenous children was 8.6/100 000/year with the highest rate being in Inuit children (54.3/100 000/year) (table 2).

Forty-three (22%) of reported cases were in Canadian-born non-Indigenous children. Thirty children (15%) were born outside of Canada of whom 13 (43%) were born in sub-Saharan Africa. Among the foreign-born, Africa was the most common continent, and the Philippines and India were the most common countries of birth (table 1). The rates of reported cases for foreign-born and Canadian-born children with at least one foreign-born parent were 2.7 and 1.4 per 100 000, respectively. Of Canadian-born non-Indigenous children, 14 (26%) travelled to an endemic country.

Most cases resided in Manitoba (n=62, 31%) followed by Ontario (n=32, 16%), Québec (n=28, 14%) and Nunavut (n=28, 14%). Annual incidence rates by province or territory of residence and First Nation and Inuit status are shown in table 2. The highest rates were in Nunavut (80.6 cases per 100 000, greater than 80 times that of the rest of Canada combined) and Manitoba (8.5 cases per 100 000). Of the 70 children identified as First Nations, 64 (91%) had their residence on reserve.¹²

Results related to exposure and previous TB diagnosis are shown in table 3. A source case was identified in 73% of cases: most (n=91, 65%) were close household contacts of either a first-degree (48%) or second-degree (37%) relative. Twenty-five children (of whom 12 (48%) were First Nation and 9 (36%) were Inuit) had previously received TB treatment, chiefly for latent TB infection.



*Deleted refers to case notifications that were deleted by the CPSP primarily for clerical reasons

*Discarded refers to case notifications that the reporting physician or healthcare professional was unable to complete the questionnaire, often because they no longer followed the patient or could not recall the case

#Excluded refers to case notifications that were noted to not meet inclusion criteria. When excluded by the CPSP this was primarily due to age 15+ years. When excluded by the Study Investigators, there were multiple demographic and clinical exclusions.

*No Response refers to case notifications that were sent questionnaires and reminders but did not return a questionnaire or correspond further with the CPSP

≥Duplicates were noted either by the CPSP program or by comparison of case demographics (sex, birth date, province/territory of residence)

Figure 1 Flowchart of cases notified, excluded and included. CPSP, Canadian Paediatric Surveillance Program.

Selected clinical features are shown in table 4. TB was intrathoracic in 183 (92%) patients of whom 25 (14%) had extrathoracic involvement. The most common extrathoracic sites were the central nervous system (CNS) and peripheral lymph nodes. Miliary or disseminated disease was seen in 20 cases. Five (14%) cases in Inuit children involved the CNS, of whom 3 (60%) had received BCG vaccine. Approximately two-thirds had symptoms, most commonly cough fever and weight loss. Only 12 (6%) children with incident TB had the classic triad of cough, weight loss and night sweats and fewer than 5 children had haemoptysis.

One hundred and sixty-five children had at least one tuberculin skin test performed of which 144 (87%) were positive. An interferon gamma release assay test was performed in 13 children of whom 10 (77%) were positive. Overall, 80 (40%) children had at least one positive culture from any site. One hundred

Table 1 Demographic features of cases

	Number (n)	%
Age (N=200)		
<1	28	14
1 to 4	82	41
5 to 9	36	18
10+	54	27
Sex (N=196)		
Male	99	50.5
Female	97	49.5
Ethnicity (N=200)		
Canadian born, Non-Indigenous	43	21.50
Canadian born, Indigenous, total	116	58
Canadian born, First Nations	(78)	(39)
Canadian born, Inuit	(35)	(17.5)
Canadian born, other	<5	n/a
Canadian born, Not Specified	11	5.5
Non-Canadian born, total (country or region of birth)	30	15
Africa	(13)	(6.5)
Philippines	(10)	(5)
South Asia	(5)	(2.5)
Other	<5	n/a

Table 2 Rates of reported case rates by province or territory of residence and Indigenous status

	Rate per 100 000	0–14 Population size	Cases (n)
Canada (N=200)			
Canada (N=200)	1.2	5 778 929	200
Province/territory of residence			
British Columbia	0.4	691 495	8
Alberta	0.9	764 638	21
Saskatchewan	3.1	213 796	20
Manitoba	8.5	243 534	62
Ontario	0.5	2 221 986	32
Québec	0.7	1 273 093	28
Atlantic Provinces*	n/a	343 482	<5
Nunavut	80.6	11 582	28
Indigenous status†			
Indigenous overall	8.6	448 865	116
First Nations overall	9.1	285 825	78
First Nations on-reserve	20.2	105 445	64
Inuit	54.3	21 495	35
Other	0.8	n/a	<5
Non-Indigenous	0.5	5 368 180	84

*Includes Newfoundland and Labrador, Prince Edward Island, Nova Scotia and New Brunswick. Fewer than five cases reported so incidence rate not calculated.

†Canada and province/territory-specific populations are averaged from 2013 to 2016 StatsCan July 1 yearly population estimates. Indigenous Status-specific populations are taken from the 2016 StatsCan Census.

and forty-four children had at least one respiratory sample taken for mycobacterial culture; culture was positive in 31 of 77 (40%) sputum and 31 of 74 (42%) gastric aspirate samples; 55% of children with intrathoracic TB in whom a respiratory sample was obtained had negative cultures. Nineteen of 77 (25%) sputa were in those younger than 5 years; of these, fewer than 5 were culture positive.

Resistance to at least one drug was reported in 5 (7%) isolates. Most were resistant to isoniazid and rifampin and thus classified as multi-drug resistant. There were no proven cases of extensively-drug-resistant TB.

The median duration of treatment for all cases was 26 weeks (IQR 24–32), for TB meningitis 48 weeks (IQR 30–65) and for disseminated disease 48 weeks (IQR 40.5–54). Median duration of therapy for the five cases with documented resistance was 48 weeks (IQR 36–48). Most children were treated with a three-drug regimen of isoniazid, rifampicin and pyrazinamide (n=99, 50%) or four-drug regimen that included ethambutol (n=79, 40%). Use of directly observed therapy was reported in 183 (96%) cases for which this information was available.

Reported and minimum estimated rates of selected clinical events are shown in online supplemental table 1. Fifty-one per cent of children were admitted to hospital for a median of 14 days (IQR 7–19, maximum 252). Intensive care unit (ICU) admission status was known for 84 children of whom 11 (5.5%) required ICU level care. Seven (54%) children admitted to ICU had CNS involvement.

In 17 cases (9%), an ADR required a change in treatment and 6 cases required hospitalisation for the ADR. The most common drugs implicated in ADR were pyrazinamide (5%, most commonly for hepatotoxicity) and isoniazid (3%, most commonly for hepatotoxicity). Other implicated drugs included amikacin (hearing loss), rifampicin (hepatotoxicity), ethambutol (visual changes), linezolid (marrow suppression) and cycloserine (neuropathy).

Longer term follow-up information was provided in 106 cases and of these, 97% and 90% had shown clinical and radiologic

Table 3 Key exposure, epidemiologic and past tuberculosis history data

	Number (n)	%
Source case (N=198)		
Known	145	73
Unknown	53	27
Source case relationship (N=128)		
First-degree relative	62	48
Second-degree relative	47	37
Friend	11	9
Other	8	6
Exposure type (N=140)		
Close household	91	65
Close non-household	34	24
Casual	6	4
Visit to endemic country	7	5
Community/other	<5	n/a
Source case known resistance to first-line agents* (N=137)		
Resistant	5	4
Not resistant	117	85
Not done or unknown	15	11
BCG vaccination (N=188)		
Yes†	86	46
No	81	43
Unknown	21	11
Previous tuberculosis diagnoses or treatment		
Latent tuberculosis, treated	17	8.5
Latent tuberculosis, untreated	<5	n/a
Active tuberculosis, treated	<5	n/a
Window prophylaxis	<5	n/a
Unspecified/unknown anti-tuberculosis therapy	<5	n/a

*All positive tuberculosis cultures in Canada undergo phenotypic drug-susceptibility testing. First-line agents are isoniazid, rifampin, pyrazinamide and ethambutol.

†For all children for whom immunisation status was known, BCG was received by 79% of Inuit children, 65% of First Nations children and 87% of foreign-born children.

improvement, respectively, at the time of final follow-up. Sixteen cases reported an extension of therapy beyond the originally planned time frame. Most common reasons for extended treatment included poor adherence to therapy (n=5), extrathoracic site of infection found after initiation of therapy (<5), poor radiologic or clinical response (<5) and drug resistance (<5). Fewer than five cases were reported as lost to follow-up and there were no TB-related deaths.

To understand the representativeness of our cases, we compared our results to the numbers of cases reported to the PHAC during the study time frame. Cases are de-identified in both reporting systems and could not be matched. For 2014 and 2015, where reporting periods were identical, CPSP reports were 74% of all cases reported to PHAC and 90% of PHAC reported cases when the province of Québec was excluded (online supplemental table 2). During the study, there were significant TB outbreaks in Nunavik, Québec, an Inuit region where TB is managed by clinicians not included in the CPSP surveillance system.¹³ Using additional demographic data from the province of Québec via PHAC (online supplemental table 3), we estimated a maximum number of 269 cases of childhood TB in Canada over the study period.¹⁴ Using these data, the minimum national incidence rates were 10.2/100 000/year for all Indigenous children, 100.8/100 000/

Table 4 Selected clinical features and results of investigations

	Number (n), n (%)	Duration, median (IQR)
Disease site*		
Only intrathoracic	158 (81)	
Intrathoracic and extrathoracic	25 (13)	
Only extrathoracic	13 (7)	
Extrathoracic sites		
Central nervous system	16 (8)	
Peripheral lymph nodes	13 (7)	
Symptoms†		
Cough	84 (42)	28 days (14–30 days)
Fever	52 (26)	16 days (7–78 days)
Weight loss	36 (18)	
Haemoptysis	<5	
No recorded symptoms	65 (33)	
Tests of infection		
TST positive	144/165 (87)	
IGRA positive	10/13 (77)	
Positive TB culture		
Any site (one or more)	80/200 (40)	
Sputum	31/77 (40)	
Gastric aspirates	31/74 (42)	

* Four cases with incomplete data excluded from analysis of disease site.

†No data on presence or absence of symptoms for 18 cases.

IGRA, Interferon gamma release assay; TB, tuberculosis; TST, tuberculin skin test.

year for Inuit children and 1.55/100 000/year for all children in Canada (online supplemental table 4).

DISCUSSION

This study is one of the first nation-wide surveys to collect TB data directly from treating clinicians. The overall rate of reported cases of childhood TB in this study was 1.2 per 100 000. This compares with an approximate incidence of rate of 1.6/100 000 from PHAC data¹⁵ and 1.9 in the Netherlands,¹⁶ 2.0 in the UK¹⁷ and 0.7 per 100 000 in the USA.¹⁸

There was wide variation across Canada geographically and by population origin of the cases. The most striking finding is the burden of TB in Indigenous children. In 2016, Indigenous people comprised 19% of all reported TB cases in all ages.¹⁵ Though Indigenous children accounted for less than 10% of Canada's childhood population, 58% of reported TB was in this group. The rates in First Nations children (9.1 per 100 000 calculated from CPSP reported cases), especially those residing on reserve (20.2 per 100 000) are the drivers for childhood TB in the provinces of Manitoba, which had the greatest absolute number of cases, and Saskatchewan. The rate in Inuit children (54.3/100 000 population) is similar to reported childhood TB rates in high TB burden international settings.¹ Furthermore, when Québec cases not reported to CPSP are included, the minimum incidence rate in Inuit children is likely greater than 100/100 000 per year. Additionally, five cases from Newfoundland and Labrador where 90% of PHAC reported cases are Inuit were reported to PHAC but not to the CPSP.

In recognition of this hugely disproportionate burden in Inuit peoples, there has been a recent focus by the national representative organisation of Inuit peoples (Inuit Tapiriit Kanatami) and the Federal Government on social determinants of health and access to care as major contributors to TB in Inuit peoples¹⁸ and a pledge to reduce rates in Inuit Nunangat (the traditional territory of Inuit peoples in Canada) by 2030.¹⁹ A similar strategy and

monitoring programme has been implemented by the Assembly of First Nations to focus on TB on First Nation reserves.¹⁹ The disproportionate burden of TB in Indigenous people in Canada has origins in the social determinants of health, historical trauma, the residential school system and racism within the healthcare system.²⁰ Reducing and eliminating TB in Indigenous communities through Indigenous-led and community-relevant approaches are the most urgent priorities for achieving elimination of childhood TB in Canada.

In keeping with other studies, most cases occurred in children under 5 years of age, reflecting the unique vulnerability of young children to TB.²¹ There was a known TB contact in 82% of Canadian-born children, reinforcing the importance of contact tracing and a public health infrastructure to diagnose and prevent TB in Canada. Only 18% of foreign-born children had a known contact; most of them likely acquired TB infection in the country of birth or by travel to a higher TB endemic country after arrival in Canada.

Presenting symptoms were non-specific but most children were symptomatic for more than 2 weeks. Haemoptysis and the classic triad of weight loss, fever and night sweats was uncommon. This study highlights acuity and health system costs of childhood TB. About half of children were hospitalised and 5.5% were known to be admitted to ICU. TB meningitis, a condition associated with poor outcomes²² was the most common extrapulmonary site occurring in 8% of cases overall and 14% of reported disease in Inuit children. Of the children with meningitis with known BCG status, 7 (54%) had received the BCG vaccine.

A strength of this study was inclusion of clinicians managing cases through a cross-Canada collaborative network. While monthly surveys of clinicians are labour-intensive, it is possible to obtain rich epidemiologic and clinical data that is not possible through public health reporting. However, it has several limitations including voluntary reporting with some cases not captured. The largest discrepancy between the reported number of CPSP and PHAC cases was in Québec. Due to under-reporting, the representativeness of the acuity of cases cannot be confirmed, though minimum rates have been estimated. Follow-up data was less well reported than the initial incident case. Reasons for missing follow-up data included the reporting physician was not the physician who provided longer term care, the physician did not consent to being recontacted or the physician did not respond. Due to CPSP privacy rules, results with size <5 cannot be shown, which limits the description of rare outcomes. We captured region of residence and of diagnosis, however, these may not reflect the region of disease acquisition. We are not able to determine which cases were identified via a symptomatic child presenting to care versus via contact tracing nor were we able to determine clinical details of prior TB infection. Our surveillance asked only which drugs TB isolates were resistant to, not all drugs tested. The determination of TB acquired during travel used dates of travel to an endemic country, contact history and onset of disease, however, infection may have been acquired at another time. We recommend that future national surveillance and statistics about childhood TB should include detailed data about indigenous status, source case characteristics, prior infection and travel.

CONCLUSION

This surveillance study identified 200 incident cases of childhood TB over 3 years. Acuity of illness and resource utilisation were high. Most cases had a known source case. Outbreaks of childhood TB in low TB burden countries are best prevented by prompt identification of source cases, and evaluation and treatment of their contacts and require a well-functioning public health infrastructure and good contact tracing. Key geographies and groups have very high incidence rates of childhood TB that are comparable with highly endemic countries. Strong community and public health engagement are required to reduce disparities and achieve elimination of childhood TB in Canada.

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ARTIGO ORIGINAL

Associações de partículas finas e ultrafinas a visitas a unidades de urgência pediátrica devido a doenças respiratórias numa megacidade

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RESUMO

Contexto As partículas finas ambientais com um diâmetro aerodinâmico inferior a 2.5 µm (PM_{2.5}) estiveram associadas a uma deterioração da saúde respiratória, mas as evidências sobre partículas de menores dimensões e a saúde respiratória das crianças foram limitadas.

Métodos Efetuamos a recolha de dados de séries cronológicas sobre visitas diárias a unidades de urgência (ERV) por motivos respiratórios em crianças <14 anos em Pequim, China, entre 2015 e 2017. Simultaneamente, foram medidas as concentrações em número de partículas fracionadas em função da sua dimensão por intervalos de tamanho de 5–560 nm (PNC_{5–560}) e as concentrações em massa de PM_{2.5}, carbono preto (BC) e dióxido de azoto (NO₂) a partir de uma estação de monitorização de localização fixa na área urbana de Pequim. Foram utilizados modelos de regressão de Poisson ajustados a confundidores para estimar os riscos excessivos (ER) de frações de tamanho das partículas nas ERV por motivos respiratórios em crianças e foram aplicados modelos de factorização de matriz positiva para distribuir as fontes de PNC_{5–560}.

Resultados Entre os 136 925 casos de ERV exclusivamente por causas respiratórias, os riscos acrescidos estiveram associados a aumentos de IQR em PNC_{25–100} (ER=5,4%, 95% IC 2,4% a 8,6%), PNC_{100–560} (4,9%, 95% IC 2,5% a 7,3%) e PM_{2.5} (1,3%, 95% IC 0,1% a 2,5%) no próprio dia e 1 dia antes (lag 0–1). Foram identificadas as principais fontes de PNC_{5–560}, incluindo nucleação (36,5%), emissões de veículos a gasolina (27,9%), emissões de veículos a gasóleo (18,9%) e aerossóis secundários (10,6%). Foram identificadas emissões de veículos a gasolina e gasóleo com associações significativas a ERV exclusivamente por causas respiratórias, com ER acrescidos de 6,0% (IC 95% 2,5% a 9,7%) e 4,4% (IC 95% 1,7% a 7,1%) com lag de 0–1 dias, respetivamente. As exposições a outros poluentes relacionados com o tráfego (BC e NO₂) também estiveram associadas ao aumento das ERV por causas respiratórias.

Conclusão Os nossos achados sugerem que a exposição a níveis mais elevados de PNC_{5–560} resultantes de emissões de tráfego poderá ser atribuída ao aumento da morbilidade respiratória infantil, o que apoia a necessidade de se dar prioridade ao controlo das emissões de tráfego nas áreas urbanas.

INTRODUCTION

Respiratory diseases contributed to large health burden around the world, and all-age disability-adjusted life year counts due to upper respiratory infections (URIs) and lower respiratory infections were 6.4 and 98.6 million in 2019, respectively.¹ Many epidemiological studies have revealed the short-term effects of particulate matter with aerodynamic diameter less than 2.5 µm (PM_{2.5}) exposure on the increased risks of respiratory diseases, such as URI, pneumonia and bronchitis.^{2–4} Experimental studies also showed that inhalation of ambient particles was capable of triggering respiratory inflammatory process through mechanisms of oxidative stress, cell signalling and activation.⁵ These deteriorated effects might be greater among children, who could be more vulnerable to ambient

Key messages

What is the key question?

► Evidence regarding the impacts of particles in smaller sizes and their sources on childhood respiratory health has been limited.

What is the bottom line?

► Our results showed increased childhood respiratory morbidity in associations with exposures to particles in size fractions of 5–560 nm from traffic emissions, as well as to other traffic-related air pollutants such as particulate matter with aerodynamic diameter less than 2.5 µm, black carbon and nitrogen dioxide.

Why read on?

► Our findings on traffic emission-related increases in childhood respiratory risks largely support that traffic emission control priority in urban areas can be of potentially important public health impact.

particles due to higher-minute ventilation with underdeveloped immune and respiratory systems. Recent birth cohort studies reported that early exposure (eg, the first year after birth) to ambient particles could have long-term impacts on lung function, at least up to adolescence.^{6,7}

There is growing evidence on stronger impacts of smaller particles, such as ultrafine particles (UFPs, with diameter less than 100 nm) that have greater surface area to mass ratio than larger particles (such as PM_{2.5}) and can adsorb more toxic components onto their surface.⁸ Examined in airway deposition models, we found that UFPs appear to be cleared less quickly and efficiently in the respiratory tract with higher deposition efficiency in the bronchioles and alveoli.⁹ Population studies have suggested that exposure to UFPs was associated with adverse childhood respiratory effects; however, the findings remain inconsistent across study populations and locations.^{9–11} The heterogeneity in the observed effects in these studies may be partially due to the differential toxicity of ambient particles across study locations, which can be largely influenced by their chemical compositions and sources.¹² Better understanding on the impacts of particle sizes and sources is of significant public health intervention importance.

Generally, ambient particles are commonly emitted from anthropogenic activities (eg, transportation and industrial operation) and natural sources (eg, dust storms and sea salts).^{13,14} Exposures to

traffic emissions and coal combustions have been found in associations with overall reduction in lung function among children.^{15–16} In recent years, positive matrix factorisation (PMF) models have been extensively applied to apportion the sources of ambient particles supporting emission control priorities.^{17–20} However, limited research has examined the potential impacts of the sources of particles in smaller sizes on respiratory health, especially in children.^{12–21} Nevertheless, identifying the sources of ambient particles most likely to increase childhood respiratory morbidity can be of significant scientific and policy importance.

Previously, we found that ambient UFPs and PM_{2.5} might affect pathophysiological pathways linking particle exposures to respiratory responses independently.²² In addition, we observed that coal burning attributed to PM_{2.5} exposure could lead to increased arrhythmias in healthy adults.²³ In this study, we aimed to examine the impacts of air pollutants, including particles in size fractions of 5–560 nm (measure as particle number concentration, PNC_{5–560}), as well as PM_{2.5}, black carbon (BC), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), carbon monoxide (CO) and ozone (O₃), on respiratory emergency room visits (ERVs) among children under 14 years old in Beijing, China. We further examined the impacts of the potential sources of PNC_{5–560} identified by PMF models on childhood respiratory ERVs.

MATERIALS AND METHODS

Study site and population

Beijing as the capital city of China has 6 urban districts and 10 suburban districts, as illustrated in online supplemental figure S1. According to Beijing Statistical Yearbooks reports (http://tjj.beijing.gov.cn/tjsj_31433/), there are approximately two million children under 14 years old in Beijing, among whom 60% live in the six urban districts with high population density (>8000 people/km²).

Health outcomes

Between July 2015 and June 2017, daily ERVs for respiratory diseases in children under 14 years old were obtained from Beijing Children's Hospital, which provides 24-hour accident and emergency services in the study area. As the largest children and adolescent healthcare facility in Beijing as well as in China, Beijing Children's Hospital has about 3 million cases of hospital visits and 27 000 cases of surgery operations per year. The study database included information on the dates of hospital visits, identification number, sex, age, residential district and diagnoses with corresponding International Classification of Diseases codes (the 10th Revision). Participants living outside Beijing were not included in this analysis. ERVs with principal diagnosis of respiratory disease (J00–J99) were identified from the database, in which the leading causes were URI (J00–J06), bronchitis (J21) and pneumonia (J12–18 and J69). Participants' ages were categorised as 0–1, 2–5 and 6–14 years old, because Chinese children generally go to kindergarten at 2–3 years old and primary school at 6 years old.

Environmental measurements

A fixed-location real-time air pollution monitoring station (N39°58'58", E116°20'52") has been under operation since 2014 on the campus of Peking University Health Science Center in northwestern central Beijing area, with monitoring sensors about 20 m above the ground on the building roof.^{23–24} Our monitoring station is within several hundred metres in distance to traffic roads including the North Fourth Ring Road and expressways. Air pollution in this area is from vehicle and residential emissions, and with limited industrial emissions.

At this location, 5 min PNC_{5–560} with a total of 32 size distribution segments were measured by a Fast Mobility Particle Sizer Spectrometer (FMPS Model 3091, TSI). Daily average PNCs in size fractions of 5–10 nm, 10–15 nm, 15–20 nm, 20–25 nm, 25–40 nm, 40–60 nm, 60–80 nm, 80–100 nm, 100–200 nm, 200–300 nm, 300–400 nm and 400–560 nm were aggregated and calculated. Further, the particles were categorised into three size fractions as follows: 5–25 nm (PNC_{5–25}, reflecting the nucleation mode), 25–100 nm (PNC_{25–100}, reflecting the Aitken mode) and 100–560 nm (PNC_{100–560}, reflecting

the accumulation mode).²⁵ Potential sources of PNC_{100–560} were assessed using PMF models with details provided in the online supplemental information. Hourly concentrations of PM_{2.5} were measured by a beta attenuation monitor (BAM-1020; Met One Instruments); minute-to-minute concentrations of BC were measured by a dual-wavelength aethalometer (AE-33, Magee Scientific); and minute-to-minute concentrations of NO₂, SO₂, CO and O₃ were measured by EC9800 series ambient gas analysers (EcoTech Pty, Australia). Hourly concentrations of ambient temperature and relative humidity (RH) were measured by a Met One unit (Met One Instruments). Daily averages for ambient air pollutants, temperature and RH were calculated from 0 AM to 0 AM, except for O₃ using 8-hour daily maximum concentrations.

Concurrently, the weekly reports of influenza were obtained from the Chinese National Influenza Center (<http://www.china-ivdc.cn/>) to control for influenza epidemic, and we assigned one to influenza epidemic or zero otherwise.

Statistical analysis

Descriptive statistics were conducted for respiratory ERVs and ambient environmental measurements. Spearman correlations were also performed between respective exposure variables. Poisson regression models were used to assess the associations between air pollutants and childhood respiratory ERVs, with adjustment for time trend, influenza epidemic, public holidays, day of the week (DOW), temperature and RH.²⁶

First, basic models were conducted without including air pollutants. A smooth function for time trend with 7 degrees of freedom (df) per year was determined to control for seasonality and long-term trends based on previous studies.¹¹ Categorical variables for public holidays and DOW were introduced into the models to control for yearly and weekly patterns of hospital visits. The temperature and RH at 1 day prior to hospital visits with natural splines function were controlled in the confounder-adjusted Poisson regression model based on minimising Akaike's information criterion.²⁶ The choice of df for temperature and RH for each respiratory outcome is shown in online supplemental table S1. After defining the basic models, air pollutants, including size-fractionated PNC_{5–560} and their major sources, were introduced separately into the model to estimate the impacts of pollutants at single lag day (up to 7 days, eg, lag0–7 days).²⁷ The associations between air pollutants and respiratory ERVs were also evaluated at moving average days (moving averages of current and several prior days, eg, lag0–1 to lag0–7 days) to reduce the respective loss of power due to the missing data in air pollutants. Subgroup analyses by cause, age and sex were performed, and the differences across strata were tested by Z-test.

Finally, we conducted sensitivity analyses to examine the robustness of main models at lag0–1 days by (1) conducting two-pollutant models to investigate whether results for size-fractionated PNC_{5–560} and their major sources were confounded by copollutants,²¹ (2) examining the associations of ambient particles with all-respiratory ERVs in the six urban districts of Beijing, (3) using alternative df for time trend (6–10 per year) in the models, (4) additional adjustment for influenza epidemic and (5) additional adjustment for high temperatures (lag0–1 days) with 3 df and low temperatures (lag1–6 days) with 2 df to reduce the correlation between the two spline terms.²⁸

All models were implemented in R V.3.5.3, and all results were presented as excess risks with 95% CIs converted from relative risks (RRs) in respiratory ERVs associated with IQR increases in air pollutant concentrations.

RESULTS

We observed a total of 136 925 cases of all-respiratory ERVs between July 2015 and June 2017, with characteristics of study participants and environmental parameters summarised in table 1 and online supplemental table S2. The mean age of study participants was 4 years old, with 90 667 (66%) cases living in urban areas and 46 258 (34%) cases living in suburban areas during the study period. Average daily concentrations (IQR) were 6604 (2054) #/cm³ for

PNC_{5-25} , 4489 (3641) $\#/ \text{cm}^3$ for PNC_{25-100} , 1551 (1754) $\#/ \text{cm}^3$ for $\text{PNC}_{100-560}$, 85.0 (73.1) $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 3.8 (3.0) $\mu\text{g}/\text{m}^3$ for BC and 62.8 (30.2) $\mu\text{g}/\text{m}^3$ for NO_2 . The average temperature and RH during the study period were 15.3°C and 41.0%, ranging from -14.1°C to 34.1°C, and from 3.7% to 84.9%, respectively. Major sources of PNC_{5-560} were identified by PMF models, which included nucleation (36.5%), gasoline vehicle emissions (27.9%), diesel vehicle emissions (18.9%) and secondary aerosols (10.6%). The detailed summary of each source profile and associated temporal variation is presented in online supplemental figures S2 and S3.

Table 2 and online supplemental table S3 showed the Spearman correlations between air pollutants, major sources of PNC_{5-560} and weather variables. Generally, PNC_{25-100} and $\text{PNC}_{100-560}$ showed overall positive correlations with $\text{PM}_{2.5}$, BC, NO_2 , SO_2 and CO ($0.28 \leq r \leq 0.74$), whereas PNC_{5-25} showed negative correlations ($-0.11 \leq r \leq -0.04$). For major sources of PNC_{5-560} , nucleation was negatively correlated with gasoline vehicle emissions, diesel vehicle emissions and secondary aerosols ($-0.81 \leq r \leq -0.39$) in online supplemental table S4.

As shown in figure 1A, we observed increases in all-respiratory ERVs associated with IQR increases in exposures to PNC_{5-25} , PNC_{25-100} , $\text{PNC}_{100-560}$, $\text{PM}_{2.5}$ and BC, with the largest increases observed at lag0–2 days, ranging from 1.1% (95% CI 0.1% to 2.2%) to 6.4% (95% CI 2.2% to 10.7%). Similar association patterns were

observed for more refined size fractions of PNC_{5-25} , PNC_{25-100} and $\text{PNC}_{100-560}$ in online supplemental figures S4 and S5. For gaseous pollutants, we observed increases of 0.9% (95% CI -0.2% to 2.1%) to 3.3% (95% CI 1.5% to 5.0%) in all-respiratory ERVs associated with IQR increases in exposures to NO_2 , SO_2 and CO at lag1 day (figure 1B). For major sources of PNC_{5-560} , we observed increases in all-respiratory ERVs associated with IQR increases in gasoline vehicle emissions, diesel vehicle emissions and secondary aerosols with the largest increases of 3.5% (95% CI 0.8% to 6.3%) to 5.6% (95% CI 2.8% to 8.5%) at lag0–1 days (figure 1C). In addition, increases in all-respiratory ERVs were observed in associations with IQR increases in size-fractioned PNC_{5-560} and PNC_{5-560} from gasoline vehicle emissions and diesel vehicle emissions in online supplemental figure S6.

In the stratified analyses shown in table 3, the impacts of size-fractioned PNC_{5-560} and their major sources at lag0–1 days were generally stronger on ERVs for bronchitis than URI and pneumonia in the cause-stratified analyses. Stronger associations with exposures to PNC_{25-100} , $\text{PNC}_{100-560}$, BC and PNC_{5-560} from gasoline vehicle emissions, diesel vehicle emissions and secondary aerosols were observed for children under 1 year old and for being female in the age-stratified and sex-stratified analyses, respectively. However, no effect modification by age and sex was observed.

Table 1 Summary statistics of daily respiratory emergency room visits, air pollutant concentrations and meteorological conditions in Beijing, China, 2015–2017

Variables	Valid days (n)	Mean (SD)	Min	Median	Max	IQR
All-respiratory	731	187 (60)	64	175	430	
Age (years)		4 (3.0)	0	3	14	
0–1	731	57 (19)	19	53	134	
2–5	731	100 (35)	19	96	234	
6–14	731	31 (14)	6	28	94	
Cause-specific						
URI	731	98 (32)	30	94	252	
Bronchitis	731	34 (19)	3	29	113	
Pneumonia	731	48 (26)	9	42	151	
Sex						
Male	731	104 (33)	33	99	235	
Female	731	83 (29)	28	78	209	
Pollutants						
PNC_{5-25} ($\#/ \text{cm}^3$)	566	6604 (1337)	4508	6361	10036	2054
PNC_{25-100} ($\#/ \text{cm}^3$)	566	4489 (2908)	345	3899	14105	3641
$\text{PNC}_{100-560}$ ($\#/ \text{cm}^3$)	566	1551 (1449)	15	1129	6336	1754
PNC_{5-560} ($\#/ \text{cm}^3$)	566	15304 (18451)	4856	13207	27707	8532
$\text{PM}_{2.5}$ ($\mu\text{g}/\text{m}^3$)	720	85.0 (86.1)	6.0	57.7	670.0	73.1
BC ($\mu\text{g}/\text{m}^3$)	579	3.8 (3.0)	0.5	3.1	18.4	3.0
NO_2 ($\mu\text{g}/\text{m}^3$)	725	62.8 (26.5)	12.9	57.5	173.5	30.2
Meteorological variables						
Temperature (°C)	731	15.3 (11.0)	-14.1	16.8	34.1	20.9
RH (%)	731	41.0 (17.8)	3.7	41.4	84.9	28.2
Sources of PNC_{5-560} *						
Nucleation ($\#/ \text{cm}^3$)	566	4853 (1508)	647	4779	9757	1788
Gasoline vehicle emissions ($\#/ \text{cm}^3$)	566	3642 (2735)	12	2924	12138	3764
Diesel vehicle emissions ($\#/ \text{cm}^3$)	566	2443 (1432)	66	2329	7260	1962
Secondary aerosols ($\#/ \text{cm}^3$)	566	1247 (1074)	11	912	4545	1594
Others† ($\#/ \text{cm}^3$)	566	812 (810)	2	524	3516	1070

*The sources of PNC_{5-560} were identified by hourly averaged particle samples each with 32 size intervals from 5 to 560 nm based on positive matrix factorisation models.

†Others, the source contribution was not resolved.

BC, black carbon; NO_2 , nitrogen dioxide; $\text{PM}_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm ; PNC_x , particle number concentrations in given size fractions (nm); RH, relative humidity; URI, upper respiratory infection.

Table 2 Spearman correlations between environmental measurements

Variables	PM _{2.5}	BC	NO ₂	SO ₂	CO	O ₃	Temperature	RH
Pollutants								
PNC _{5–25}	–0.25*	–0.11	–0.09	–0.04	–0.17*	–0.11	–0.17*	–0.22*
PNC _{25–100}	0.28*	0.45*	0.46*	0.41*	0.43*	–0.41*	–0.27*	0.13
PNC _{100–560}	0.64*	0.74*	0.71*	0.59*	0.74*	–0.39*	–0.14	0.41*
PM _{2.5}		0.86*	0.81*	0.70*	0.89*	–0.45*	–0.17*	0.39*
BC			0.92*	0.63*	0.86*	–0.43*	–0.01	0.42*
NO ₂				0.68*	0.84*	–0.48*	–0.08	0.29*
Major sources of PNC_{5–560}[†]								
Nucleation	–0.60*	–0.65*	–0.64*	–0.57*	–0.69*	0.36*	0.13*	–0.33*
Gasoline vehicle emissions	0.40*	0.52*	0.53*	0.49*	0.56*	–0.42*	–0.23*	0.19*
Diesel vehicle emissions	0.21*	0.37*	0.39*	0.34*	0.34*	–0.41*	–0.27*	0.05*
Secondary aerosols	0.60*	0.71*	0.68*	0.59*	0.70*	–0.42*	–0.21*	0.32

*P<0.05.

†The sources of PNC_{5–560} were identified by hourly averaged particle samples each with 32 size intervals from 5 to 560 nm based on positive matrix factorisation models. BC, black carbon; CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter with aerodynamic diameter less than 2.5 µm; PNC_x, particle number concentrations in given size ranges (nm); RH, relative humidity; SO₂, sulfur dioxide.

In the sensitivity analyses shown in online supplemental table S5, the results remained robust after excluding 10 suburban districts, using alternative df for time trend (6, 8–10 per year), adjusting for influenza epidemic, or adjusting for both high temperatures and low temperatures. In two-pollutant model analyses with adjustment for PM_{2.5}, BC or NO₂, the respiratory morbidity risks attributable to PNC_{5–25}, PNC_{25–100} and PNC_{100–560} remained consistent with main results (online supplemental figure S7). For each source of PNC_{5–560}, the results also remained robust to cosource adjustment by including both the source-related particles numbers and the remaining particles numbers (eg, nucleation and PNC_{5–560} minus nucleation) in online supplemental table S6.

DISCUSSION

In this time-series study, we observed increased childhood respiratory morbidity in associations with exposures to PM_{2.5} and size-fractionated PNC_{5–560}. Higher levels of PNC_{5–560} from gasoline and diesel vehicle emissions, as well as other traffic-related air pollutants (eg, BC and NO₂), were also associated with increased respiratory ERVs for all-cause, bronchitis and pneumonia in children living in urban Beijing areas. Stronger effects were observed for children under 1 year old and being female. Our results highlight the public health importance of continued and targeted efforts to reduce traffic emissions in urban areas.

In this analysis, we observed positive associations between ambient PM_{2.5} and ERVs for all-respiratory, URI, bronchitis and pneumonia, which were consistent with previous studies.^{4 29 30} Darrow *et al*³⁰ reported that an IQR increase in PM_{2.5} was associated with an RR of 1.015 for ERVs for URI among children under 4 years old in Atlanta, Georgia. A multicity study in Central and Eastern Europe reported a 3.5% increase in all-respiratory hospital admissions with a 12.4 µg/cm³ increase in PM_{2.5} at lag0–1 days.²⁹ A Chinese study reported that an IQR increase in PM_{2.5} increased childhood hospital visits for acute bronchitis (RR=1.09).⁴ Some studies have reported that exposure to PM_{2.5} was associated with increased pneumonia ERVs in adults,^{2 3} but the evidence among children has been limited. As children can be more vulnerable, better understanding of the associations between air pollution exposure and childhood respiratory health is of significant public health impact.

There is also existing evidence, although inconsistent, that particles in smaller sizes may increase respiratory ERVs. Halonen *et al*³¹ reported that IQR increases in PNC_{0–30}, PNC_{30–100} and PNC_{100–290} at lag5 day were associated with 5.4%, 5.2% and 2.5% increases in asthmatic ERVs among children under 14 years old in Helsinki, Finland. A Chinese study reported that all-respiratory ERVs increased by 9% and 7% with IQR increases

in PNC_{50–100} and PNC_{100–300} at lag2 day, respectively, but did not observe consistent associations for PNC_{3–50}.⁹ Another Chinese study categorised UFPs into PNC_{5.6–20.5} and PNC_{20.5–100} and found that the association of a biomarker of acute respiratory inflammation, the fraction of exhaled nitric oxide, was strongest with PNC_{20.5–100}, weaker with PNC_{100–560} and insignificant with PNC_{20.5–100} in a panel of 55 elderly people.²⁵ The inconsistent impacts of nucleation-mode particles could be partially attributed to their short lifetimes and large spatial-temporal variations. In this study, we extended the evidence on ambient particles in smaller sizes that can be responsible for increased respiratory ERVs among children.

In this study, traffic emissions, which made the largest contribution to PNC_{5–560} in the area, were found in association with increased childhood respiratory ERVs. Studies previously reported that traffic emissions were the major sources of ambient particles in Beijing, China.^{23 24} A case-control study in Israel reported that children (0–14 years old) who experienced bus traffic passing within 50 m of their home had increased odds of respiratory hospitalisation with ORs of 1.10–1.16 when compared with the different control groups.³² A cross-sectional study in the San Francisco Bay Area reported that proximity to traffic was associated with adverse respiratory health effects in children.³³ Consistently, our study also found significant increases in respiratory ERVs associated with exposures to BC and NO₂. These results largely supported traffic pollution-related adverse respiratory impact. Secondary aerosols, which formed through atmospheric processing of SO₂ and nitrogen oxide originated from traffic, industries and urban background,¹⁷ were also found in association with increased risk of respiratory ERVs in this study. Consistently, Li *et al*¹² reported that an IQR increase in PNC of secondary origin was significantly associated with a decrease of 0.17 L in forced vital capacity at lag1 day among children in Taipei, China. The seemingly protective effects of nucleation on childhood respiratory ERVs are likely due to its negative correlations with other sources of PNC_{5–560} (eg, traffic emissions and secondary aerosols). It is important to evaluate the source-specific effects on respiratory health, which can better support traffic emission control priorities.

Collectively, our results provided evidence on the adverse impacts of ambient size-fractionated PNC_{5–560} and their major sources on respiratory health. Existing evidence suggested that inhaled particles caused oxidative stress and lung inflammation via a release of proinflammatory mediators or vasoactive molecules from lung cells.²⁹ The expressions of oxidative stress biomarkers were highly correlated with presence of high organic chemical components of ambient particles.³⁴ UFPs were found to be more potent than PM_{2.5} toward inducing oxidative

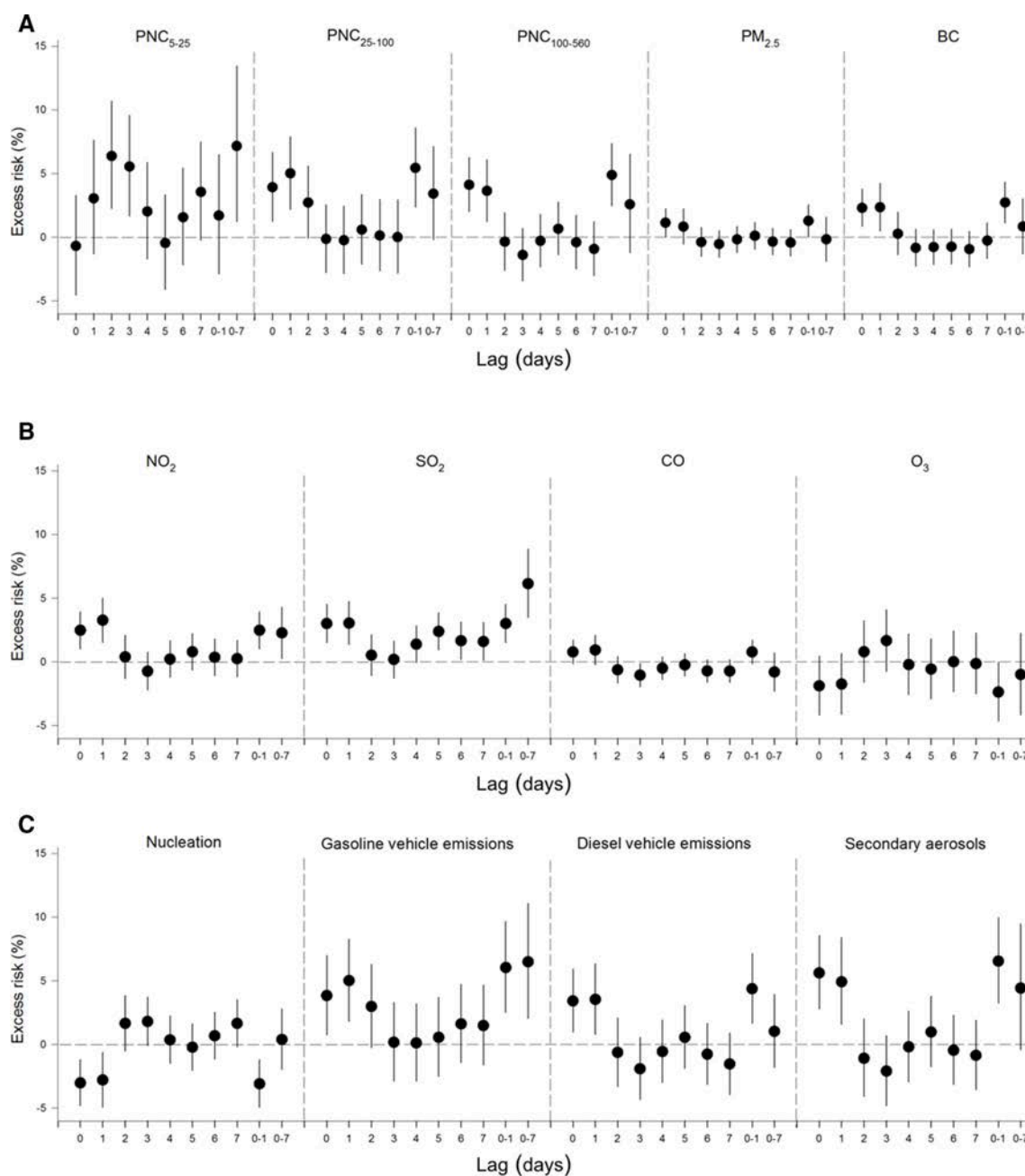


Figure 1 Excess risks% (95% CIs) of childhood respiratory emergency room visits associated with IQR increases in ambient (A) particles, (B) gaseous pollutants and (C) major sources of PNC₅₋₅₆₀ at different lag days in Beijing, China, 2015–2017. BC, black carbon; CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter with aerodynamic diameter less than 2.5 µm; PNC_x, particle number concentrations in given size fractions (nm); SO₂, sulfur dioxide.

stress in macrophages and epithelial cells,³⁵ because the smaller particles tend to adsorb more organic components and their oxidative derivatives due to small size and large surface area to mass ratio.³⁶ It is worth noting that the traffic emissions make an important contribution to organic chemical components of ambient particles (eg, polycyclic aromatic hydrocarbons) and might be responsible for the increased respiratory morbidity.³⁷ Our results supported that exposure to PNC₅₋₅₆₀ from traffic emissions could be more responsible for increased childhood respiratory morbidity.

The main strength of our study was continuous measurement of PNC in size fractions of 5–560 nm at every 5 min, which allowed us to conduct the apportionment of the sources of PNC₅₋₅₆₀. The estimated impacts of exposures to ambient size-fractionated PNC₅₋₅₆₀ and potential sources on childhood respiratory ERVs also enhanced the understanding of increased risks of respiratory morbidity from exposure to ambient particles as a mixture. Our study also had some limitations. First, the population's exposure was estimated from a single fixed-location

monitoring station and without time–activity information, which might introduce the potential exposure misclassification to underestimate the pollutant effects. However, previous studies examined the spatial and temporal variations of ultrafine and fine particles across urban and suburban Beijing areas, which showed similar day-to-day changing patterns.^{22 38 39} Second, the interpretation on the association between nucleation-mode particles and increased childhood respiratory morbidity should be cautious due to a high measurement uncertainty on particles in this size fraction. Third, potential selection bias may still exist in our study population, as we were not able to include all facilities carrying children's healthcare services in Beijing. However, as the largest children's hospital in the area that most children tend to visit for healthcare, we consider the study population is representative and selection bias can be minimum. Fourth, we examined the associations between ambient particles and respiratory health among children under 14 years old, which might have limited the generalisability of study results to a broader population, such as adults and the elderly.

Table 3 Excess risk % (95% CI) of childhood respiratory emergency room visits associated with IQR increases in PNC_{25-100} , $PNC_{100-560}$, $PM_{2.5}$, BC , NO_2 and source-specific PNC_{5-560} in Beijing, China, 2015–2017, stratified by cause, age and sex at lag0–1 days

Variables	Diseases				Age (years)			Sex	
	All-cause	URI	Bronchitis	Pneumonia	0–1	2–5	6–14	Male	Female
Particles									
PNC _{5–25}	1.7 (–2.9 to 6.5)	–1.1 (–8.0 to 6.3)	4.6 (–2.8 to 12.7)	2.6 (–3.3 to 8.9)	1.8 (–4.0 to 7.9)	2.1 (–3.0 to 7.6)	1.2 (–6.2 to 9.3)	2.7 (–2.3 to 7.9)	0.4 (–4.6 to 5.7)
PNC _{25–100}	5.4 (2.4 to 8.6)*	4.5 (–0.4 to 9.7)	9.4 (4.5 to 14.6)*	1.5 (–2.2 to 5.4)	7.2 (3.3 to 11.3)*	4.7 (1.2 to 8.3)*	5.3 (0.3 to 10.6)*	4.4 (1.1 to 7.7)*	6.7 (3.3 to 10.3)*
PNC _{100–560}	4.9 (2.5 to 7.3)*	4.9 (1.1 to 8.9)*	6.8 (2.9 to 10.8)*	2.1 (–1.0 to 5.2)	7.1 (4.1 to 10.2)*	3.6 (0.8 to 6.4)*	4.9 (0.9 to 9.0)*	3.9 (1.3 to 6.5)*	6.1 (3.4 to 8.9)*
PM _{2.5}	1.3 (0.1 to 2.5)*	1.1 (–0.8 to 3.1)	2.0 (0.1 to 4.0)*	1.0 (–0.6 to 2.6)	1.1 (–0.4 to 2.7)	1.1 (–0.4 to 2.6)	2.1 (–0.1 to 4.5)	0.9 (–0.5 to 2.3)	1.7 (0.3 to 3.2)*
BC	2.7 (1.1 to 4.3)*	3.7 (1.2 to 6.3)*	3.3 (0.9 to 5.8)*	0.4 (–1.6 to 2.5)	3.4 (1.3 to 5.5)*	2.7 (0.9 to 4.6)*	1.7 (–0.9 to 4.4)	1.9 (0.2 to 3.6)*	3.7 (1.9 to 5.5)*
Major sources of PNC _{5–560} [†]									
Nucleation	–3.1 (–4.9 to –1.2)*	–3.3 (–6.1 to –0.3)*	–4.6 (–7.5 to –1.6)*	–0.8 (–3.2 to 1.7)	–3.7 (–5.9 to –1.4)*	–2.5 (–4.6 to –0.3)*	–3.8 (–6.8 to –0.7)*	–2.2 (–4.2 to 0.2)*	–4.2 (–6.2 to –2.1)*
Gasoline vehicle emissions	6.0 (2.5 to 9.7)*	4.5 (–0.9 to 10.1)	9.0 (3.3 to 15.1)*	5.0 (0.5 to 9.7)*	7.1 (2.8 to 11.7)*	5.6 (1.6 to 9.7)*	5.7 (0.1 to 11.8)*	5.1 (1.4 to 9.1)*	7.1 (3.2 to 11.2)*
Diesel vehicle emissions	4.4 (1.7 to 7.1)*	4.2 (0.1 to 8.5)*	6.9 (2.4 to 11.5)*	1.7 (–1.7 to 5.2)	5.4 (2.1 to 8.9)*	3.7 (0.7 to 6.9)*	4.7 (0.3 to 9.3)*	3.3 (0.4 to 6.2)*	5.7 (2.7 to 8.8)*
Secondary aerosols	6.5 (3.9 to 9.9)*	6.0 (1.0 to 11.3)*	9.7 (4.3 to 15.3)*	3.9 (–0.3 to 8.3)	9.3 (5.2 to 13.6)*	4.9 (1.2 to 8.8)*	6.2 (0.8 to 11.9)*	5.4 (1.8 to 9.0)*	8.0 (4.3 to 11.8)*

* $P < 0.05$.

†The sources of PNC_{5-560} were identified by hourly averaged particle samples each with 32 size intervals from 5 to 560 nm based on positive matrix factorisation models. BC, black carbon; $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm ; PNC_{5-560} , particle number concentrations in given size ranges (nm); URI, upper respiratory infection.

CONCLUSION

We have shown here for the first time that exposures to PNC_{5-560} , specifically from gasoline and diesel vehicle emissions, could significantly increase childhood respiratory morbidity risks. Our findings highlight the importance to support traffic emission control priority in urban areas.

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Intervenções BReATHE (Beating Regional Asthma Trough Health Education) – uma abordagem inovadora no cuidado da asma infantil no Nordeste e Norte da Cúmbria, Reino Unido: um estudo intervencional

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RESUMO

O objetivo deste projeto foi reduzir as taxas de admissão hospitalar não previstas de crianças relacionada com asma no *Newcastle Upon Tyne Hospitals National Health Service Trust* (NUTH).

Foram apresentadas múltiplas iniciativas educativas, tanto a nível local como regional, incluindo: uma coleção de materiais educativos destinados ao público jovem e famílias, escolas, unidades de cuidados primários e secundários no *website* www.beatasthma.co.uk, dias de formação regional, uma clínica de serviço integrado liderada por enfermeiros; um novo percurso após atendimento hospitalar devido a episódio de asma grave e formação em cascata para escolas. O parâmetro de avaliação primário foi a redução de taxas de admissão hospitalar não previstas em crianças devido a asma no NUTH. Os resultados demonstraram que as taxas de admissão tinham vindo a aumentar a uma taxa contínua de aproximadamente 30% por ano nos 3 anos anteriores à nossa intervenção. Após as intervenções do *Beating Regional Asthma Through Health Education*, as admissões não previstas no NUTH reduziram 29% e esta redução manteve-se nos últimos 3 anos. Estes valores são comparáveis com um aumento de 10% no período homólogo.

Em conclusão, estas intervenções educativas simples mas eficazes resultaram numa redução significativa e constante das admissões por asma não previstas no NUTH. Estão a ser desenvolvidos esforços para alargar o alcance destas intervenções aos cuidados primários e às escolas.

INTRODUCTION

Asthma is the most common chronic condition in childhood¹ and the incidence is increasing. The UK has amongst the worst asthma outcomes in Europe and young people in the UK are more likely to die from asthma than those in other high-income countries.² Asthma can impact on all areas of a child's well-being and children who are treated for asthma have been shown to have poorer educational and health outcomes than their peers.³

The National Review of Asthma Deaths 2014 (NRAD)⁴ highlighted systemic failings in the way we deliver asthma care in the UK with common avoidable factors contributing to deaths. It concluded that in all but one case, the care of children and young people (CYP) who had died from asthma in the UK had been inadequate and that their deaths were most likely preventable. It made 19 recommendations for how practice in the UK needed to change. But, with no funding to match, little has been done to implement these recommendations. Since the publication of NRAD, three coroner's enquiries into the deaths of young people due to asthma, summarised in Regulation 28 statements,^{5–7} only serve to highlight our ongoing failure to meet these recommendations.

The National Health Service Long Term Plan⁸ sets out ambitious plans to prevent 80 000 hospital admissions a year from respiratory conditions and to tackle unacceptable outcomes in children's asthma through a CYP's Transformation Board and CYP clinical networks for long-term conditions focusing on asthma. If sustainable change is to be achieved, new thinking and approaches are needed at a systems level that allow care to be delivered seamlessly across geographical and institutional boundaries with a lack

What is already known on this topic?

- The UK has the worse asthma outcomes in Europe and a lack of patient understanding as well as failure of health professionals to follow guidelines have been shown to be contributing factors.

What this study adds?

- Simple interventions aimed at promoting health professionals' adherence to national guidelines and supporting patient self-management through improved patient education can improve asthma control and reduce unplanned hospital admissions in a sustained way in a paediatric population.

of barriers between services. Importantly, there needs to be a focus on education both of healthcare professionals and families and young people, allowing them to feel empowered and more able to self-manage their condition, a factor which is known to lead to improved outcomes.⁹

We report on one such approach: BReATHE (Beating Regional Asthma Through Health Education) is a new, innovative approach to improving asthma care and outcomes for CYP across the North East and North Cumbria, co-designed with patients, families, local authorities and health professionals and guided by the NRAD recommendations. This paper reports on the outcomes of these interventions across the city of Newcastle in the North East of England, UK.

The aim of the approach was to reduce unplanned hospital admission rates in children due to asthma to the Great North Children's Hospital at the Royal Victoria Infirmary, a large tertiary centre in the North East of England, UK and 1 of only 14 major children's medical centres in the UK, providing the full range of children's health services.

METHODS

Intervention design process

We used an experience-based co-design approach enabling users to be involved with all stages of development and provide feedback on key issues which were likely to impact on whether the final intervention can be successfully implemented. This included a regional paediatric partnership comprised of health professionals including representatives from primary to tertiary care, pharmacy as well as the local authority. Here, key problem areas were identified, and potential workable solutions were found that were broadly acceptable to all.

We ran co-design workshops for key service users involving (1) primary care professionals, (2) parents of

children with asthma and (3) young people with asthma. These were run in collaboration with Open Lab at Newcastle University. Volunteers were recruited through adverts on General Practitioner websites and in hospital outpatients. The aim of the workshops was to elicit discussion and identification of areas of potential barriers and facilitators of quality care provision and suggestions for improvement.

Clinical intervention development

Using the results from the regional partnership discussions, the co-design workshops, the NRAD recommendations, national guidelines, Regulation 28 reports and the literature, a number of interventions were developed. The key areas of focus were (1) standardisation of paperwork and resources. The aim was for every healthcare professional in the North East and North Cumbria to use the proformas, flow sheets and resources to guide management, so as to ensure all were following the same management approach and offering the same high-quality care for CYP wherever they went to receive it. The aim was also to offer a consistent message for CYP and their families through the information sheets and leaflets, action plans and videos so they were getting the same message in the same way, wherever they received their care, thus promoting a sustained change in behaviour; and (2) education of healthcare professionals, families and CYP. It is well recognised that a multifaceted approach has the biggest impact (Szefer 2020), and with this in mind the following interventions were developed:

BeatAsthma

The foundation of the BReATHE interventions was BeatAsthma. This is a collection of over 150 resources hosted on www.beatasthma.co.uk (figure 1). The webpage has different portals of entry for different users as follows: families and children with asthma, young people with asthma, primary healthcare professionals, secondary healthcare professionals and schools. Each area has resources co-designed with and specific to the user and aims to offer a standardised approach to diagnosing and managing asthma meeting national recommendations, be that at home, in a healthcare setting or in a school, as well as educational materials to support management and understanding. It does this using management templates, information leaflets, educational videos and resources, and patient stories.

Regional training days

Supported by the BeatAsthma resources and using a face-to-face lecture format, five study mornings were held for primary care, focusing on the basics of children's asthma including the NRAD report, managing children's asthma, inhaler devices and technique, educating CYP and families, personalised asthma action plans (PAAPs) and spirometry.

One-stop clinic

A 'one-stop nurse-led clinic' was set up with the aim of targeting children being cared for in primary care. The clinic ran two times per month with four slots available in each. Children attending had either been referred from primary care or secondary care or had been invited to attend by a specialist asthma nurse doing the post-attack review phone call following

an unscheduled hospital visit due to their asthma if deemed necessary. Those reviewed had pre-diagnosed asthma and it was felt would benefit from nurse time providing education, advice and support around managing their condition. The visits were a once only 45-minute review, were supported by the BeatAsthma resources and covered the basics of asthma including a detailed Personalised Asthma Action Plan (PAAP), review of inhaler technique, an education session detailing what asthma is, what happens during an asthma attack and how the inhalers work, spirometry and a written report with recommendations to the referrer. If there were significant concerns regarding poor control following this appointment, patients were referred into a newly established asthma clinic for further follow-up. Every child/young person completed an Asthma Control Test (ACT) prior to their consultation which was repeated during a follow-up phone call 8–12 weeks later.

New pathway following an acute attendance to hospital with asthma

An asthma discharge bundle was developed comprising a collection of resources to help educate and empower families in asthma self-management. The bundle was given to families at the time of initial review and included a patient information leaflet, PAAP, inhaler technique information sheets, peak flow normal values, a checklist to outline what families should expect prior to discharge and a peak flow token to remind families to collect a peak flow metre prior to discharge. There were also prompt sheets for clinicians to ensure long-term control and potential risk factors were explored, as well as an acute management flow chart.

Weekly data were collected of the CYP present acutely to the Trust, coded as asthma. Families of these CYP were contacted by telephone during the following week to determine the progress of symptoms post-presentation. A proforma was developed to ensure that the families were asked the same questions about their child and their experience. As part of the phone call, they were asked if they had been given a PAAP, had their inhaled technique checked and had been given immediate post-discharge advice including a GP follow-up within the 48-hour national recommendation. Some of these families were invited along to the one-stop nurse-led clinic, particularly if they had repeated admissions or if the nurse making the call felt they would benefit from it. Unfortunately, resources did not allow for all families to be offered this.

Local asthma service

A local asthma service was created, run by a paediatrician with special training in paediatric asthma and supported by a respiratory nurse specialist. The clinic ran monthly and took referrals from primary and secondary care, as well as those patients highlighted at the one-stop clinic, the post-discharge phone calls or following an acute admission as being at higher risk. Supported by the BeatAsthma resources, patients had a review of overall asthma control, lung function, fractional exhaled nitric oxide level, education, inhaler technique review, discussion on adherence and if required, allergy tests as well as treatment changes as needed.

Cascade training for schools

Alongside the Newcastle Council School improvement service, training sessions were developed and delivered to local schools

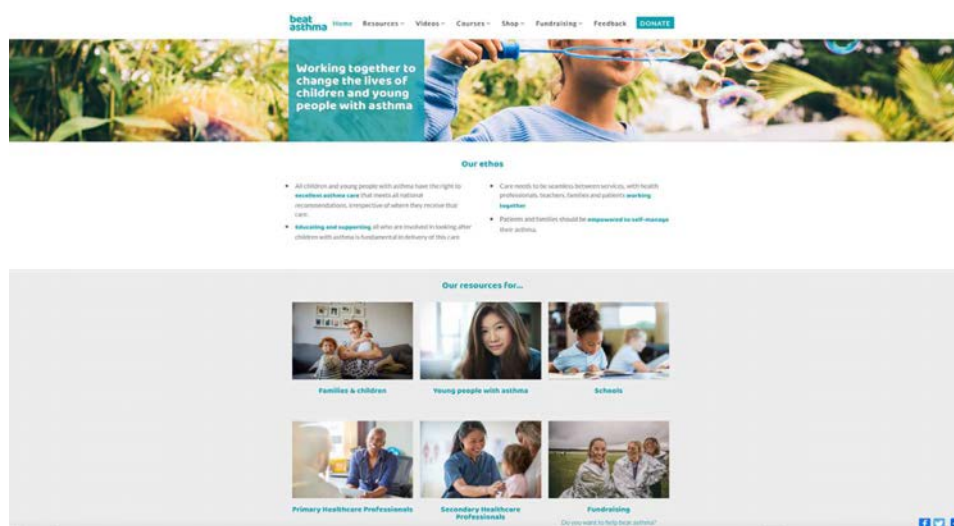


Figure 1 BeatAsthma online resource.

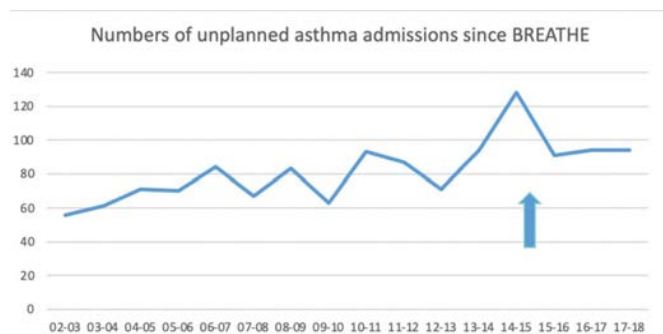


Figure 2 Changes in asthma-related unplanned admission rates over time. BReATHE, Beating Regional Asthma Through Health Education.

around managing asthma. These incorporated the use of generic emergency salbutamol inhalers at school.¹⁰ A BeatAsthma emergency inhaler guidance pack for schools was developed which included an asthma attack procedure flow sheet, inhaler device information and various templates for record keeping to be used in schools.

Two times per year, managing medical conditions in schools' training sessions in line with the Department for Education statutory guidance were delivered to school staff with a session on asthma being part of this.¹¹

Work raising asthma awareness among school health nurses was undertaken. A PowerPoint presentation was prepared for this group of professionals to deliver to their allocated schools. The session was delivered as part of school health nurse training days across five local regions for them to cascade out.

Patient and public involvement

Patients were involved in all stages of the design and conduct of this study and continue to be involved in the further development of BeatAsthma. The work was initially prompted following conversations with families of children with asthma about the lack of resources available to them to help them understand and manage their child's asthma during acute and routine care visits. Choice of interventions, design of the BeatAsthma online resource and the specific resources included as well as the outcome measures for the study were informed by discussions during patient and family focus groups. A number of the participants from these focus groups then became editors on the BeatAsthma editors' group and wrote and reviewed resources. One has been involved in the promotion in the local media. Once the trial has been published, the results will be made available through the 'patients and families' portal of the BeatAsthma website in a format that is suitable for a non-specialist audience.

Finance

The intervention was implemented with minimal upfront funding. Time was given freely by all BeatAsthma editors both for the development and delivery of the website, and interventions were either temporarily incorporated into existing job plans or done in the free time of the professionals involved. The project received a one-off charitable donation from the Children's Foundation Charity for the build of the website and 1 day per week nursing time for a band 7 nurse was provided by Newcastle upon Tyne Hospitals NHS Trust (NUTH) for 1 year.

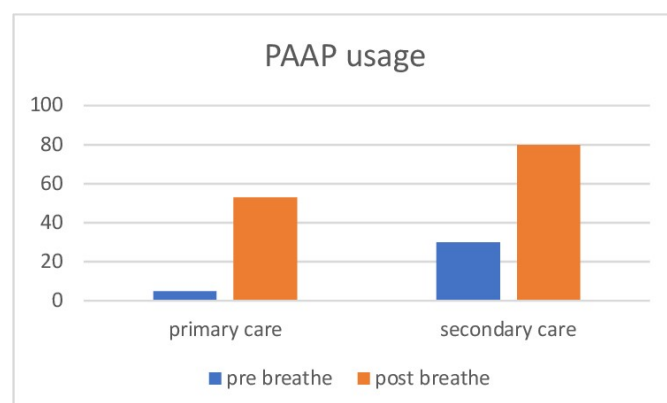


Figure 3 Percentage of eligible patients in receipt of a personalised asthma action plan (PAAP).

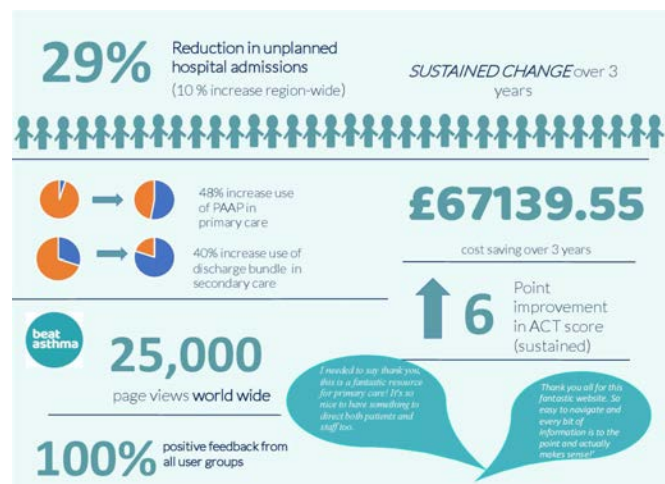


Figure 4 Results infographic. ACT, Asthma Control Test; PAAP, personalised asthma action plan.

Outcomes

The primary outcome measure was a reduction in unplanned hospital admission rates in children due to asthma to the NUTH. An unplanned admission is defined as any completed spell where the admission method was an emergency or a transfer from another hospital provider and the International Classification of Diseases, 10th revision primary diagnosis code of the admitting episode of the spell was in the range J45–J46 (asthma and status asthmaticus) or R06.2 (wheezing). Children were eligible if they were between the ages of 5 and 16 years inclusive.

Secondary outcomes were (1) an improvement in the number of eligible children with asthma who had received a PAAP in the previous 12 months in both primary and secondary care, and (2) an improvement in asthma control overall. This would be measured using the validated ACT score with a 2-point change being recognised as a clinically significant difference.¹²

RESULTS

Admission rates had been increasing in a sustained way of approximately 30% year on year in the 3 years prior to our intervention. After the BReATHE interventions, unplanned admissions to NUTH reduced by 29% (128 to 91 admissions) and this reduction has been sustained for the last 3 years. This is on a region-wide increase of 10% over the same time period (figure 2). On admission costs alone, this equates to a cost saving of over £67 000.00 and this figure does not take into account the cost of lost working days for parents, lost school days for CYP and impact on quality of life. Each of the 13 secondary care provider trusts and a number of primary care providers in the North East and North Cumbria adopted the standardised BeatAsthma paperwork and resources.

The number of eligible children receiving a PAAP increased from 5% to 53% in primary care (Newcastle Gateshead Clinical Commissioning Group) and from 30% to 80% in secondary care (NUTH) (figure 3).

One hundred and twelve professionals attended the morning training, with representation from 64 GP practices in the North East. Delegates were mainly practice nurses but included 13 GPs and 6 school health nurses. Feedback was positive with all sessions rated as good or excellent on evaluation.

Sixty-six children (age range 5–16 years, M:F 1.9:1) were reviewed in the nurse-led one-stop clinic over a period of 12 months. Sixty children completed ACTs and 43 completed a repeat ACT during a follow-up phone call. From being seen in the one-stop clinic to 3 months later, the mean ACT score changed from 15.4 points (SD 5.85) to 21.9 points (SD 5.06). The proportion of children whose score suggested inadequate control changed from 70% (42 children) to 30% (13 children). A score of 19 or below suggests inadequately controlled asthma. Feedback from patients was overwhelmingly positive.

One hundred and eighty children were recorded as being emergency presentations to Emergency Department. Attempts by a specialist nurse to contact the family by telephone following the acute presentation were made in 71% of cases. In 59% of these cases, the nurse was able to speak with the family and perform a follow-up review. The remaining calls were unsuccessful due to either the family not answering or returning the call or incorrect telephone details. Nine per cent (17 patients) were

reviewed during their inpatient admissions, a further 4% were already known to specialist services and reviewed accordingly.

The BeatAsthma online resource has had over 35 000-page views worldwide to date and 100% positive feedback from all user groups. There has been increasing use nationally and approaches for translation for international use. Three school training sessions were delivered around emergency inhaler use in schools with 55 schools attending and all delegates rating the session as excellent.

The 'managing medical conditions in schools' sessions were set up prior to this work and were attended by 370 delegates—again feedback for the asthma session rated excellent by the majority of delegates.

A summary of the results can be seen in figure 4.

DISCUSSION

Principal findings

We assessed longitudinal lung function trajectories in comparable populations of children in the USA and UK using data from national registries and found that lung function was better in US

With simple educational interventions, we have been able to reduce unscheduled admissions for children's asthma by almost one-third. In addition, these reductions have been sustained while elsewhere admissions have continued to increase. Overall, asthma control has also improved, and the interventions have been well received by patients, families and professionals alike.

Strengths and limitations

The interventions used were relatively simple and have been easily transferred to other healthcare settings. As the study had multiple levels of intervention, it is impossible to pinpoint which individual intervention was responsible for this change. However, the aim for all interventions was the same, to improve asthma control in children in the North East and Cumbria by improving education of healthcare professionals and patients alike. Using unscheduled admissions as the main outcome measure is a fairly gross tool and other subtler measures are likely to have also improved, as demonstrated by the increase in ACT score following attendance at the one-stop clinic. Unfortunately, we were only able to hold the one-stop clinic in one centre due to lack of funding, this may explain the 10% increase in admissions seen elsewhere in the region. The study would have been stronger if we had been able to have multiple one-stop clinics (ideally in a primary care setting) throughout the region.

Comparison with the literature

Previous studies have shown that asthma education for children and families can reduce hospital admissions.¹³ Despite this, there continues to be excessive hospital admissions with childhood asthma in the UK.² There are limited data of this kind of multiple intervention study to improve asthma care in childhood. Further work is underway to increase the spread of these interventions across the region, in particular into primary care including the development of a comprehensive, online paediatric asthma education module for healthcare professionals which will be available next year.

CONCLUSIONS

In conclusion, a series of simple but effective educational interventions resulted in a significant and sustained reduction in unscheduled asthma admissions in the NUTH. The resources are freely available, and these interventions can be easily replicated in other centres. The provision of a named paediatrician and asthma nurse with appropriate training was essential to the success of these interventions, both in the delivery of care and lead on whole system change within the local area and would be essential to any area wanting to replicate this work.

Acknowledgements Thanks to the BeatAsthma editors from across the North East and Cumbria, including health professionals, the families of children with asthma and the children and young people themselves, all of whom contributed to the design of the interventions and development of the resources and continue to do so. Special thanks to public/patient contributor Samantha Berry for her ongoing dedication to BeatAsthma. Thanks to Professor Julia Newton for her help with preparation of the final manuscript.

Contributors JKT led the design, delivery, analysis and write-up of the project. SH, RL, PD, MM and SM contributed to the design, delivery, analysis and write-up of the project.

Funding The study received a one-off charitable donation from the Children's Foundation Charity for the build of the website. One day per week nursing time was provided by Newcastle upon Tyne Hospitals NHS Trust for 1 year.

Competing interests JKT is a subject matter advisor of the HSIB investigation into childhood asthma and an unpaid member of CYP Transformation Team Asthma oversight group, no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years. SM has received funding to speak at educational events from Novartis Pharmaceuticals UK, unrelated to this article, no other relationships or activities that could appear to have influenced the submitted work.

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Declaração clínica da BTS sobre viagens aéreas para passageiros com doença respiratória

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INTRODUCTION

BTS recommendations for managing passengers with stable respiratory disease planning air travel were published in *Thorax* in 2011.¹ This followed original guidance published in 2002² and an online update in 2004.³ The 2011 recommendations provided an expert consensus view based on literature reviews, aimed at providing practical advice for lung specialists in secondary care. Recognising that knowledge in this area has grown since 2011, and that updated, pragmatic advice regarding which respiratory patients need specialist assessment is required, the Society has commissioned a new clinical statement.

Although air travel appears generally safe for those with respiratory disease assessed previously by a lung specialist,⁴ a decision to undertake air travel should not be taken lightly. Diverted flights incur significant expense and inconvenience, and a patient whose condition deteriorates during flight can pose huge challenges to airline crew and other passengers. High altitude destinations may also be problematic.

European and North American regulatory authorities limit maximum cabin altitude to 2438 m (8000 ft) under normal operating conditions.^{5–7} The choice of 2438 m was based on the oxyhaemoglobin dissociation curve, which shows that up to this level arterial oxygen saturations (SaO₂) remain >90% in the average healthy individual.⁸ Some newer commercial aircraft have a lower normal cabin altitude, for example, the Boeing 787 Dreamliner. However, passengers booking such flights should note that airlines may, for operational reasons, switch at short notice to an aircraft with a higher normal cabin altitude.

Besides the passenger's respiratory condition and significant comorbidities, a decision regarding suitability for air travel should consider flight duration and timings, destination (especially if at altitude or subject to extreme weather conditions), equipment and medications, and whether equipment will operate effectively and safely at altitude.

There have been developments in three key areas over the last decade. The first is an attempt, with research from several groups, to define more precisely the value and role of the hypoxic challenge test (HCT). This has included examining the accuracy of other, more routinely available lung function parameters, in predicting hypoxaemia during air travel. HCT can be expensive in terms of equipment and consumables; and demands additional staff time. A 'negative' HCT (where in-flight oxygen is not considered necessary) takes around 30 min; if oxygen titration is needed it takes around 60 min. In contrast, spirometry requires 20 min, a walk test 30 min, and 'full' lung function testing 45 min.⁹ Results of such assessments may already be available as part of routine clinical care.

The second development has been increasing recognition that, although early research in this area focused on patients with chronic obstructive pulmonary disease (COPD), other patient groups may respond differently to altitude-related hypoxaemia. Although data remain limited, available evidence no longer appears to support a 'one size fits all' approach.

Finally, the equipment used to deliver oxygen has changed significantly over the last decade, with much greater availability of portable oxygen concentrators (POCs). For overseas travel, patients usually need to lease a POC privately, since UK companies do not generally allow their equipment to be taken out of the country. If a POC is to be used in-flight, the equipment must be approved by the airline before travel. There are now a wide variety of such devices, providing varying flow rates and modes of delivery (continuous flow vs pulse-dose), and not all are suitable for all individual patients.

Attention has, therefore, been drawn in this Statement to newer data, especially those published since the 2011 BTS recommendations.¹ Readers wanting more detailed background information on physiology and the flight environment should consult the 2002 and 2011 BTS documents.^{1,2}

Scope

The clinical statement provides practical advice for healthcare professionals in primary and secondary care managing passengers with pre-existing respiratory conditions planning commercial air travel, including those recovering from an acute event/exacerbation. It provides information for patients and carers; and is also intended to be helpful to patient support groups, airlines and associated medical services. Passengers returning home with a new diagnosis should be reviewed in the light of the presenting condition and individual circumstances. The document does not cover emergency aeromedical evacuation, or travel on non-commercial flights. Pregnant passengers with respiratory disease should also consult Royal College of Obstetricians and Gynaecologists guidance (see online supplemental appendix 1).

The Statement addresses adults and children with the following conditions or undergoing the following procedures:

- Airflow obstruction including asthma and COPD.
- Bronchopulmonary dysplasia.
- Cystic fibrosis (CF).
- Non-CF bronchiectasis.
- Restrictive respiratory disease including interstitial lung disease (ILD), respiratory muscle and chest wall disorders.
- Thoracic surgery or other interventional procedures.
- Pleural disease including pneumothorax and pleural effusion.
- Respiratory infections.
- Obstructive sleep apnoea syndrome (OSAS) and obesity hypoventilation syndrome (OHS).
- Venous thromboembolism (VTE).
- Pulmonary hypertension (PH).
- Lung cancer and mesothelioma.
- Hyperventilation and dysfunctional breathing (DB).

Pre-flight assessment is described. Appendix A provides information on logistics for air travel with equipment (nebulisers, oxygen and ventilators); Appendix B provides technical information for

respiratory physiologists. Sources of useful information, Information for primary care healthcare practitioners and for patients are provided in online supplemental appendices 1–3.

Heart disease and HIV are excluded, as are emergency repatriation and travel on military or other non-commercial flights including helicopter travel. The Terrence Higgins Trust and British Heart Foundation provide advice on travel with HIV and heart conditions respectively (see online supplemental appendix 1).

METHODOLOGY

Dr Robina Coker chaired the clinical statement group (CSG). Membership was drawn from respiratory medicine, paediatrics, nursing, respiratory physiology, physiotherapy and primary care. The CSG identified key areas requiring Clinical Practice Points. The group reviewed previous BTS recommendations on this topic^{1–3} and supplemented the evidence with up-to-date literature searches. The overall content was developed to reflect the scope approved by the BTS Standards of Care Committee (SOCC). Following discussions of broad statement content, individual sections were drafted by group members. A final edited draft was reviewed by the BTS SOCC before posting for public consultation and peer review on the BTS website in January 2020. The document was revised in the light of consultation feedback and approved by the BTS Standards of Care Committee in July 2021 before final publication.

Summary of clinical practice points

Preflight screening

- ▶ All patients should undergo careful initial evaluation with history and physical examination by a clinician who is competent. The history should include:
 - Review of symptoms, baseline exercise capacity, recent exacerbation history, treatments and previous experience of air travel.
 - Consideration of the logistics of the intended journey, to include (if known):
 - Number and duration of flights, including whether day-time or overnight,
 - Location of stop-over(s) and destination: these determine air quality, altitude and available medical facilities,
 - Time away from home
 - Return journey.
- ▶ Further assessment by a respiratory specialist is advised for those in whom screening raises concerns, and HCT may be advised.

The following clinical practice points are specific to infants and children

- ▶ For infants born at term (>37 weeks) it is prudent to delay flying for 1 week after birth to ensure they are healthy.
- ▶ Infants born prematurely (<37 weeks) with or without a history of respiratory disease who have not reached their expected date of delivery at the time of flying should have in-flight oxygen available. HCT may not be a reliable guide of oxygen requirement in this group. If air travel is essential, they should travel with oxygen at a tolerable low flow, recognising that this may be a minimum of 1 L/min depending on equipment.
- ▶ Infants under 1 year with a history of chronic respiratory problems should be discussed with a respiratory paediatrician and HCT considered. Those with SpO₂ <85% on HCT should have in-flight oxygen available; paediatrician discretion should be used for infants with SpO₂ 85%–90% recognising that sleep or respiratory infection may further reduce saturations in this group.
- ▶ In children with chronic lung disease able to perform spirometry whose forced expiratory volume in 1 s (FEV₁) is consistently <50% predicted, HCT should be considered. This includes children with CF and primary ciliary dyskinesia (PCD). Children with chronic lung disease who are too young to perform spirometry reliably should have a clinical assessment of disease severity and their likely tolerance of hypoxia. In children with CF the disease is rarely severe enough to compromise lung function significantly at this age.
- ▶ Infants and children who have required long-term oxygen in the last 6 months should be discussed with a respiratory paediatrician and HCT considered.

Patient selection for HCT

See figures 1 and 2.

The following patients should not require HCT

- ▶ Those with stable disease who have previously undergone HCT (no recent hospital admissions, exacerbations, or significant changes to treatment).
- ▶ Patients with COPD with baseline SpO₂ ≥95% and either MRC score 1–2 or desaturation to no less than 84% during 6 min walk test (6MWT) or shuttle walking test (SWT), should be able to travel without in-flight oxygen.
- ▶ Those with previous significant intolerance to air travel, such as mid-air emergency oxygen or diversion. These should have in-flight oxygen available at 2 L/min provided there is no history of hypercapnia.
- ▶ Preterm infants who have not reached their due date at the time of travel, as testing is not a reliable guide of oxygen requirement in these infants. These should have in-flight oxygen available, delivered at 1–2 L/min if they develop tachypnoea, recession, or other signs of respiratory distress.

HCT should be considered for the following patients

- ▶ Patients with COPD with resting SpO₂ ≤95%, MRC score 3 or greater, or desaturation to <84% on 6MWT or SWT, and in whom there are concerns about hypercapnia.
- ▶ Infants and children with a history of neonatal respiratory problems, or existing severe chronic lung disease including those with FEV₁ persistently <50% predicted.
- ▶ Adults and children with severe asthma, evidenced by persistent symptoms and/or frequent exacerbations despite optimal treatment regardless of resting sea level SpO₂.
- ▶ Patients with ILD in whom SpO₂ falls to <95% on exercise, and whose resting sea level arterial oxygen tension (PaO₂) is ≤9.42 kPa or whose TLCO is ≤50%.
- ▶ Those with severe respiratory muscle weakness or chest wall deformity in whom forced vital capacity (FVC) is <1 L.
- ▶ Those with existing or previous hypercapnia and those at risk of hypercapnia, including those taking medication(s) which can cause respiratory depression.
- ▶ Patients with a history of type 2 respiratory failure already on LTOT at sea level. However, if there is no evidence of hypercapnia, it seems reasonable to recommend an increase in flow rate by 2 L/min in-flight, provided the equipment can provide it (see Appendix A)

HCT results

- ▶ PaO₂ ≥6.6 kPa (≥50 mm Hg) or SpO₂ ≥85%: in-flight oxygen not required.
- ▶ PaO₂ <6.6 kPa (<50 mm Hg) or SpO₂ <85%: in-flight oxygen recommended.
- ▶ Where required, titrate oxygen to maintain PaO₂ ≥6.6 kPa or SpO₂ ≥85% in adults, SpO₂ 90% in children aged 1 year or more.

Asthma

- ▶ The patient's condition should be optimised before travel, with attention paid to inhaler technique and smoking cessation referral as required.
- ▶ All medications and spacer devices should be carried in hand luggage to mitigate the risk of lost or missing hold baggage.
- ▶ Emergency medications, including salbutamol inhalers and spacers, must be immediately accessible.
- ▶ Individuals prescribed epinephrine auto-injectors should have them readily available.
- ▶ For acute exacerbations on board, the passenger's own bronchodilator inhaler should be given, with a spacer if needed.
- ▶ The passenger should alert the cabin crew if symptoms do not respond rapidly to use of the inhaler, or if they recur after a short interval.
- ▶ If the passenger does not have their own inhaler with them, or if it is inaccessible, the airline may carry an inhaler in the emergency medical kit. Spacers are not commonly available.
- ▶ Those with severe asthma should consult their respiratory specialist beforehand and consider taking an emergency supply of oral corticosteroid in their hand luggage in addition to their usual medication.

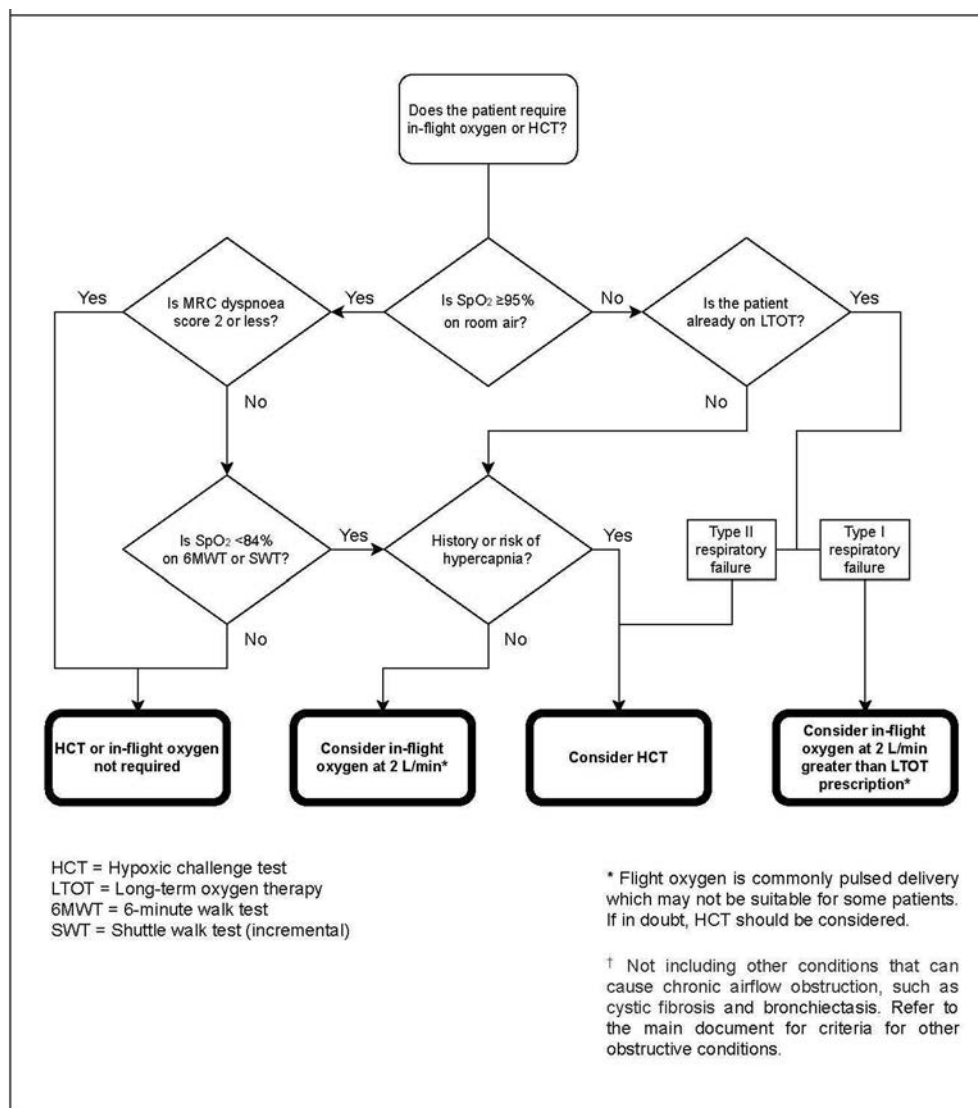


Figure 1 Preflight assessment of patients with chronic airflow obstruction.

- ▶ Passengers with severe asthma are advised to carry copies of their asthma management plan and/or relevant clinic letters. Information can be held securely as scanned copies on a mobile phone, or on a digital platform such as the National Health Service (NHS) App.
- ▶ Food allergy affects up to 8.5% of children and adults with asthma and asthma is a risk factor for severe or fatal anaphylaxis. Appropriate precautions for those affected include wiping tray tables and hands, informing the airline beforehand and the cabin crew of allergies, and not eating during flights or bringing known 'safe' foods from home.
- ▶ Patients requiring long-term oxygen therapy should also plan for oxygen supplementation at their destination (see online supplemental appendix 1).
- ▶ Wherever possible, those who have had a recent exacerbation of their condition should not fly until their condition is stable and use of reliever therapy has returned to their usual base-line. If their condition deteriorates while overseas, medical advice should be sought before undertaking the return flight.

Chronic obstructive pulmonary disease

- ▶ The patient's condition should be optimised before travel, with attention paid to inhaler technique and smoking cessation referral where appropriate.
- ▶ All medications and spacer devices should be carried in hand luggage to mitigate the risk of missing hold baggage.
- ▶ Emergency medications, including salbutamol inhalers and spacers, must be immediately accessible.
- ▶ For acute exacerbations on board, the passenger's own bronchodilator inhaler should be given, with a spacer if appropriate.
- ▶ Passengers with severe COPD are advised to carry a copy of their COPD management plan and/or relevant clinic letters. This information can be held securely as scanned copies on their mobile phone. A history of previous pneumothorax or bullous lung disease necessitates assessment by a respiratory specialist to determine the potential risk of complications from reduced cabin pressure.
- ▶ Patients with COPD are at greater risk of VTE as a direct consequence of the underlying condition, as well as after an exacerbation. They should be advised accordingly, especially if planning longer flights when the risk is further enhanced.

Cystic fibrosis

- ▶ All medications and spacer devices should be carried in hand luggage to mitigate the risk of missing hold baggage.
- ▶ Patients with CF under the age of 6 are likely to be well enough to fly at the paediatrician's discretion.
- ▶ In those with CF who are old enough for spirometry and whose FEV₁ is <50% predicted, HCT is recommended. If SpO₂ falls below the 90% cut-off, as outlined above, in-flight oxygen is advised.
- ▶ In children with chronic lung disease able to perform spirometry whose FEV₁ is consistently <50% predicted, HCT should be considered. This includes children with CF and non-CF bronchiectasis. Children with chronic lung disease who are too young to reliably perform spirometry should have a clinical assessment of disease severity and their likely tolerance of hypoxia. For children with CF disease is rarely severe enough to severely compromise lung function at this age.

Non-CF bronchiectasis

- ▶ Regular airway clearance is essential for those dealing with over-production of mucus.

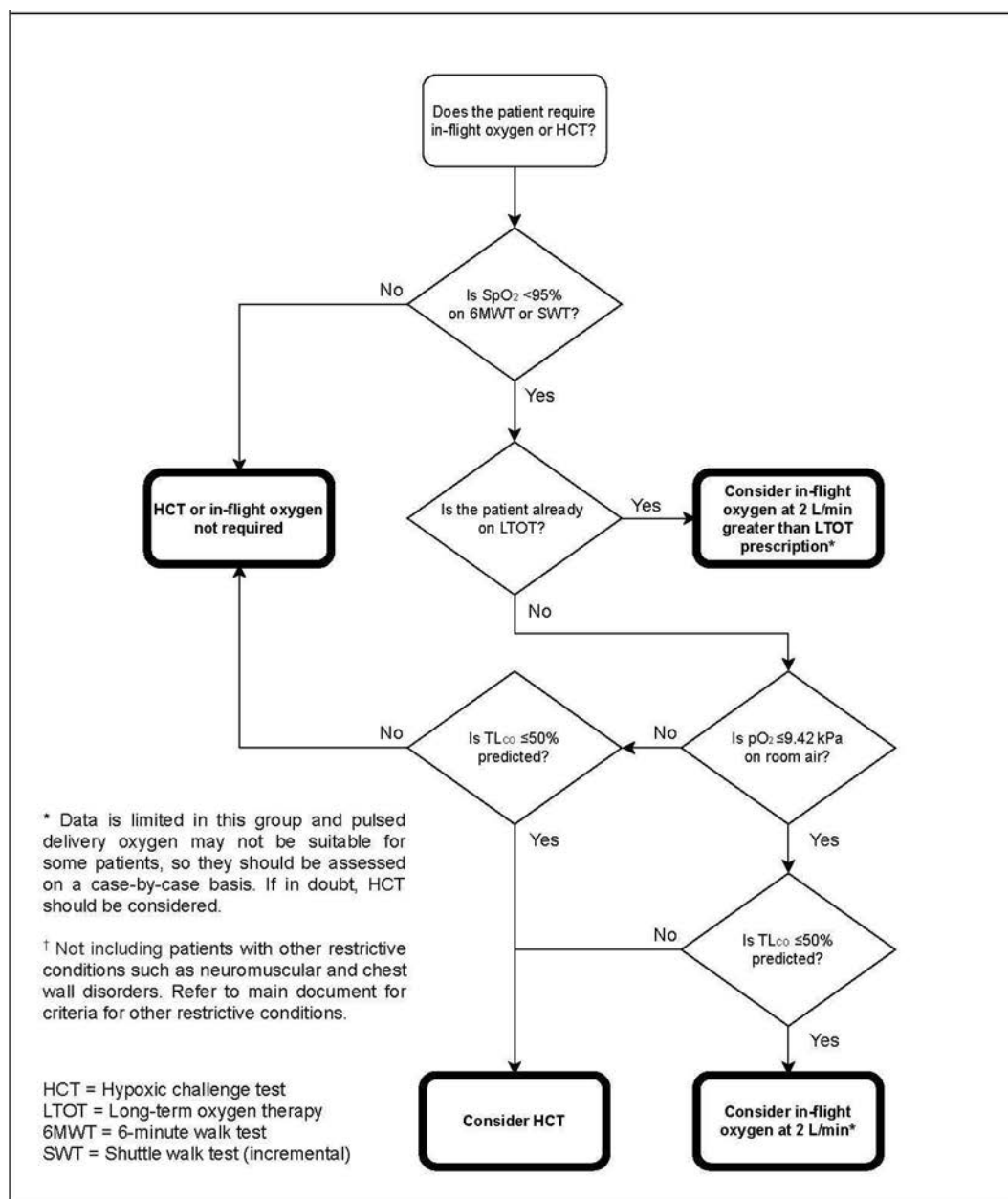


Figure 2 Preflight assessment of patients with restrictive respiratory disease.

- ▶ Advice from a respiratory physiotherapist on adapting airway clearance techniques should be sought for long-haul flights.
- ▶ Portable nebulisers and positive expiratory pressure (PEP) devices may be considered, but use of these devices in-flight must be approved by the airline before travel.
- ▶ Careful clinical assessment of the patient is required. This should include consideration of their baseline status including comorbidities, SpO₂, postprocedure complications such as infection and/or pain, flight duration and destination.

Interstitial lung disease

- ▶ In patients with comorbidity, including PH and/ or cardiovascular disease, attention should also be paid to the impact of air travel on these conditions.
- ▶ Physicians may wish to consider HCT in those whom SpO₂ falls to <95% on exercise, and/or in those in whom either Transfer Factor Carbon Monoxide (TLCO) ≤50% or PaO₂ ≤9.42 kPa (if available).
- ▶ Patients with TLCO <50% of predicted or PaO₂ ≤9.42 kPa are likely to need in-flight oxygen. If there are no concerns about hypercapnia it may be reasonable to recommend 2L/min without recourse to HCT. In those in whom there are concerns about CO₂ retention, titration HCT is advised to determine the oxygen flow rate.

Thoracic surgery

The opinion of the surgeon or interventionalist should be obtained before the patient travels by air. Patients, professionals and their carers should be aware that this may result in a delay of 4 weeks for non-essential air travel and 2 weeks for essential air travel.

Other interventional procedures

- ▶ The opinion of the interventionalist should be obtained before the patient travels by air.
- ▶ Careful clinical assessment of the patient is required. This should include consideration of baseline status including co-morbidities, SpO₂, postprocedure complications such as infection or pain, flight duration and destination.
- ▶ Patients with no pneumothorax seen on the postprocedure chest X-ray should wait for 1 week before air travel.
- ▶ Patients with a pneumothorax seen on the post-procedure chest X-ray should wait for one week after resolution on chest X-ray before air travel.

Trapped lung

- ▶ The opinion of the interventionalist should be obtained before the patient travels by air.
- ▶ Patients should be assessed carefully and advised on a case-by-case basis.
- ▶ Patients should be clinically stable before air travel.

Bronchoscopic procedures

- The opinion of the interventionalist should be obtained before the patient travels by air.
- Patients should be clinically stable before they travel.
- After interventional bronchoscopy including Transbronchial Needle Aspiration (TBNA), Transbronchial Lung Biopsy (TBB), Endobronchial Ultrasound Bronchoscopy (EBUS) and endobronchial valve insertion, those with no pneumothorax seen on the postprocedure chest X-ray should wait for 1 week before air travel.
- After interventional bronchoscopy including TBNA, TBB and EBUS, those with a pneumothorax seen on the post-procedure chest X-ray should wait for 1 week after resolution on chest X-ray before air travel.

Pneumothorax

- Passengers should not travel by air until 7 days after full resolution on chest X-ray.
- Those at higher risk of recurrent pneumothorax should be advised accordingly.
- Higher-risk groups, including those with cystic lung disease such as lymphangioleiomyomatosis (LAM) and Birt-Hogg-Dubé (BHD) syndrome, should be advised accordingly.
- Patients with trapped lung and a chronic air space thought to present a low risk should be evaluated in secondary care before travel.

Upper respiratory infection including otitis media and sinusitis

- In passengers who develop sinus barotrauma after flying, it may be helpful to consider topical and oral decongestants as well as appropriate analgesia. Prolonged use of decongestants is not advised owing to the risk of rebound congestion on withdrawal.
- If there is an allergic component, intranasal steroids used for a week prior to travel, and/or oral corticosteroids may be considered.
- Symptoms and signs of barotrauma should have resolved before flying again. This usually takes between 1 and 6 weeks.
- After an episode of acute otitis media, patients are usually advised not to fly for 2 weeks.

Viral infections

- Patients with highly contagious infections including measles, chickenpox, mumps, SARS, Middle East respiratory syndrome (MERS) or COVID-19 should not be allowed to travel until they are considered non-infectious.
- Passengers should familiarise themselves with current national and international regulations regarding air travel, which should always be observed.

Tuberculosis

- Smear positive patients must not fly until they have provided two smear negative samples on treatment.
- Those starting treatment for pulmonary tuberculosis (TB), where not all the information is yet available, should not travel by air for the first 2 weeks.
- For those who are smear negative and have a fully sensitive organism, treatment would be expected to render them non-infectious after 2 weeks.
- For patients with multidrug resistant/extensive drug resistant (MDR/XDR) TB, travel is prohibited until two negative culture samples have been produced and there is clinical evidence of improvement on treatment.
- Extrapulmonary TB does not usually warrant additional precautions before air travel.

Pneumonia

- All but essential travel should be postponed for 7 days in those who have reduced baseline sea level SpO₂ (<94%).

Obstructive Sleep Apnoea (OSAS) and Obesity Hypoventilation Syndrome (OHS)

- Daytime flights are advised wherever possible.
- The patient should be advised to carry their continuous positive airway pressure (CPAP) device as hand luggage, and a hospital letter to advise that the patient uses CPAP.
- Careful planning and preparation are required, and use of the patient's own CPAP device is advised.

Table 1 Summary of risk factors for VTE during air travel

Risk status	Risk factors	Advice
All passengers	Low	Avoid excess alcohol and caffeine-containing drinks Remain mobile/exercise legs
Moderate risk	Examples include: Aged over 60 Extensive varicose veins Recent minor surgery Pregnancy	Above plus consider: Take short periods of sleep Support hosiery/graduated compression stockings
High risk	Examples include: Previous VTE (and not on current anticoagulation) Thrombophilia Within 6 weeks of major surgery Current malignancy	If travel is essential, consider: low-molecular-weight heparin or formal anticoagulation (including return journey) This requires careful clinical assessment

VTE, venous thromboembolism.

- Alcohol and sedatives should be avoided in the 12 hours before, and during, airline travel.
- Patients should use their CPAP device on board if they are travelling overnight, and avoid sleeping during daytime flights.
- Consideration should be given to device settings and whether adjustment is required for operation at altitude.
- Airline approval for carriage and use of device, including battery specification, must be gained before travel.
- Consideration should be given to the whole journey. If driving is required the following day, an overnight stay at destination may be advisable. Patients are advised to refrain from driving if tired and sleepy.

Respiratory muscle and chest wall disorders

- HCT is recommended for all adult patients with FVC <1L, pending further data, and may be considered in others thought to be at particular risk, including children with reduced FVC due to respiratory muscle or chest wall disorders.
- If patients are unable to perform spirometry reliably, a walk test may be considered as an alternative.
- Patients should be advised to take daytime flights where possible.
- Further planning and support are required for those established on non-invasive ventilation (NIV) (see Appendix A). (online supplemental appendix 2)

Prevention of VTE during air travel

See table 1.

- Limit the risk of dehydration with adequate fluid intake.
- Avoid alcohol.
- Keep mobile, if possible, by walking around or doing seat-based exercises once an hour.
- Consider graduated compression stockings (class 1 with 15–30 mm Hg).
- Low molecular weight heparin (LMWH) or a Direct Acting Oral Anticoagulant (DOAC) are advised for both outward and return long haul flights (long haul defined as flights of 6–12 hours) in high-risk patients including those with a history of VTE; local policy should be followed regarding liaison with primary care and/or haematology services to teach the patient how to administer the injection and dispose safely of the equipment. There is no formally recommended dose, but enoxaparin at a dose of 40 mg or weight based 1 mg/kg injected once 4–5 hours before the flight has been suggested.
- The prophylactic doses of the DOAC may also be used.
- All patients with a recent (<6 weeks) history of VTE, especially any who presented with significant right ventricular strain and decompensation should be reassessed before air travel.

Air travel after VTE

- Air travel should be delayed for 2 weeks after a diagnosis of DVT or pulmonary embolism (PE).

Pulmonary hypertension

- Those in New York Heart Association (NYHA) WHO functional class 3 or 4 are usually advised to have in-flight oxygen. If there is no evidence of hypercapnia it seems reasonable to suggest 2 L/

min by nasal cannulae. If there are concerns about hypercapnia, HCT should be considered if available.

- ▶ Those eligible for LTOT (sea level $\text{PaO}_2 < 8 \text{ kPa}$ at rest on air) should have in-flight oxygen at double the flow rate recommended at sea level, provided there is no evidence of hypercapnia.

Lung cancer and mesothelioma

- ▶ Patients undergoing chemotherapy should not travel while they are at increased risk of infection or suffering from significant side effects, such as vomiting.

Hyperventilation and DB

- ▶ Patients with DB, inducible laryngeal obstruction (ILO) and/or vocal cord dysfunction (VCD) should be referred to a respiratory physiotherapy specialist for advice on symptom management before travel.
- ▶ Those with anxiety disorders should be reviewed before travel; compliance with medication assessed; and use of short acting anxiolytics encouraged.
- ▶ Other life-threatening conditions presenting with dyspnoea should be excluded on board as far as possible.
- ▶ Supplemental oxygen should be given on board if the cause of breathlessness is unclear
- ▶ Rebreathing via a paper bag is not recommended.

HCT outcomes

Preflight respiratory screening

Why?

Medical incidents have been reported in around 1 in 600 flights,¹⁰ or 1 in 30 000 passengers.^{11 12} Estimates vary and reliable data are difficult to obtain, but respiratory events account for around 12% of in-flight incidents. In a recent study of 1260 healthy volunteers, no significant changes occurred in pulse oximetry (SpO_2) during a simulated 8-hour flight at cabin altitudes up to 2438 m (8000 ft).¹³ However, if cabin altitude exceeds 3048 m (10 000 ft), hypoxaemia becomes more prominent and SaO_2 falls to ~89% in healthy individuals.¹⁴ Other potential hazards for passengers with respiratory conditions include low relative humidity, and altitude-related expansion of gases within enclosed pulmonary parenchymal spaces. It follows from Boyle's Law that a cabin altitude of 2438 m (8000 ft) will result in a 38% expansion of humidified gas.

Who?

There is no good-quality evidence to determine who should have a formal respiratory review before air travel. Experts generally advise preassessment or screening for the following adults, children and infants:

- ▶ Those with a respiratory condition with the potential to deteriorate acutely resulting in incapacitation and/or the need for medical intervention. This includes (but is not exclusive to):
 - Severe ($\text{FEV}_1 < 50\%$ predicted¹⁵ or poorly controlled obstructive airway disease (evidenced by symptoms, oxygen requirements, severe and/or frequent exacerbations).
 - Symptomatic restrictive lung or chest wall conditions, or known respiratory muscle weakness causing breathlessness and exercise limitation.
 - PH.
 - Comorbid conditions which may be worsened by hypoxaemia (cerebrovascular or cardiac disease).
 - Recent (<6 weeks) hospital treatment for a respiratory condition.
 - Requirement for CPAP or ventilator support such as NIV.
 - Active cancer with lung involvement.
 - Patients requiring domiciliary oxygen.
- ▶ Recent (<6 weeks) pneumothorax and those at higher risk of pneumothorax (cystic lung disease or recurrent pneumothorax), and patients with trapped lung and a chronic air space.
- ▶ Recent (<6 weeks) pulmonary embolus or deep venous thrombosis, or increased risk of VTE.
- ▶ Anyone who has experienced significant symptoms during previous air travel, or whose condition is of concern to their physician.

The following are generally considered contraindications to air travel:

- ▶ Untreated respiratory failure.
- ▶ Untreated pneumothorax.
- ▶ Active infection representing a risk to others for example, TB, SARS, MERS, COVID-19.
- ▶ Bronchogenic cysts. Cerebral air embolism, in some cases fatal, has been reported in aircraft passengers after rupture of a bronchogenic cyst.¹⁶
- ▶ Patients with severe hypoxaemia requiring $> 4 \text{ L/min}$ in-flight oxygen were previously advised against air travel, because 4 L/min was the maximum fixed flow rate routinely available on commercial aircraft. With the availability of flight approved POCs delivering a range of continuous and intermittent flow rates, this cut-off no longer applies. In-flight oxygen delivery is more varied, and maximum flow rate is determined by the equipment available. Pulse-dose delivery systems can however complicate determination of the flow delivered and may not be well tolerated. The effects of mouth-breathing, speech, snoring and/or sleeping should be considered. High-flow nasal oxygen (HFNO) cannot be delivered on board commercial aircraft.

In-flight oxygen may be contraindicated in adults and children with a history of type 2 respiratory failure.^{17 18} Hypoxic challenge with arterial carbon dioxide tension (PaCO_2) measurement was advised for this group in 1996¹⁷ but there has been little research since. This document, therefore, follows the 2015 BTS Guideline for Home Oxygen Use in Adults¹⁹ when making recommendations for managing patients with previously documented hypercapnia.

Clinical practice points

- ▶ All patients should undergo careful initial evaluation with history and physical examination by a clinician who is competent. The history should include:
 - Review of symptoms, baseline exercise capacity, recent exacerbation history, treatments and previous experience of air travel.
 - Consideration of the logistics of the intended journey, to include (if known):
 - Number and duration of flights, including whether day-time or overnight.
 - Location of stop-over(s) and destination: these determine air quality, altitude and available medical facilities.
 - Time away from home.
 - Return journey.
- ▶ Further assessment by a Respiratory Specialist is advised for those in whom screening raises concerns, and hypoxic challenge testing may be advised.

Infants and children

In general, similar considerations apply to both adults and children if they have severe chronic airway disease, or require chronic supplementary oxygen, or non-invasive or tracheostomy ventilation. Both children and adults with these conditions require a preflight assessment. Similarly, unless otherwise stated, recommendations for individuals with previous thoracic surgery, pneumothorax or empyema apply to both adults and children. There are, however, some specific considerations for infants and younger children since several factors place infants at greater risk of developing hypoxia. These factors include left shift of the oxygen dissociation curve (due to the presence of foetal haemoglobin), smaller airway diameter, relatively fewer alveoli, compliant rib cage and increased tendency to pulmonary vasoconstriction and bronchoconstriction and thus ventilation-perfusion mismatch under hypoxic conditions. Moreover, preterm infants and infants under 2 months of age may develop apnoea/hypoventilation in response to hypoxia or infection.^{20 21} Beyond 3 months of age there is no evidence that ex-preterm infants, without bronchopulmonary dysplasia, are at significantly greater risk of desaturation during a HCT than term infants.²²

In addition to very young and ex-preterm infants, the children most at risk of hypoxia are those with anaemia, congenital heart disease with an actual or potential right to left shunt,²³ neuromuscular disorders or chronic or acute lung disease. Low humidity during air travel can also present a problem for children with respiratory conditions such as CF. Those most at risk of complications associated with reduced air pressure are children with upper respiratory tract

infections, or trapped intrathoracic air, including those with recent pneumothorax or cystic lung disease.²⁴

For infants born at term (>37 weeks) it is prudent to delay flying for 1 week after birth to ensure they are healthy.²⁵ In view of their greater risk of apnoea and hypoxia, infants born prematurely (<37 weeks) with or without a history of respiratory disease who have not reached their expected date of delivery at the time of flying should have in-flight oxygen available. HCT may not be a reliable guide of oxygen requirement in this group.²⁶ If air travel is essential, they should travel with oxygen at a tolerable low flow, recognising that this may be a minimum of 1 L/min depending on equipment. The following Clinical Practice Points are specific to infants and children.

Clinical practice points

- ▶ For infants born at term (>37 weeks) it is prudent to delay flying for 1 week after birth to ensure they are healthy.
- ▶ Infants born prematurely (<37 weeks) with or without a history of respiratory disease who have not reached their expected date of delivery at the time of flying should have in-flight oxygen available. HCT may not be a reliable guide of oxygen requirement in this group. If air travel is essential, they should travel with oxygen at a tolerable low flow rate, recognising that this may be a minimum of 1 L/min depending on equipment.
- ▶ Infants under 1 year with a history of chronic respiratory problems should be discussed with a respiratory paediatrician and HCT considered. Those with SpO₂ <85% on HCT should have in-flight oxygen available; paediatrician discretion should be used for infants with SpO₂ 85%–90% recognising that sleep or respiratory infection may further reduce saturations in this group.
- ▶ In children with chronic lung disease able to perform spirometry whose FEV₁ is consistently <50% predicted, HCT should be considered. This includes children with CF and PCD. Children with chronic lung disease who are too young to perform spirometry reliably should have a clinical assessment of disease severity and their likely tolerance of hypoxia. In children with CF the disease is rarely severe enough to compromise lung function significantly at this age.
- ▶ Infants and children who have required long-term oxygen in the last 6 months should be discussed with a respiratory paediatrician and HCT considered.

How?

Pulse oximetry is the easiest and usually the first screening test.⁴ It has generally been accepted in the past that those with resting SpO₂ >95% at sea level should not require in-flight oxygen.^{2 25 27–30} Spirometry results may already be available in patients with known acute or chronic lung disease, or with symptoms suggesting lung disease.^{31 32} However, lung function parameters are in many cases poor at predicting hypoxaemia or complications.^{28 33–35}

Many airlines have historically considered that those able to walk 50 m or climb up 10–12 steps without distress have sufficient cardiopulmonary reserve to fly.^{2 36} The role of the 6MWT in preflight evaluation, widely used to assess functional capacity and exercise-induced hypoxaemia in COPD^{37–40} and ILD including IPF,^{41–43} has also been examined. Current data suggest that the 50 m walk test is an insensitive assessment of 'fitness to fly'^{38 44 45} although still sometimes referenced.^{36 46 47} Several studies show no correlation between walking distance and HCT outcome in patients with COPD, ILD or extrapulmonary restriction.^{38 44 45 48} One study showed no correlation between exertional dyspnoea and HCT outcome.³⁸ The 50 m walk test alone thus appears unsuitable for preflight assessment.

The 6MWT and externally paced incremental SWT may be of value. Baseline values do not reliably predict in-flight hypoxaemia in a number of respiratory conditions^{1 4 33 34 44 49–51} but changes in SpO₂ during 6MWT and SWT may correlate with HCT outcome in COPD, ILD and chest wall deformity.^{30 38 44 45} Walk tests cannot predict the in-flight oxygen flow rate required, but they may help inform the decision as to who needs further assessment.

A walk test is not always practical. Data from one small study in COPD suggest that MRC scores may help predict the likelihood of exercise desaturation.⁵² From this it appears that patients with COPD, MRC score 1 or 2 and resting oxygen saturations >95% do not usually need further testing before air travel. If there are still

concerns, a walk test may help decide whether HCT is required. In those with COPD who do undergo 6MWT or SWT and do not desaturate below 84%, in flight oxygen should not be required and they should not need HCT.

If resting oxygen saturations are SpO₂ 92%–95% and they desaturate <84% but have no evidence of CO₂ retention, data from Edvardsen *et al*³⁰ suggest it is reasonable to recommend in-flight oxygen at 2 L/min without proceeding to HCT. Patients in whom there are concerns about hypercapnia should proceed to HCT.

Data are much more limited in restrictive disease, including ILD, and baseline SpO₂ does not appear to predict outcome. In general, it seems reasonable to suggest that if baseline saturations are >95% at rest and there is no desaturation below 95% on 6MWT or SWT, HCT should not be required. Those with ILD and TLco ≤50% of predicted and PaO₂ ≤9.42 kPa are likely to need in-flight oxygen or HCT. If there are no concerns about hypercapnia it may be reasonable to recommend 2 L/min without recourse to HCT. If there are concerns about CO₂ retention, titration HCT will be required to determine the oxygen flow rate.

Hypoxic challenge testing

HCT is performed using an inspired gas mixture containing 15% oxygen, which gives an approximate similar inspired oxygen tension (PO₂) to breathing air at the maximum allowable cabin pressure altitude (2438 m or 8000 ft).^{53 54} HCT is usually performed in a specialist respiratory physiology unit. The provision of a 15% oxygen gas mixture can be achieved using one of the methods described in online supplemental appendix B.

The closest approximation to aircraft cabin conditions entails exposure to simulated altitude in a hypobaric chamber, but such chambers are not available for clinical assessment. A reasonable substitute is the normobaric HCT, described by Gong *et al*⁵⁵ in patients with chronic airflow obstruction. This assesses the response to hypoxaemia achieved by breathing a hypoxic gas mixture at sea level. Various methods of hypoxic gas delivery produce equivalent results to tests in a hypobaric chamber or during real flights in adults with COPD.^{1 39 56–58} Data are limited in other conditions as well as for children and neonates.

The HCT is used to help decide whether passengers with respiratory disease need in-flight oxygen and at what flow rate. It does not assess fitness for air travel, despite its reputation as a 'fitness to fly' test. If healthcare providers give this impression in patient information, they must manage patient and carer expectations accordingly. A 'preflight oxygen test' is a more accurate description. Most patients do not require HCT as part of preflight medical assessment, and there should not be pressure on physicians to arrange, or healthcare professionals to perform, unnecessary HCT.

The physiological response to hypobaric hypoxia (PaO₂ <8 kPa) is increased ventilation.⁵⁹ Alterations in respiratory pattern may adversely impact on lung mechanics,⁶⁰ which may be further impaired by gas expansion, reducing vital capacity and increasing residual volume.⁶¹ The increase in ventilatory drive is likely to be limited on commercial flights,⁶² but a modest increase in ventilation can exhaust an already reduced ventilatory reserve.^{16 60 63}

The usual consensus is to recommend in-flight oxygen if PaO₂ is predicted to fall below 6.6 kPa (50 mm Hg) or SpO₂ below 85% in flight. There is little high-quality evidence supporting these cut-off values, but this PaO₂ value ensures that SpO₂ remains above the steep portion of the oxyhaemoglobin dissociation curve.⁶⁴ Some authors consider 6.6 kPa to represent the lower safe limit for hypoxaemia,^{65 66} as PVR increases sharply in response to arterial pO₂ below this level.⁶⁷ with the potential for an acute increase in right ventricle afterload and right ventricular dysfunction.^{16 29} As many patients with COPD have cardiac comorbidity,⁶⁸ hypoxaemia in these patients could precipitate cardiac ischaemia; this is unlikely in those with stable disease in NYHA functional class I or II (no or mild limitation of physical activity).^{69 70} In the absence of new evidence to the contrary, the cut-off PaO₂ of 6.6 kPa during HCT appears reasonable.

HCT outcomes do not predict respiratory symptoms during air travel.^{71 72 73} Such symptoms do not appear to result directly from hypoxaemia,⁶² but from a combination of poor respiratory mechanics and reduced respiratory reserve impairing the response to hypoxaemia. Symptoms are more likely to occur in those with

more severe breathlessness at sea level.^{4 72} Limited evidence suggests that those who desaturate during HCT and have previously experienced respiratory symptoms during air travel can avoid these by using in-flight oxygen.^{29 71} Symptoms may also result from anxiety regarding air travel (see section on hyperventilation and DB).

Patient selection for HCT

Those with stable respiratory disease without history of air travel intolerance, normal resting and exercise SpO₂ at sea level and no significant cardiac comorbidity, are unlikely to need in-flight oxygen and should not require HCT. Those who have had HCT in the past should not need it repeated unless their clinical condition has changed. The patient's plans should, however, be discussed with the patient's respiratory physician, paediatrician or specialist nurse.

Those already using LTOT will need in-flight oxygen. Ideally, the flow rate required at cruising altitude should be determined using HCT. If HCT is not readily available and there are no concerns about hypercapnia, passengers already on LTOT should be advised that they will need a flow rate 2 L/min greater than their baseline flow rate. This should be sufficient to compensate for the relative hypoxia at normal cabin altitude. However, current POCs do not routinely offer continuous flow rates above 3 L/min, and a pulse-dose delivery mode at higher levels may not always be suitable.⁷⁴

As noted above, it is not practical for all patients with COPD who want to fly to undergo 6MWT. Respiratory physicians may however wish to consider 6MWT if there has been a significant change in the patient's condition since the last assessment, or in new patients previously unknown to the service. Those who desaturate below 84% may then be referred for HCT at the discretion of the respiratory physician.

Some data are available in smaller numbers of patients with restrictive lung disease, but there is currently no consensus regarding the best walk test or cut-off values. In a study of 14 patients with primary thoracic scoliosis, Bandyopadhyay *et al* found that resting SpO₂ >95% did not accurately identify those who do not desaturate during HCT, and recommend a low threshold for performing HCT on patients with thoracic scoliosis.⁴⁴ Likewise, in a study of 13 patients with OHS, baseline SpO₂ did not predict HCT outcome.⁴⁹ In a study including 42 patients with ILD and 20 with extra-pulmonary restriction³⁵ before and after '2 min of moderate exercise', Ling *et al* proposed that a postexercise SpO₂ of no less than 95% could be used to exclude the need for HCT. Further research is required to determine the most appropriate assessments for patients with a variety of restrictive lung diseases, including which (if any) can reliably eliminate the need for HCT.

Clinical practice points: patient selection for HCT

See figures 1 and 2

The following patients should not require HCT

- ▶ Those with stable disease who have previously undergone HCT (no recent hospital admissions, exacerbations, or significant changes to treatment).
- ▶ Patients with COPD with baseline SpO₂ ≥95% and either MRC score 1–2 or desaturation to no less than 84% during 6MWT or SWT, should be able to travel without in-flight oxygen.
- ▶ Those with previous significant intolerance to air travel, such as mid-air emergency oxygen or diversion. These should have in-flight oxygen available at 2 L/min provided there is no history of hypercapnia.
- ▶ Preterm infants who have not reached their due date at the time of travel, as testing is not a reliable guide of oxygen requirement in these infants. These should have in-flight oxygen available, delivered at 1–2 L/min if they develop tachypnoea, recession, or other signs of respiratory distress.

HCT should be considered for the following

- ▶ Patients with COPD with resting SpO₂ ≤95%, MRC score 3 or greater, or desaturation to <84% on 6MWT or SWT, and in whom there are concerns about hypercapnia
- ▶ Infants and children with a history of neonatal respiratory problems, or existing severe chronic lung disease including those with FEV₁ persistently <50% predicted (see page 7).

- ▶ Adults and children with severe asthma, evidenced by persistent symptoms and/or frequent exacerbations despite optimal treatment (see BTS/SIGN Asthma Guideline⁷⁵) regardless of resting sea level SpO₂.
- ▶ Patients with ILD in whom SpO₂ falls to <95% on exercise, and whose resting sea level PaO₂ is ≤9.42 kPa or whose TLCO is ≤50%.
- ▶ Those with severe respiratory muscle weakness or chest wall deformity in whom FVC is <1 L.
- ▶ Those with existing or previous hypercapnia and those at risk of hypercapnia, including those taking medication(s) which can cause respiratory depression.
- ▶ Patients with a history of type 2 respiratory failure already on LTOT at sea level. However, if there is no evidence of hypercapnia, it seems reasonable to recommend an increase in flow rate by 2 L/min in-flight, provided the equipment can provide it (see Appendix A).

Clinical practice points: HCT results

- ▶ PaO₂ ≥6.6 kPa (≥50 mm Hg) or SpO₂ ≥85%: in-flight oxygen not required.
- ▶ PaO₂ <6.6 kPa (<50 mm Hg) or SpO₂ <85%: in-flight oxygen recommended.
- ▶ Where required, titrate oxygen to maintain PaO₂ ≥6.6 kPa or SpO₂ ≥85% in adults, SpO₂ 90% in children aged 1 year or more.

Air travel may be contraindicated in infrequent cases when supplementary oxygen, at the flow rate needed to maintain PaO₂ ≥6.6 kPa or SpO₂ ≥85%, causes significant changes to pH and pCO₂. The 2015 BTS Guidelines for Home Oxygen Use in Adults¹⁹ consider that a pH <7.35, and a PaCO₂ increase >1 kPa from baseline (within 20 min) is significant. Specialist respiratory physicians should use their discretion to determine the risk in individual cases and advise accordingly. Where hyperventilation is suspected, especially in response to anxiety rather than hypoxaemia, results should be interpreted with caution as there is a risk of false negative results.⁷⁶

HCT methods

These are described in Appendix B.

Exertion on board

Studies in adults with COPD^{33 77 78} or CF⁷⁹ have shown that patients can develop profound hypoxaemia when exercising under hypoxic conditions, whether on board a commercial aircraft at cruising altitude or during HCT. This has been reported in patients whose HCT results would otherwise not warrant oxygen. In some cases, PaO₂ values as low as 3.9 kPa have been recorded.^{33 78}

The combination of further hypoxaemia and increased ventilatory demand from exertion while flying may challenge those already approaching the limits of their respiratory reserve. It therefore seems prudent to recommend that passengers with significant respiratory limitation, regardless of whether they travel with in-flight oxygen, should request an aisle seat near a toilet to avoid long periods of walking.^{1 29 80} Passengers should keep active by undertaking seat-based exercises and/or standing at intervals if flight conditions permit.

Patients who cannot tolerate withdrawal of supplemental oxygen for even a short period of time should not travel by air, as there will be periods of time when oxygen cannot be supplied. POC use below 10 000 ft may in some circumstances be prohibited by cabin crew. The reduction in cabin pressure between an aircraft taking off and reaching 10 000 ft is small (10%) and unlikely to have any clinical impact on those who do not usually require oxygen at rest at sea level. Aircraft descent may however take longer than ascent, and the time to landing may be less predictable.

Disease/condition-specific advice

Chronic airflow obstruction including asthma and COPD

Most adults and children with well-controlled mild or moderate airflow obstruction and no other co-morbidities should have no problem with commercial air travel, but they should be prepared for the possibility of an exacerbation of their condition. Air travel presents a theoretical risk of bronchospasm because of mucosal water loss due to low cabin humidity.

Cigarette smokers are at a physiological disadvantage during exposure to altitude.⁸¹ Every opportunity should be taken, when reviewing travel plans, to take a smoking history and offer brief intervention and smoking cessation referral as appropriate.

Asthma

While asthma is prevalent and has the potential to be life-threatening, most episodes are not.^{82,83}

Most passengers with asthma will have relatively mild disease and do not require HCT. HCT should however be considered for those with severe asthma, regardless of baseline sea level oxygen saturation. In a retrospective study of 37 adults with severe asthma (as defined in the BTS/SIGN Asthma guideline⁷⁵) undergoing HCT, two-thirds who fulfilled the criteria for in-flight oxygen on HCT had baseline sea level oxygen saturations of >95%.⁸⁴

The role of HCT has not been studied in children with severe stable asthma. A study in 51 children aged 2–12 years requiring transient oxygen therapy during an acute asthma attack ($\text{SpO}_2 < 92\%$) showed that although 5% failed HCT within 24 hours of discontinuing oxygen therapy, all passed the HCT when retested at 48 hours.⁸⁵

Food allergy affects up to 8.5% of children and adults with asthma,⁸⁶ and asthma is a risk factor for severe or fatal anaphylaxis.⁸⁷ Appropriate precautions for those affected include wiping tray tables and hands, informing the airline beforehand and the cabin crew of allergies, and not eating during flights or bringing known 'safe' foods from home.⁸⁸

Clinical practice points

- ▶ The patient's condition should be optimised before travel, with attention paid to inhaler technique and smoking cessation referral as required.
- ▶ All medications and spacer devices should be carried in hand luggage to mitigate the risk of lost or missing hold baggage.
- ▶ Emergency medications, including salbutamol inhalers and spacers, must be immediately accessible.
- ▶ Individuals prescribed epinephrine auto-injectors should have them readily available.
- ▶ For acute exacerbations on board, the passenger's own bronchodilator inhaler should be given, with a spacer if needed.
- ▶ The passenger should alert the cabin crew if symptoms do not respond rapidly to use of the inhaler, or if they recur after a short interval.
- ▶ If the passenger does not have their own inhaler with them, or if it is inaccessible, the airline may carry an inhaler in the emergency medical kit. Spacers are not commonly available.
- ▶ Those with severe asthma should consult their respiratory specialist beforehand and consider taking an emergency supply of oral corticosteroid in their hand luggage in addition to their usual medication.
- ▶ Passengers with severe asthma are advised to carry copies of their asthma management plan and/or relevant clinic letters. Information can be held securely as scanned copies on a mobile phone, or on a digital platform such as the NHS App.
- ▶ Food allergy affects up to 8.5% of children and adults with asthma and asthma is a risk factor for severe or fatal anaphylaxis. Appropriate precautions for those affected include wiping tray tables and hands, informing the airline beforehand and the cabin crew of allergies, and not eating during flights or bringing known 'safe' foods from home.

Chronic obstructive pulmonary disease

Patients with COPD planning air travel need careful evaluation, not only because of their respiratory disease, but also because of their high levels of comorbidity.^{71,89}

Respiratory symptoms in those with COPD are common during air travel, but Edwards *et al* have shown that HCT does not predict respiratory symptoms during air travel in patients with moderate to very severe COPD.⁷¹ They suggest that exacerbation of comorbidities such as cardiovascular disease (the most common cause of death in COPD) is the most threatening consequence of severe hypoxaemia. This is consistent with data showing a risk of cardiac arrhythmias and ischaemic chest pain in patients with COPD unable to respond to the physiological stressors of air travel.^{55,70} Work by Robson *et al* shows that resting sea level saturations alone do not predict HCT outcome.²⁸

Spirometry does not reliably predict hypoxaemia or complications in COPD.²⁹ It seems prudent to avoid air travel within 6 weeks of an exacerbation although there are few data to support this recommendation. Patients with COPD are at greater risk of VTE as a direct consequence of the underlying condition, as well as after an exacerbation. They should be advised accordingly, especially if planning longer flights when the risk is further enhanced (see section on VTE).^{90–92} See Figure 1.

Clinical practice points

- ▶ The patient's condition should be optimised before travel, with attention paid to inhaler technique and smoking cessation referral where appropriate.
- ▶ All medications and spacer devices should be carried in hand luggage to mitigate the risk of missing hold baggage.
- ▶ Emergency medications, including salbutamol inhalers and spacers, must be immediately accessible.
- ▶ For acute exacerbations on board, the passenger's own bronchodilator inhaler should be given, with a spacer if appropriate.
- ▶ Passengers with severe COPD are advised to carry a copy of their COPD management plan and/or relevant clinic letters. This information can be held securely as scanned copies on their mobile phone. A history of previous pneumothorax or bullous lung disease necessitates assessment by a respiratory specialist to determine the potential risk of complications from reduced cabin pressure.
- ▶ Patients with COPD are at greater risk of VTE as a direct consequence of the underlying condition, as well as after an exacerbation. They should be advised accordingly, especially if planning longer flights when the risk is further enhanced.
- ▶ Patients requiring long-term oxygen therapy should also plan for oxygen supplementation at their destination (see online supplemental appendix 1).
- ▶ Wherever possible, those who have had a recent exacerbation of their condition should not fly until their condition is stable and use of reliever therapy has returned to their usual baseline. If their condition deteriorates while overseas, medical advice should be sought before undertaking the return flight.

CF (adults and children)

The risks associated with air travel are greater for those with CF than for healthy individuals.⁹³ This is despite the fact that people with CF have been shown to tolerate PaO_2 values below 6.6 kPa (50 mm Hg) for several hours without cardiac decompensation or cerebral symptoms⁹⁴; do not usually have cardiovascular comorbidities; and are generally younger than patients with other respiratory conditions. Hypoxaemia results mainly from ventilation/perfusion mismatch attributable to chronic inflammation and mucus plugging. It is not clear which physiological values measured at sea level best predict hypoxaemia or complications during flight.

In 1 study of 30 adults with CF undergoing HCT, four fulfilled the study's criteria for supplemental oxygen ($\text{PaO}_2 < 6.6 \text{ kPa}$) at rest and a further 11 dropped below this threshold while walking slowly. Variables obtained during CPET (including SpO_2 and PaO_2) showed a stronger correlation with arterial oxygen tension (PaO_2) during HCT than baseline SpO_2 or spirometry.⁷⁹ However, in children with CF the sensitivity and specificity of preflight HCT have been reported as 20% and 99% (using a cut-off of $\text{SpO}_2 < 90\%$ during HCT with $\text{FiO}_2 0.15$), compared with 70% and 96% for spirometry (cut-off $\text{FEV}_1 < 50\%$ predicted).⁹⁵ Combining spirometry and HCT increased sensitivity to 80%. Spirometry may, therefore, usefully predict who may desaturate during flight, and a cut-off of $\text{FEV}_1 50\%$ has been used to recommend HCT.

Passengers with CF should practise good hand hygiene using soap and water or an alcohol-based hand gel, and avoid touching their face, particularly after touching arm rests, food trays or toilet doors to minimise risk of infection. These measures are included within recommendations from the European Centres of Reference Network for Cystic Fibrosis project, endorsed by the European Cystic Fibrosis Society.⁹³ These also advise checking the relevant airline policy and levels of CF healthcare provision at the proposed destination before travel (see online supplemental appendix 1).

Clinical practical points

- All medications and spacer devices should be carried in hand luggage to mitigate the risk of missing hold baggage.
- Patients with CF under the age of 6 are likely to be well enough to fly at the paediatrician's discretion.
- In those with CF who are old enough for spirometry and whose FEV₁ is <50% predicted, HCT is recommended. If SpO₂ falls below the 90% cut-off, as outlined above, in-flight oxygen is advised.
- In children with chronic lung disease able to perform spirometry whose FEV₁ is consistently <50% predicted, HCT should be considered. This includes children with CF and non-CF bronchiectasis. Children with chronic lung disease who are too young to reliably perform spirometry should have a clinical assessment of disease severity and their likely tolerance of hypoxia. For children with CF disease is rarely severe enough to severely compromise lung function at this age.

Non-CF bronchiectasis

Passengers with bronchiectasis should not necessarily be discouraged from flying, but air travel can pose challenges.

Clinical practice points

- Regular airway clearance is essential for those dealing with overproduction of mucus.
- Advice from a respiratory physiotherapist on adapting airway clearance techniques should be sought for long-haul flights.
- Portable nebulisers and PEP devices may be considered, but use of these devices in-flight must be approved by the airline before travel.

Interstitial lung disease

Like individuals with airflow limitation, patients with ILD, including pulmonary fibrosis, respond to hypoxaemia at altitude with increased heart rate and minute ventilation. In severe disease the ability to increase minute ventilation is limited and the resulting hypoxaemia may be marked. However, unlike COPD, where many patients appear to be able to tolerate marked hypoxia,⁶⁵ patients with ILD may have acute or subacute disease and be less able to withstand marked hypoxia. There are fewer relevant studies available in ILD, and patient numbers are smaller than in COPD studies.

Two studies in patients with ILD (n=15 and 10, respectively) have shown that sea level oxygen saturations do not reliably predict HCT outcome, and that oxygen saturations fall significantly after light exercise performed under conditions of normobaric hypoxia.^{73–76} These findings are consistent with those from the UK Flight Outcomes Study,⁴ a prospective observational study of 431 patients including 186 with ILD. This showed that neither FEV₁ nor sea level SpO₂ reliably predict desaturation at altitude, and that patients with ILD were more likely than others to require unscheduled healthcare for respiratory events within 4 weeks of air travel.

In a study including 15 patients with ILD, Martin *et al* found that predictive equations overestimated the need for in-flight oxygen in patients with ILD, as they did for those with COPD and CF.⁷⁷

More recently, Barratt *et al* examined the predictive value of various parameters for HCT outcome in 106 ILD patients (69 with IPF).⁹⁸ Only the combined parameters of TLCO >50% predicted and sea level PaO₂ >9.42 kPa independently predicted a successful HCT outcome. From analysis of a subset of 88 patients with a complete dataset available the authors propose a new preflight algorithm for patients with ILD with a sensitivity of 86% and specificity of 84%. In patients with both sea level PaO₂ ≤9.42 kPa and TLCO ≤50% predicted, in-flight oxygen is recommended without recourse to an initial diagnostic HCT. HCT for titration of the oxygen flow rate required on board is still advised. For patients in whom either TLCO ≤50% or PaO₂ ≤9.42 kPa, diagnostic HCT is advised. This promising approach requires further validation in a larger, prospective cohort of patients with ILD, preferably supported by patient reported outcomes from actual flight(s).

Clinical practice points

- In patients with comorbidity, including PH and/or cardiovascular disease, attention should also be paid to the impact of air travel on these conditions.

- Physicians may wish to consider HCT in those whom SpO₂ falls to <95% on exercise, and/or in those in whom either TLCO ≤50% or PaO₂ ≤9.42 kPa (if available).
- Patients with TLCO <50% of predicted or PaO₂ ≤9.42 kPa are likely to need in-flight oxygen. If there are no concerns about hypercapnia it may be reasonable to recommend 2 L/min without recourse to HCT. In those in whom there are concerns about CO₂ retention, titration HCT is advised to determine the oxygen flow rate.

Thoracic surgery and other interventional procedures

There is no high-quality evidence in this area and further research and/or data collection are needed. The following are suggested time periods before which a medically unaccompanied commercial flight can safely be undertaken after the specific thoracic interventions described below. The advice is conservative. Shorter recovery periods may be appropriate in individual cases, but only if approved by the doctor/surgeon carrying out the procedure. It is also important to note that the potential risks of travel are not just those associated with a postprocedure pneumothorax, but include wound infection and pain, which could require medical attention at destination and would need approval by the travel insurer.

Thoracic surgery, including VATS procedures

In the absence of published evidence, we advocate a conservative and safe minimum time interval, with the caveat that flying sooner after such procedures may be possible and/or desirable, but that this should be agreed with the surgeon and discussed with the airline. At least two UK centres independently advise against non-essential air travel for 4 weeks after removal of drains (Jon Naylor, personal communication). If air travel is essential, a minimum delay of 2 weeks is advised, depending on the type of surgery and the surgeon's advice.

Clinical practice points

- The opinion of the surgeon or interventionalist should be obtained before the patient travels by air. Patients, professionals, and their carers should be aware that this may result in a delay of 4 weeks for non-essential air travel and 2 weeks for essential air travel.
- Careful clinical assessment of the patient is required. This should include consideration of their baseline status including comorbidities, SpO₂, postprocedure complications such as infection and/or pain, flight duration and destination.

Percutaneous lung biopsy, pleural procedures (including thoracocentesis, medical thoracoscopy and insertion of indwelling pleural catheter)

A North American study of 179 patients, who between them underwent 183 percutaneous transthoracic needle biopsies, suggested that air travel was safe within 24 hours of procedure, even in the 65 patients (35%) who developed a small, stable postbiopsy pneumothorax.⁹⁹ Fifty (77%) of them flew within 4 days of the final postbiopsy chest radiograph. During a brief telephone survey after the flight, 14 (8%) reported worsening of pre-existing respiratory symptoms or new respiratory symptoms. There were no reported events requiring in-flight medical attention or flight diversion. These were, however short, internal North American flights over land, where diversion is relatively straightforward if required. The situation for a UK-based patient travelling on a long-haul flight to the Middle East, USA, Far East or Australasia is quite different.

Clinical practice points

- The opinion of the interventionalist should be obtained before the patient travels by air.
- Careful clinical assessment of the patient is required. This should include consideration of baseline status including comorbidities, SpO₂, postprocedure complications such as infection or pain, flight duration and destination.
- Patients with no pneumothorax seen on the postprocedure chest X-ray should wait for 1 week before air travel.
- Patients with a pneumothorax seen on the postprocedure chest X-ray should wait for 1 week after resolution on chest X-ray before air travel.

Trapped lung' after drainage of pleural space

Only very limited data are available, from a report of two patients with a small chronic pneumothorax.¹⁰⁰ This suggests that such patients may be able to travel safely by air, but require thorough clinical assessment, CT imaging and HCT as a minimum beforehand.

Clinical practice points

- ▶ The opinion of the interventionalist should be obtained before the patient travels by air.
- ▶ Patients should be assessed carefully and advised on a case-by-case basis.
- ▶ Patients should be clinically stable before air travel.

Bronchoscopic procedures

The risks associated with air travel are not only those of a possible pneumothorax, but also the effects of sedation, exacerbation of pre-existing or new symptoms such as cough, hoarse voice haemoptysis and dyspnoea, respiratory infection and the consequences of arrhythmias observed during the procedure.

Clinical practice points

- ▶ The opinion of the interventionalist should be obtained before the patient travels by air.
- ▶ Patients should be clinically stable before they travel.
- ▶ After interventional bronchoscopy including TBNA, TBB, EBUS and endobronchial valve insertion, those with no pneumothorax seen on the postprocedure chest X-ray should wait for 1 week before air travel.
- ▶ After interventional bronchoscopy including TBNA, TBB and EBUS, those with a pneumothorax seen on the postprocedure chest X-ray should wait for 1 week after resolution on chest X-ray before air travel.

Pleural disease

Pleural effusion

Patients with stable pleural disease and normal resting oxygen saturations should be able to fly without further precautions. Those who have indwelling long-term drainage catheters should be reminded that the manufacturers do not advise air travel. Those who choose to travel should be encouraged to take a supply of drainage bottles for their time away.

In those with a recent onset pleural effusion, investigation should be delayed if air travel is planned within 2 weeks, since intervention may increase the risk of pneumothorax. The risk of delaying investigation should be discussed with the individual to determine whether travel plans can be modified.

Pneumothorax

The prevalence of in-flight pneumothorax in passengers with existing lung disease appears low overall, being zero in the UK Flight Outcomes Study.⁴ It increases, however, in those at increased risk: 3.6% in a study of 276 patients with LAM¹⁰¹; and 9% within 1 month of air travel in a retrospective survey of 145 patients with BHD syndrome.¹⁰²

Most individuals with an untreated, closed pneumothorax should not travel by air. In exceptional cases where the pneumothorax is long-standing and thought to present a low risk, secondary care evaluation is strongly advised before travel.

In individuals with a treated pneumothorax, exposure to altitude poses a risk of recurrence. The 2010 BTS Pleural Disease guidelines state that patients '...should be cautioned against commercial flights ... until full resolution of the pneumothorax has been confirmed by a chest X-ray'.¹⁰³ These guidelines state that patients should wait a week after pneumothorax resolution before flying. There is limited, more recent evidence to suggest that in the case of traumatic pneumothorax, air travel as early as 72 hours after chest drain removal with full lung inflation may be safe.¹⁰⁴ A prospective observational study of 20 patients with a small residual traumatic pneumothorax, exposed to hypobaric hypoxia for 2 hours suggested no significant clinical effects despite expansion of up to 171%.¹⁰⁵ The data should, however, be interpreted with caution given the small numbers involved, the small size of the pneumothorax in each case, and the limited duration of hypobaric exposure. They are not sufficiently robust to justify overriding current BTS guidance.

In those who have undergone thoracotomy and surgical pleurodesis, the recurrence rate is so low that no subsequent restriction on travel is necessary.¹ The recurrence rate has been reported to be four times greater after video-assisted thoracoscopy,¹⁰⁶ suggesting that this procedure may not be as definitive. The risk of recurrence is greatest in those with pre-existing lung disease, cigarette smokers and taller men.¹

Clinical practice points

- ▶ Passengers should not travel by air until 7 days after full resolution on chest X-ray.
- ▶ Those at higher risk of recurrent pneumothorax should be advised accordingly.
- ▶ Higher-risk groups, including those with cystic lung disease such as LAM and BHD syndrome, should be advised accordingly.
- ▶ Patients with trapped lung and a chronic air space thought to present a low risk should be evaluated in secondary care before travel.

Respiratory tract infections

Upper respiratory infection including otitis media and sinusitis

During air travel with acute infection of the upper airway, the main risks are unpredictable, but may reflect previous experience. They are of pain and potential rupture of the tympanic membrane. Those with significant symptomatic viral upper respiratory tract infection may wish to delay travel because of the risk of pain and disseminating infection to others.

Barotrauma, characterised by otalgia, is a consequence of inability to equilibrate the pressure differential between the external and middle ear. This is usually more severe during landing than take-off. Most passengers, including older children, can equilibrate the pressure through yawning, swallowing, chewing or a Valsalva manoeuvre (eg, pinching the nose and blowing). Infants and young children may be unable to perform these manoeuvres, but swallowing may be encouraged by drinking. It is also more frequent when the child is awake and/or crying.

It has been estimated that 10% of adults and 22% of children may have changes to the ear drum after a flight, although perforation is rare and symptoms usually resolve spontaneously.^{107 108}

Historically, oral (and to a lesser extent topical) decongestants have been recommended for adults with risk factors for sinus or middle ear barotrauma.¹ The evidence is very weak, and there is no evidence in children. Treatment with intranasal steroids (commenced at least a week before the flight) can however improve symptoms, as for inflammatory rhinosinusitis. After an episode of acute otitis media, patients are usually advised not to fly for 2 weeks.¹⁰⁷

Clinical practice points

- ▶ In passengers who develop sinus barotrauma after flying, it may be helpful to consider topical and oral decongestants as well as appropriate analgesia. Prolonged use of decongestants is not advised owing to the risk of rebound congestion on withdrawal.
- ▶ If there is an allergic component, intranasal steroids used for a week prior to travel, and/or oral corticosteroids may be considered.
- ▶ Symptoms and signs of barotrauma should have resolved before flying again. This usually takes between 1 and 6 weeks.
- ▶ After an episode of acute otitis media, patients are usually advised not to fly for 2 weeks.

Viral infections

Although viral infections may be transmitted on board, as in any environment where people are in proximity for prolonged periods, available data suggest this is not common on modern commercial aircraft. This may reflect lack of face-to-face contact, the barriers afforded by seat backs, and the characteristics of cabin airflow on board, which is not front to back. Viruses are within the particle size range captured by HEPA filters on modern commercial aircraft, which are like those used in hospitals. Transmission by droplet spread, including via fomites, is applicable to all environments.^{100 101} This may be reduced by passengers wearing masks, frequent use of hand sanitiser and disinfectant wipes for hard surfaces, and by regular deep cleaning of the aircraft cabin. The risk of infection in airport facilities on departure, during stopovers, and on arrival should also be considered. More general hygiene practices, such as handwashing

and covering the mouth and nose when coughing or sneezing, have also been shown to reduce spread of viral infections.^{109 110}

Some respiratory viral infections may be more infectious than others. A review of passengers on a flight carrying a confirmed case of SARS in 2003 reported 16 cases of SARS developing in fellow passengers,¹¹¹ but it seems likely that affected individuals were in close proximity in the airport lounge, so transmission may have occurred before boarding. To date there is just one reported case of possible aircraft transmission of COVID-19,¹¹² but the literature is clearly evolving.

The principal public health concern around air travel is the role it plays in carrying infected persons (who may be asymptomatic and are not always contagious) long distances within a short space of time, with the associated risk of disseminating novel contagious disease to new locations. This has been especially evident during the COVID-19 pandemic. Special attention should therefore be paid to the clearance of people wishing to fly who have respiratory tract symptoms during outbreaks of such infections. At any time, and not just during outbreaks of serious infectious respiratory disease, airport screening measures may be implemented and travellers with a fever can be refused boarding by the airline. In cases of serious epidemics and/or pandemics such as MERS and COVID-19, even urgent travel may be prohibited. The Centers for Disease Control and Prevention website has regular updates on air travel (www.cdc.gov). The 2020 BTS COVID-19 Statement on Air Travel contains practical advice for potential passengers with lung disease during the COVID-19 pandemic.¹¹³

Clinical practice points

- ▶ Patients with highly contagious infections including measles, chickenpox, mumps, SARS, MERS or COVID-19 should not be allowed to travel until they are considered non-infectious.
- ▶ Passengers should familiarise themselves with current national and international regulations regarding air travel, which should always be observed.

Tuberculosis

WHO provides comprehensive information about the risk of air travel with TB.¹¹⁴ Risk is determined by two factors: whether acid fast bacilli are present on smears of respiratory samples, or a sputum smear is culture positive; and whether drug resistance is present. Patients with sputum smear or culture positivity are considered potentially infectious.

Clinical practice points

- ▶ Smear positive patients must not fly until they have provided two smear negative samples on treatment.
- ▶ Those starting treatment for pulmonary TB, where not all the information is yet available, should not travel by air for the first 2 weeks.
- ▶ For those who are smear negative and have a fully sensitive organism, treatment would be expected to render them non-infectious after 2 weeks.
- ▶ For patients with MDR/XDR TB, travel is prohibited until two negative culture samples have been produced and there is clinical evidence of improvement on treatment.
- ▶ Extrapulmonary TB does not usually warrant additional precautions before air travel.

Pneumonia

Patients suffering from acute lobar bacterial pneumonia present a low risk to other passengers. They are, however, more likely to experience in-flight desaturation during flight.

Clinical practice points

- ▶ All but essential travel should be postponed for 7 days in those who have reduced baseline sea level SpO₂ (<94%).

OSAS and OHS

The most recent available guidance states that for patients with OSAS, the potential risks during commercial airline travel are worsening hypoxaemia when asleep, and exacerbation of jet lag with potential adverse effects on driving.¹

Data are sparse regarding risks for passengers with OSAS during air travel. Some data suggest there is a risk of cardiovascular and

other adverse events in this group when staying at high altitude destinations. Hypobaric hypoxia can promote central apnoeas in addition to obstructive events, which may cause tachycardia, cardiac arrhythmia and systemic hypertension.¹¹⁵ It is not, however, clear how quickly this response develops, and therefore whether the findings are relevant to air travel.

Using hypobaric chamber simulation testing, studies have shown that there is an association between hypoxaemia, decreased sleep time and an increased frequency of hypopnoeas for patients with OSAS who are acutely exposed to high altitude.¹¹⁶ There are further adverse effects on sleep and OSAS if alcohol¹¹⁷ or sedatives¹¹⁸ are taken.

Many patients with OSAS are already established on CPAP. Some studies have shown that patients with OSAS have lower oxygen saturations at baseline and at cabin altitude simulation than normal subjects.¹¹⁹ The changes are more marked in those with severe OSAS. Use of CPAP at altitude is associated with decreased central sleep apnoea and increased sleep efficiency.¹¹⁶

Consideration must be given to the whole journey including the return flight. This is especially important if the flight involves an overnight element and patients expect to drive the next day. Studies have identified that not using CPAP for one night during the flight increases the risk of drowsiness at destination the following day.¹²⁰

Careful planning is required. A retrospective survey of 394 patients who undertook air travel with CPAP reported that over a third encountered problems with their equipment, power cord, adapter or transport of the CPAP machine.¹²¹ These findings highlight the need for clinical teams to understand the logistics so that they can support safe patient travel (see Appendix A).

In summary, the potential physiological risks for this group include cardiac stress; increased frequency of hypopnoeas; possible central apnoeas; hypoxaemia and exacerbation of jet lag.

There are no data relating specifically to air travel in OHS, which is considered a restrictive disorder. For these patients, physicians should refer to guidance around the use of NIV in those with respiratory muscle and chest wall disorders.

Clinical practice points

- ▶ Daytime flights are advised wherever possible.
- ▶ The patient should be advised to carry their CPAP device as hand luggage, and a hospital letter to advise that the patient uses CPAP.
- ▶ Careful planning and preparation are required, and use of the patient's own CPAP device is advised.
- ▶ Alcohol and sedatives should be avoided in the 12 hours before, and during, airline travel.
- ▶ Patients should use their CPAP device on board if they are travelling overnight, and avoid sleeping during daytime flights.
- ▶ Consideration should be given to device settings and whether adjustment is required for operation at altitude.
- ▶ Airline approval for carriage and use of device, including battery specification, must be gained before travel.
- ▶ Consideration should be given to the whole journey. If driving is required the following day, an overnight stay at destination may be advisable. Patients are advised to refrain from driving if tired and sleepy.

Respiratory muscle and chest wall disorders

There is little good evidence to guide decision-making around the need for oxygen or NIV during air travel for patients with severe extrapulmonary restriction resulting from chest wall disorder or respiratory muscle weakness. One case report suggests that a long-haul flight may have precipitated a first episode of PH and right heart failure requiring intubation and ventilator support in a man aged 59 with congenital kyphoscoliosis and apparently stable cardiorespiratory function before travel. FVC was documented as 0.98 L on recovery.¹²²

Some work has been conducted to understand which patients require HCT. The authors of a study of 21 adults with idiopathic kyphoscoliosis or neuromuscular disease¹²³ concluded that those with FVC <1 L, even with resting SpO₂ >95%, are likely to desaturate significantly at cabin altitude. In some restrictive conditions, for example, bulbar MND, FVC is difficult to reproduce. Walk tests may aid decision-making in patients with scoliosis,³⁵ but may also be inaccessible to those with MND and similar conditions where spirometry is a challenge.

Since the 2011 BTS recommendations,¹ several studies have tried to identify factors that may predict the need for in-flight oxygen for patients with neuromuscular disease. One study aimed to identify parameters that predict HCT outcome in 40 patients with MND. Baseline PaCO₂ was the only independent predictor of hypoxaemia during HCT.¹²⁴ This appears to be supported by a more recent study examining baseline PaCO₂ as a predictor of HCT outcome.¹²⁵ Patients likely to fail HCT have a higher baseline PaCO₂, but the authors were unable to determine an absolute threshold PaCO₂ value that could identify patients needing in-flight supplementary oxygen.

Another study in 36 patients with MND examined baseline lung function as a predictor of hypoxaemia in response to altitude simulation.¹²⁶ The authors concluded that maximum inspiratory pressure (MIP) and sea level SpO₂ may help identify MND patients who will develop hypoxaemia at altitude. Despite the small numbers, none of the patients with an MIP >30 mm Hg or with sea level SpO₂ >96% desaturated below 85% during HCT. Preliminary data from a smaller study of 12 patients with MND suggested that sniff nasal inspiratory pressure (SNIP) may more accurately predict the risk of hypoxia during air travel in those with neuromuscular disease and respiratory muscle weakness.¹²⁷

While evidence to date addresses specific patient groups, the principles may be applied to any individual with a restrictive disorder resulting from respiratory muscle weakness or chest wall deformity. Further research on the value of FVC, PaCO₂, MIP and/or SNIP in predicting HCT outcome in this group is desirable. In the meantime, it seems reasonable to recommend that individuals with severe respiratory muscle weakness or chest wall deformity (FVC <1 L) should undergo HCT before air travel. Physicians should use their discretion for considering HCT if there are additional reasons for concern, such as a history of previous travel intolerance, hypoxaemia or hypercapnia.

In those with respiratory muscle weakness, the possibility of respiratory failure should also be considered. For patients established on NIV, further planning and advice are required to support the use of NIV during flight. If continuous flow oxygen cannot be provided by the airline or by POC, oxygen and NIV cannot be used simultaneously. A decision around whether NIV or supplementary oxygen is of greatest physiological importance to the patient is then required on an individual basis. The previous travel history, current clinical condition and the presence or absence of overnight travel should also be considered. (see Appendix B, table 2).

In summary, the potential physiological risk for patients with restrictive respiratory disease is respiratory failure resulting from inadequate ventilation. It is therefore essential to assess ventilatory requirements before deciding whether supplementary oxygen is required. The risk of respiratory failure must be understood and assessed before travel, and there are currently no absolute predictors to guide which patients are likely to require supplementary oxygen.

Clinical practice points

- ▶ HCT is recommended for all adult patients with FVC <1 L, pending further data, and may be considered in others thought to be at particular risk, including children with reduced FVC due to respiratory muscle or chest wall disorders.
- ▶ If patients are unable to perform spirometry reliably, a walk test may be considered as an alternative.
- ▶ Patients should be advised to take daytime flights where possible.
- ▶ Further planning and support are required for those established on NIV (see Appendix A).

VTE (DVT and PE)

Prevention of VTE during air travel

The risk of VTE during air travel appears low overall, and prophylaxis is unnecessary for most travellers. Prolonged travel (exceeding 6 hours) and/or the coexistence of another risk factor for VTE increase the risk. The incidence of symptomatic VTE has been estimated at 0.5% on flights over 12 hours, but asymptomatic rates may be higher.^{128–130} The reasons for the increased risk are not entirely clear. Potential contributory factors include prolonged immobility and dehydration, but these are not conclusively proven. Other risk factors for VTE such as obesity, recent surgery, pregnancy,

malignancy and previous VTE all increase the overall risk for travel-related VTE and may necessitate additional prophylaxis.

General measures, including getting up and walking around where possible every 2–3 hours; ankle and calf exercises and avoidance of alcohol or sedating drugs; are advisable for most travellers. Although there is no conclusive evidence that flying causes dehydration, the fall in cabin humidity along with alcohol consumption and reduced fluid intake, may increase the risk on long haul flights. Remaining well hydrated is, therefore, advisable. Wearing graduated compression stockings during travel may reduce the incidence of deep venous thrombosis.¹³¹ Data are sparse regarding the method or duration of pharmacological prophylaxis, and recommendations rely on consensus expert opinion. Physicians may wish to recommend pharmacological prophylaxis for those at higher risk of VTE, for example an obese patient planning a flight exceeding 6 hours with a history of recent surgery. The risks of prophylaxis are thought to be low. There is limited evidence for LMWH as prophylaxis.¹³² There is no formally recommended dose, but enoxaparin 40 mg at a dose of 40 mg or weight based 1 mg/kg injected once 4–5 hours before the flight has been suggested.¹³² The use of factor Xa inhibitors is off-licence in this situation and currently has no evidence base.

Clinical practice points

- ▶ Limit the risk of dehydration with adequate fluid intake.
- ▶ Avoid alcohol.
- ▶ Keep mobile, if possible, by walking around or doing seat-based exercises once an hour.
- ▶ Consider graduated compression stockings (class 1 with 15–30 mm Hg).
- ▶ LMWH or a DOAC are advised for both outward and return long haul flights (long haul defined as flights of 6–12 hours) in high-risk patients including those with a history of VTE; local policy should be followed regarding liaison with primary care and/or haematology services to teach the patient how to administer the injection and dispose safely of the equipment. There is no formally recommended dose, but enoxaparin at a dose of 40 mg or weight based 1 mg/kg injected once 4–5 hours before the flight has been suggested.
- ▶ The prophylactic doses of the DOAC may also be used.
- ▶ All patients with a recent (<6 weeks) history of VTE, especially any who presented with significant right ventricular strain and decompensation should be reassessed before air travel.

Air travel after VTE

Although the risks of prolonged air travel and development of VTE are well known, there are fewer data on the risks associated with flying after a diagnosis of VTE. A patient with a confirmed diagnosis of PE is highly likely to start anticoagulation, with the aim of preventing the formation of new deep venous thrombi and further PEs. There is a general acceptance that flying immediately after a diagnosis of PE/DVT should be avoided. It appears reasonable to assume that the sooner air travel occurs after a PE the greater the likelihood that hypoxic pulmonary vasoconstriction will exacerbate ventilation-perfusion mismatch and raise pulmonary pressures, affecting cardiac output.

Some authors, but not all, suggest that most clots are resolved after 14–21 days.¹³³ Consensus opinion is to delay air travel, if possible, usually for at least 2 weeks, although there are no concrete data to support a safe time interval. Clearly the risk-benefit ratio needs to be assessed if more urgent air travel is needed. Clot resolution depends principally on in vivo fibrinolysis. Consideration should be given to the severity of the initial presentation. It is good practice, before any proposed air travel, to reassess clinically a patient who has presented with significant right ventricular strain and decompensation.

The probability of recurrent VTE while anticoagulated is extremely low. Recovered, stable patients who remain on anticoagulation should be reassessed accordingly and advised to follow the above general measures.

Clinical practice point

- ▶ Air travel should be delayed for 2 weeks after a diagnosis of DVT or PE.

Table 2 Clinical practice points: Hypoxic challenge test (HCT) outcomes

PaO ₂ ≥ 6.6 kPa (≥ 50 mm Hg); SpO ₂ ≥ 85%	In-flight oxygen not required
PaO ₂ < 6.6 kPa (<50 mm Hg); SpO ₂ <85%	Repeat HCT with oxygen (flow rate and modality ideally the same as that to be given on board aircraft): ▶ Titrate oxygen to maintain PaO₂ ≥ 6.6 kPa or SpO₂ ≥ 85% ▶ Monitor pH and pCO₂ if there is a history of hypercapnia
	Consider advising against air travel if pH falls to <7.35 and PCO ₂ increases by > 1 kPa (7.5 mm Hg) from baseline when PaO ₂ is maintained at ≥ 6.6 kPa or SpO ₂ ≥85%

The use of arterial or capillary blood gas sampling is preferred if available. Blood gases are not routinely measured in children. Recommendations on pCO₂ and pH changes are based on the 2015 BTS guideline for home oxygen use in adults.¹⁹

Pulmonary hypertension

Data are sparse, and recommendations are largely based on expert consensus opinion. The concern in PH is the risk of hypoxia causing increased pulmonary arterial pressure and right ventricular strain. Most studies have employed HCT. They have shown that most patients with PH can tolerate this degree of hypoxia with minor increases in dyspnoea.¹³⁴ Furthermore, the effect on the right ventricle in one study has been shown to be minimal.¹³⁴ However, most of these studies only covered a short time period.¹³⁴ Longer exposure to hypoxia on long haul flights may have more significant effects.

One study has monitored patients during commercial flights.¹³⁵ This showed that up to a quarter of patients with PH desaturate during short haul flights, with higher altitude, ambulation and longer flights correlating with desaturations. Most tolerated this well, with fewer than 40% of participants reporting symptoms. A larger questionnaire based retrospective study has also confirmed that in most patients with stable PAH, flight is well tolerated with minimal clinical effects.¹³⁶ Around half those surveyed travelled with supplementary oxygen.

Hypoxia reduces exercise capability; breathing oxygen-enriched air improves exercise capacity.¹³⁴ It therefore appears logical to give patients with impaired functional capacity supplemental oxygen on board the aircraft. Whether patients should have oxygen while walking around as well as when sitting is unknown; ambulatory oxygen on board presents obvious logistical challenges.

The 2011 BTS Recommendations advised that patients in NYHA WHO functional class 3 or 4 should have supplemental oxygen during air travel.¹ This recommendation is pragmatic rather than evidence based; and may result in over-prescribing of in-flight oxygen. One study suggests that more than double the number of patients would be recommended in-flight oxygen based on functional class rather than HCT outcome.¹³⁴

If HCT is not readily available and there are no concerns about hypercapnia, passengers already on LTOT should be advised that they will need a flow rate 2L/min greater than their baseline flow rate. This should be sufficient to compensate for the relative hypoxia at normal cabin altitude.

Clinical practice points

- ▶ Those in NYHA WHO functional class 3 or 4 are usually advised to have in-flight oxygen. If there is no evidence of hypercapnia it seems reasonable to suggest 2L/min by nasal cannulae. If there are concerns about hypercapnia, HCT should be considered if available.
- ▶ Those eligible for LTOT (sea level PaO₂ <8kPa at rest on air) should have in flight oxygen at double the flow rate recommended at sea level, provided there is no evidence of hypercapnia.

Lung cancer and mesothelioma

When evaluating those with lung cancer or mesothelioma it is important to consider the nature and extent of their condition as well as their treatment. A pragmatic approach is to evaluate their risk of

haemorrhage, pneumothorax, pleural effusion, VTE and any recent surgical and/or bronchoscopic interventions.

If taking medication, and particularly controlled drugs, patients must be aware of the appropriate documentation required for the countries they are visiting. Advance-planning is essential.

Clinical practice point

- ▶ Patients undergoing chemotherapy should not travel while they are at increased risk of infection or suffering from significant side effects, such as vomiting.

Hyperventilation and DB

There are few data on the implications of functional breathing disorders for air travel, whether DB, VCD or ILO. Asthma should not be overlooked as a possible association in those with DB.¹³⁷

Acute shortness of breath is one of several symptoms for which flight diversion is advised.¹³⁸ Diversions are costly, typically ranging from £10 000–£80 000 depending on aircraft size and diversion destination.¹³⁹ Dyspnoea caused by DB or hyperventilation is unlikely to have serious clinical consequences; but it must be distinguished from dyspnoea attributable to life-threatening acute medical conditions such as acute coronary syndrome or PE.¹⁴⁰

Data from the last two decades suggest that 65% of in-flight medical emergencies were due to exacerbations of pre-existing conditions and that respiratory problems were most common; half were due to asthma or 'asthma-like' presentations.^{141–143}

Air travel can be stressful. Physiological or psychological stress may precipitate acute breathlessness in patients with respiratory disease.¹⁴⁴ Acute hyperventilation can be a response to stress independent of lung pathology, usually in those with known panic and anxiety disorders.¹⁴⁵

Hyperventilation can cause bronchoconstriction resulting in 'asthma-like' symptoms¹⁴⁶ which are unresponsive to standard asthma medication.^{147–148} A perception that the usual 'rescue' medication is 'not working' may worsen an individual's breathing pattern, causing concern to them, other passengers and air crew. Similar situations can arise with ILO or VCD, and onset of symptoms is often sudden.¹⁴⁹

Where DB is linked to respiratory conditions, particularly asthma, national and international guidelines endorse breathing exercise programmes provided by a specialist respiratory physiotherapist as an adjuvant to pharmacological treatment. Patients should be advised to use breathing techniques in situations where breathlessness may become problematic.^{75–150} ILO and VCD, which can present with acute respiratory distress and stridor, may be treated with breathing exercises taught by a respiratory physiotherapist or a speech therapist with specialist expertise in paradoxical vocal cord movement.¹⁵¹

Paper bag rebreathing is no longer recommended, because inspired oxygen concentration decreases sufficiently to endanger hypoxic patients. There are data reinforcing that significant harm to patients can result from acute myocardial infarction, pneumothorax and PE being misdiagnosed as hyperventilation.^{152–153}

Clinical practice point

- ▶ Patients with DB, ILO and/or VCD should be referred to a Respiratory Physiotherapy Specialist for advice on symptom management before travel.
- ▶ Those with anxiety disorders should be reviewed before travel; compliance with medication assessed; and use of short acting anxiolytics encouraged.
- ▶ Other life-threatening conditions presenting with dyspnoea should be excluded on board as far as possible.
- ▶ Supplemental oxygen should be given on board if the cause of breathlessness is unclear.
- ▶ Rebreathing via a paper bag is not recommended.

Appendix A Logistics of air travel with equipment Oxygen

Passengers requiring oxygen and travelling overseas will usually need to lease a POC privately, since UK companies do not generally allow equipment provided through the NHS to be taken out of the country. Furthermore, most airlines have moved away from supplying routine medical oxygen. Where battery powered mechanical devices are required in-flight, including a POC, sufficient batteries should be carried for 1.5 times the anticipated duration of the journey to cope

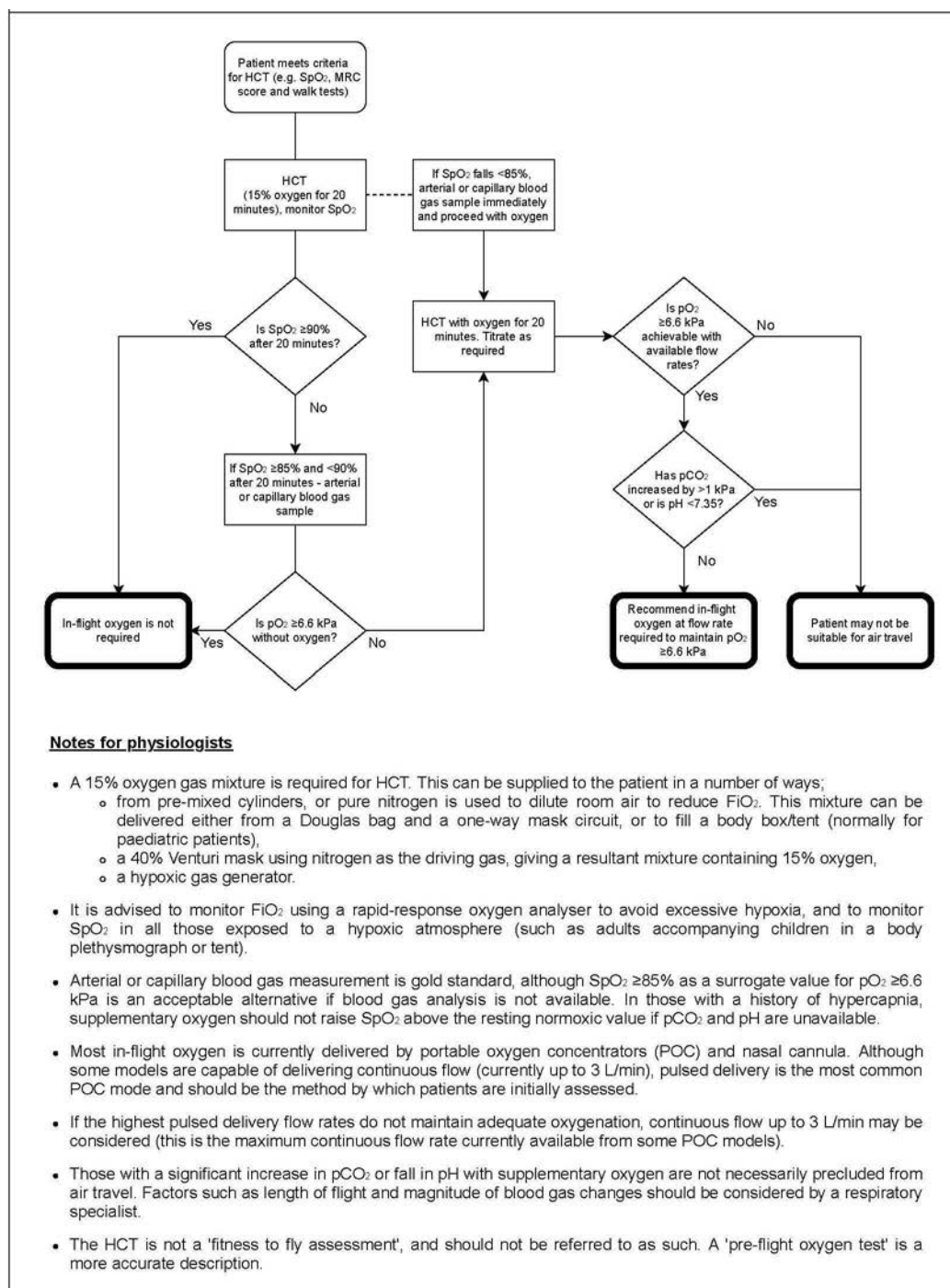


Figure 3 HCT for physiologists.

with delays or diversions. For example, a patient using a POC on a 4-hour flight should have 6 hours of battery life. Any spare batteries must be correctly packaged and should be carried in cabin baggage. The airline must be notified in advance of these plans, or airline staff can refuse to allow the equipment to be taken on board.

Pulse-dose oxygen may not be suitable for patients with a fast and shallow respiratory pattern, or during sleep.^{154 155} Pulse-dose settings do not equate to the equivalent continuous flow rates,⁷⁴ and not every POC functions well at altitude.¹⁵⁶ In contrast, pulse-dose oxygen functions reliably when provided by a cylinder and conserving device.¹⁵⁶ One author found significantly lower PaO_2 values when using a POC, compared with compressed oxygen with a conserving device. Acceptable in-flight values are achievable with POCs, but the dose may need to be increased.⁵⁶ Pulse-dose delivery systems can complicate determination of the flow delivered; and may not be well tolerated. The effects of mouth-breathing, speech, snoring and/or sleeping should be considered. HFNO cannot be delivered on board commercial aircraft.

Pulse-dose oxygen has not been studied in infants and children; and should not be used unless they have been shown to trigger the

device's inspiratory flow. Currently available POCs that do supply continuous flow oxygen cannot provide flow rates above 3 L/min. Passengers must refer to POC documentation to check that the equipment meets their requirements before they lease it for air travel.

For all these reasons, assessments would ideally take place using the same equipment as that which will be used on board the aircraft. This is only likely to be possible when the patient has leased or purchased a POC for their own long term, private use.

Continuous positive airway pressure

Few airlines, if any, allow any medical device to be powered via the aircraft power supply. An appropriate battery must, therefore, be used. The device and battery specifications must be approved for use by the airline before travel. Battery performance should be checked by the user beforehand, so there is an understanding of operating times on their usual settings.

Further consideration needs to be given to CPAP use during flight and at high altitude destinations, as it requires a machine that will perform adequately at low ambient pressure. The 2011 BTS

guidance¹ reported that a fixed-pressure CPAP machine without pressure compensation, set to deliver a pressure of 12 cm H₂O at sea level, may deliver only 9 cm H₂O at 8000 ft. The machine may therefore require adjustment to ensure a safe level of treatment throughout the flight. If continuous flow oxygen cannot be provided by the airline or by POC, oxygen and CPAP cannot be used simultaneously. The availability of distilled water for humidifiers may be restricted.

Non-invasive ventilation

For patients established on NIV, further planning and advice are required to support the use of NIV during flight. If continuous flow oxygen cannot be provided by the airline or by POC, oxygen and NIV cannot be used simultaneously. A decision around whether NIV or supplementary oxygen is of greatest physiological importance to the patient is then required on an individual basis. Previous travel history, current clinical condition and the presence or absence of overnight travel should also be considered. The level of clinical and personal dependency must be considered in the context of requirements for trained supervision and assistance by the caregiver.

Appendix B Quick reference guide for respiratory physiologists

Most patients with respiratory conditions are able to fly safely without any additional support. The following guide provides specific information for respiratory physiologists regarding patients who do need further investigation before embarking on air travel. See figure 3.

HCT methods

The HCT uses an inspired gas mixture containing 15% oxygen, which gives an approximate similar PO₂ to breathing air at the maximum allowable cabin pressure altitude (2438 m or 8000ft).^{53 54} HCT is usually performed in a specialist respiratory physiology unit. The provision of a 15% oxygen gas mixture can be achieved as follows:

- ▶ A premixed cylinder containing a 15% oxygen gas mixture can be obtained from medical gas providers, or Douglas bags can be mixed with air and nitrogen to reduce the percentage of inspired oxygen to 15%, both to supply a tight-fitting face mask in a closed circuit.¹
- ▶ Pure nitrogen can be introduced into a sealed chamber such as a body plethysmograph for paediatric or mask-intolerant patients, removing the need for a face mask.¹⁷ Paediatric patients can be sat in a body plethysmograph on an adult's lap throughout;¹ the adult should also undergo SpO₂ monitoring to avoid excessive hypoxaemia. A body box is generally used for children, although some paediatric laboratories use masks
- ▶ A 40% Venturi oxygen mask can be used with pure nitrogen as the driving gas, giving a resultant gas mixture containing approximately 15% oxygen.^{11 58}
- ▶ A hypoxic gas generator, like an oxygen concentrator, can be used to provide a continuous supply of variable hypoxic gas mixtures to supply a mask or closed chamber. This can be the most cost-effective method for centres with a high demand for HCT.¹²

The patient usually breathes the hypoxic gas mixture for 20 min, or until SpO₂ reaches 85%. Although this is shorter than the briefest commercial flight, oxygenation equilibrium is usually reached within this time.^{134 157} The patient is advised to have in-flight oxygen if PaO₂ falls below 6.6 kPa (<50 mm Hg) or SpO₂ remains <85%^{1 17} (see page 11).

HCT with oxygen

If PaO₂ or SpO₂ values meet the criteria, in-flight oxygen is recommended.¹ The flow rate required can be assessed as part of the HCT.¹⁷ Previous BTS recommendations advised in-flight oxygen to be supplied at two or 4 L/min via nasal cannulae, which were for many years the only fixed flow rates routinely available on commercial aircraft. As airline-supplied in-flight oxygen becomes less common and greater numbers of patients travel with flight-approved POCs delivering a wide range of continuous and intermittent flow rates, these figures are less critical. The HCT should ideally be performed with the modality that is intended for use in-flight.

Most airlines have moved away from supplying routine medical oxygen. In-flight oxygen is thus now likely to be supplied by an FAA approved POC, leased by the patient. These are mostly pulse-dose delivery. It is, therefore, advisable to conduct a titrated HCT with pulsed dose oxygen to maintain PaO₂ at ≥6.6 kPa or SpO₂ ≥85%, using setting 2 as the starting point. This approximates to the 2 L/min originally stated. If pulse-dose oxygen at higher settings is insufficient to maintain PaO₂ at ≥6.6 kPa or SpO₂ ≥85%, then continuous oxygen should be considered. It should be noted that POC models supplying continuous flow are limited, and they do not currently supply >3 L/min.

Pulse-dose delivery is not suitable for young children, for use during sleep^{154 155} or for certain adults. Not all POCs function as expected under conditions of simulated altitude¹⁵⁶ and pulse-dose settings may not equate to equivalent continuous flow rates⁷⁴ (see Appendix A).

Patients with hypercapnia

Previous BTS advice was to err on the side of recommending oxygen if in doubt,¹ and other authors have recommended doubling oxygen flow rates for patients with a pre-existing oxygen requirement.^{1 29} However, there is a potential risk of developing hypercapnia and respiratory acidosis from oxygen during HCT in patients with type 2 respiratory failure.¹⁸ Patients with a history of hypercapnia should ideally undergo HCT with blood gas sampling. In these cases, the minimum amount of oxygen should be delivered to maintain PaO₂ ≥6.6 kPa while monitoring PaCO₂ and pH. If blood gas sampling is not available then care should be taken not to raise SpO₂ above the resting level with supplementary oxygen in this group of patients.¹⁷ In some cases it may be unsafe to undertake air travel even if good oxygenation can be achieved, if adverse PCO₂ and pH changes are evident.¹⁸

An incidental finding of an elevated COHb during HCT represents an important opportunity to take a smoking history and offer smoking cessation referral as appropriate.

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INDICAÇÃO¹

DUPIXENT® está indicado para adultos e adolescentes com idade igual ou superior a 12 anos como tratamento complementar de manutenção para asma grave com inflamação do tipo 2 caracterizada por eosinófilos elevados no sangue e/ou FeNO aumentada, que são inadequadamente controlados apesar das doses elevadas de corticosteroides inalados associada a outro medicamento para tratamento de manutenção.

1. Resumo das Características do Medicamento DUPIXENT®, 2022. 2. GINA 2020
EOS: eosinófilos; FeNO: Fração exalada de Óxido Nítrico; CCT Orais: Corticosteroides Orais



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INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO