

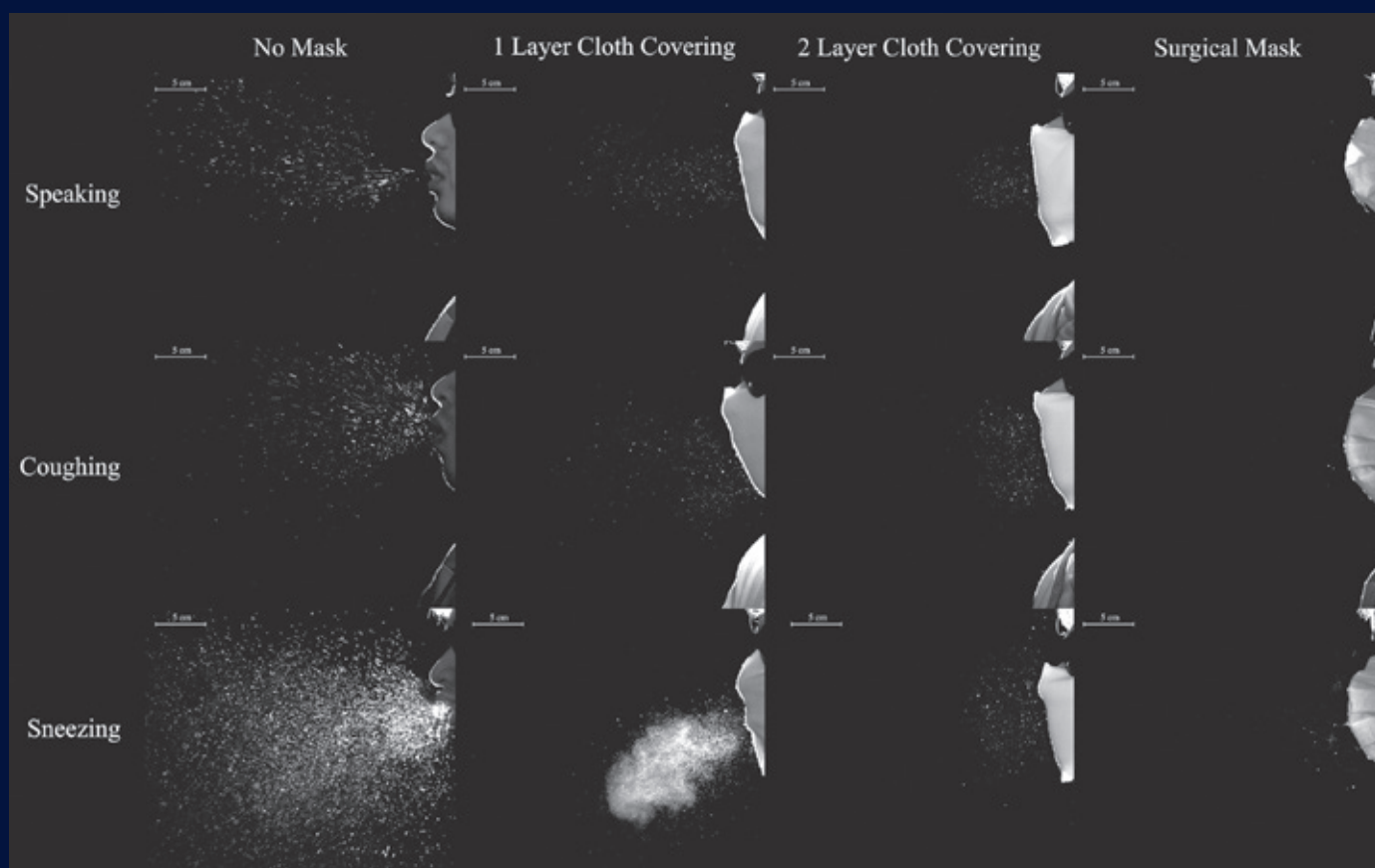
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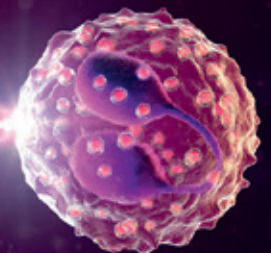


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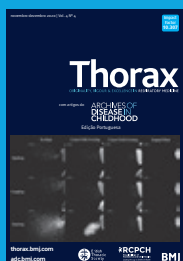
1. Ferguson et al., "Single-Use Autoinjector Functionality And Reliability For At-Home Administration Of Benralizumab For Patients With Severe Asthma: GRECO Trial Results", Journal of Asthma and Allergy 2019;12 363–373;
2. RCM de Fasenra consultado a 24/07/2020 em www.infarmed.pt.

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Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaooram> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel: +351 21 798 73 73; Linha do medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Fasenra 30 mg solução injetável em caneta pré-cheia.** Cada caneta pré-cheia contém 30 mg de benralizumab* em 1 ml. *Benralizumab é um anticorpo monoclonal humanizado produzido por tecnologia de ADN recombinante em células ovárias do hamster chinês. Solução injetável em caneta pré-cheia (injetável) (Fasenra Pen). Solução clara a opalescente, incolor a amarela e pode conter partículas translúcidas ou brancas a esbranquiçadas. **Indicações terapêuticas:** Fasenra é indicado como tratamento adjuvante de manutenção em doentes adultos com asma eosinofílica grave, inadequadamente controlada apesar das doses elevadas de corticosteroides inalados em associação a agonistas-β de longa duração de ação. **Posologia e modo de administração:** O tratamento com Fasenra deve ser iniciado por um médico com experiência no diagnóstico e tratamento da asma grave. Após o treino adequado da técnica de injeção subcutânea e educação sobre sinais e sintomas de reações de hipersensibilidade, os doentes sem história conhecida de ocorrência de anafilaxia, ou os seus cuidadores, podem administrar Fasenra se o seu médico considerar apropriado, com seguimento médico se necessário. A autoadministração só deve ser considerada em doentes tratados anteriormente com Fasenra. **Posologia:** A dose recomendada de benralizumab é 30 mg administrados por injeção subcutânea a cada 4 semanas para as primeiras 3 doses, e depois a cada 8 semanas. Se uma injeção não for administrada na data planeada, a dose deve ser administrada assim que possível de acordo com o regime indicado; não deve ser administrada uma dose a duplicar. Fasenra destina-se ao tratamento de longa duração. A decisão de continuar a terapêutica deve ser efetuada pelo menos uma vez por ano, com base na severidade da doença, no nível de controlo das exacerbações e na contagem sanguínea de eosinófilos. Não é necessário qualquer ajuste de dose em doentes idosos ou em doentes com compromisso da função renal ou hepática. **População pediátrica:** A segurança e eficácia de Fasenra em crianças com 6 a 18 anos de idade não foram estabelecidas. Não estão disponíveis dados em crianças com 6 a 11 anos de idade. Os dados atualmente disponíveis em crianças com 12 a 18 anos de idade encontram-se descritos nas secções 4.8, 5.1 e 5.2 do RCM mas não pode ser feita qualquer recomendação posológica. **Modo de administração:** Fasenra é administrado por injeção subcutânea. Deve ser injetado na coxa ou abdómen. Se o profissional de saúde ou o cuidador administrar a injeção, esta pode ser efetuada na parte superior do braço. Não deve ser injetado em áreas onde a pele está sensível, ferida, eritematosa ou endurecida. **Contraindicações:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Fasenra não deve ser utilizado para tratar exacerbações agudas da asma. Os doentes devem ser informados a procurar aconselhamento médico se a sua asma permanecer não controlada ou se agravar após o início do tratamento. A descontinuação abrupta de corticosteroides após o início do tratamento com Fasenra não é recomendada. Se necessário, a redução das doses de corticosteroides deve ser gradual e efetuada sob supervisão de um médico. **Reações de hipersensibilidade:** Após a administração de benralizumab ocorreram reações sistémicas agudas, incluindo reações anafiláticas e reações de hipersensibilidade (por exemplo, urticária, urticária papular, erupção cutânea). Estas reações podem ocorrer horas após a administração, mas em alguns casos tiveram um início tardio (i.e. dias). História de anafilaxia não relacionada com benralizumab pode ser um fator de risco para a ocorrência de anafilaxia após a administração de Fasenra. Os doentes devem ser monitorizados por um período de tempo adequado após a administração de Fasenra, de acordo com a prática clínica. Em caso de reação de hipersensibilidade, Fasenra deve ser descontinuado permanentemente e deve ser iniciado o tratamento adequado. **Infecção parasitária (Helmíntica):** Os eosinófilos podem estar envolvidos na resposta imunitária a algumas infeções helmínticas. Os doentes com infeções helmínticas conhecidas foram excluídos da participação nos ensaios clínicos. Desconhece-se se Fasenra pode influenciar uma resposta do doente contra infeções helmínticas. Os doentes com infeções helmínticas pré-existentes devem ser tratados antes de iniciar o tratamento com Fasenra. Se os doentes ficarem infetados durante o tratamento com Fasenra e não responderem ao tratamento anti-helmíntico, o tratamento com Fasenra deve ser descontinuado até a infeção se resolver. **Interações medicamentosas e outras formas de interação:** Em doentes com idades compreendidas entre 12 e 21 anos com asma grave, a resposta humoral induzida pela vacinação contra o vírus da gripe sazonal não parece ser afetada pelo tratamento com benralizumab. Não é esperado um efeito de benralizumab na farmacocinética de medicamentos administrados concomitantemente. As enzimas do citocromo P450, bombas de efluxo e os mecanismos de ligação a proteínas não estão envolvidos na depuração de benralizumab. Não existe evidência da expressão de IL-5Rα nos hepatócitos. A depleção de eosinófilos não produz alterações sistémicas crónicas das citocinas pró-inflamatórias. **Efeitos indesejáveis:** **Frequentes:** Faringite, Reações de hipersensibilidade, Cefaleia, Pirexia, Reação no local de injeção; **Desconhecida:** Reação anafilática. **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** AstraZeneca Produtos Farmacêuticos, Lda., Rua Humberto Madeira, 7, Queluz de Baixo, 2730-097 Barcarena. Informações revistas em julho de 2020. Para mais informações deverá contactar o representante local do titular da Autorização de Introdução no Mercado. Medicamento de receita médica restrita, de utilização reservada a certos meios especializados. Financiada no âmbito da avaliação prévia à utilização hospitalar. Versão 1.0 (julho 2020).

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Contribuinte N.º PT 502 942 240 | Capital Social 1.500.000 €
PT-7378 aprovado a 07/08/2020



Journal of the British Thoracic Society
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ISSN: 0040-6376 (print)
ISSN: 1468-3296 (online)
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novembro / dezembro 2020

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**Archives of
Disease in Childhood**

Edição bimestral em língua portuguesa
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ISSN: 0003-9888 (print)

ISSN: 1468-2044 (online)

Impact factor: 3.158

Journal of the Royal College of

Paediatrics and Child Health

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ADC is published by BMJ Publishing Group

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Bengaluru & Chennai, India and printed in the

UK on acid-free paper from sustainable forests.

ADC (ISSN No: 0003-9888) is published

monthly by BMJ Publishing Group Ltd and is

distributed in the USA by Air Business Ltd.

Periodicals postage paid at Jamaica NY 11431

and additional mailing offices. POSTMASTER:

send address changes to Archives of Disease

in Childhood, Air Business Ltd, c/o Worldnet

Shipping Inc., 156-15, 146th Avenue, 2nd Floor,

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Editorial

Neste final de um ano muito atípico e cheio de mudanças, angústias e alterações das nossas rotinas, regressamos com um novo número da edição em língua Portuguesa de artigos das Revistas Thorax e Archives of Disease in Childhood, tendo selecionado alguns artigos que esperamos sejam do vosso interesse.

O primeiro realce vai para artigo “*Como as crianças aprendem a fazer uma autogestão independente da asma*”. Trata-se de um estudo qualitativo realizado com crianças com asma e respetivos pais em que foi usada uma amostra intencional e foram realizados grupos focais com o objetivo de explorar os pontos de vista das crianças malaias e dos seus pais sobre asma com o objetivo de melhorar a compreensão das primeiras influências no desenvolvimento de competências de autogestão. Concluiu-se que as crianças aprenderam as técnicas de autogestão da asma desde os seus 7 anos com uma independência crescente a partir dos 10 anos. O reconhecimento que as crianças experimentam a autogestão da asma (às vezes sem o conhecimento de seus pais) oferece boas oportunidades para uma abordagem centrada nas crianças.

O segundo destaque vai para o artigo “*Preferências de terapêutica de inaladores de manutenção de doentes com asma ou doença pulmonar obstrutiva crónica: uma experiência de escolha discreta*”. Os autores realizaram um estudo para perceber quais são os atributos dos inaladores de manutenção que são mais valorizados por pacientes com asma ou DPOC. A conclusão é que os atributos mais importantes para estes pacientes são o início rápido de alívio dos sintomas e uma menor taxa de exacerbações.

Em seguida recomenda-se a leitura do artigo “*Acompanhamento respiratório de doentes com pneumonia COVID-19*”. Neste documento de orientação são abordadas as complicações a longo prazo da pneumonia COVID-19 que começam a surgir. Os autores sugerem uma estrutura para o acompanhamento respiratório de doentes com confirmação clínico-radiológica da pneumonia COVID-19, definem dois algoritmos separados que integram a gravidade da doença, a probabilidade de complicações respiratórias a longo prazo e a capacidade funcional na alta hospitalar.

Na secção de “*Revisão do estado da arte*” poderão ler o artigo “*Aplicações da inteligência artificial e aprendizagem de máquina na medicina respiratória*” que analisa o progresso nesta área ao longo dos últimos 5 anos, salientando também as atuais limitações da IA e da aprendizagem automática e o potencial de desenvolvimentos futuros.

O último artigo, “*Pneumonite por hipersensibilidade potencialmente fatal associada ao uso de cigarros eletrónicos*”, fala-nos de um caso de pneumonite por hipersensibilidade (PH) num jovem indivíduo associada ao uso de produtos de *vaping* e destaca duas aprendizagens. A primeira é considerar sempre podermos estar perante uma reação aos cigarros eletrónicos em alguém que apresente uma doença respiratória atípica. A segunda é o risco de considerarmos os cigarros eletrónicos “muito mais seguros do que o tabaco”.

Esperamos que a seleção de artigos vos agrade e desejamos uma boa leitura.

A todos os leitores desejamos umas Boas Festas com saúde e em segurança, neste que será, sem dúvida um ano que marcou profundamente as nossas vidas profissionais, pessoais e familiares.

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ISSN 0003-9888 (print); 1468-2044 (online)

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Como as crianças aprendem a fazer uma autogestão independente da asma: um estudo qualitativo na Malásia

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2019-318127>).

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Published Online First
3 July 2020



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RESUMO

Objetivo O nosso objetivo foi explorar os pontos de vista das crianças malaias com asma e dos seus pais para melhorar a compreensão das primeiras influências no desenvolvimento de competências de autogestão.

Desenho Trata-se de um estudo qualitativo realizado com crianças com asma e respetivos pais. Utilizámos amostragem intencional e realizámos grupos de foco e entrevistas utilizando um guia de tópicos semiestruturado na língua de preferência dos participantes. Todas as entrevistas foram gravadas em áudio, transcritas integralmente, inseridas em NVivo e analisadas utilizando uma abordagem teórica fundamentada.

Cenários Identificámos crianças entre 7 e 12 anos de idade com asma reportada pelos pais, diagnosticada por médicos de sete escolas primárias suburbanas na Malásia. Foram realizados grupos de foco e entrevistas, tanto em escolas como em centro de saúde.

Resultados Noventa e nove participantes (46 prestadores de cuidados de saúde, 53 crianças) contribuíram para 24 grupos de foco e 6 entrevistas individuais. As crianças adotaram a gestão da asma feita pelos seus pais, mas, em paralelo, aprenderam e ganharam confiança para autogerir a asma de forma independente a partir das suas próprias experiências e experimentação. O aumento da independência foi mais evidente em crianças com 10 anos ou mais. Normas e crenças culturais influenciaram a independência das crianças para autogerir a asma, seja direta ou indiretamente, através das suas redes sociais. As influências externas, como por exemplo o apoio da escola e dos cuidados de saúde, também desempenharam um papel na transição.

Conclusão As crianças aprenderam as técnicas de autogestão da asma desde os seus 7 anos com uma independência crescente a partir dos 10 anos. Os profissionais de saúde devem utilizar uma abordagem centrada na criança e envolver as escolas para facilitar a autogestão da asma e apoiar uma transição suave para a autogestão independente.

Número de registo do ensaio Malaysian National Medical Research Register (NMRR-15-1242-26898).

INTRODUCTION

With an estimated prevalence in Malaysia of 8.9% in schoolchildren, asthma is the most common chronic disease among children and responsible for significant morbidity and mortality.¹⁻³ Supported self-management is a key component of asthma management which improves asthma control and reduces asthma exacerbations.⁴⁻⁶ Self-management involves discussion of a personalised asthma action plan empowering children and their parents to identify triggers, recognise deteriorating control, and take timely and appropriate action.⁴

Despite strong recommendations from international asthma guidelines on the importance of supported self-management,^{4,7} and

explicit promotion of asthma action plans by Malaysian guidelines since 1996,⁸⁻¹⁰ the concept of self-management is not widely understood in Malaysia.^{11,12} Compared with adults, the concept is more complex among children as many children with asthma are diagnosed at an age when parents are responsible for making all management decisions.¹³ Once at school and away from their parents for periods of time, children are expected to begin to learn to selfmanage aspects of their own asthma.¹⁴ This transition is vitally important, as asthma may continue into adulthood¹⁵ and an understanding of how children learn to self-manage will inform effective delivery of supported self-management.

The process of transition to independent self-management of long-term conditions in children is part of normal development, but how this plays out is influenced by culture, beliefs and parenting style.¹⁶⁻¹⁸ Most studies have been conducted among adolescents in the USA, UK and European countries with very little research done among children in the Asian region.^{16,19-22} We therefore aimed to explore the perceptions of Malaysian children (aged 7-12 years) with asthma complemented by perceptions of their parents on the development of selfmanagement skills. This will enhance understanding of the early influences on asthma self-management skills in children.

METHODS

We conducted a qualitative study among children with asthma and their parents in seven primary schools in Port Dickson, a suburban district of Malaysia. For simplicity, we use the term 'parents' to describe parents and other family carers, for example, grandparents.

Context and school recruitment

Malaysia is a multicultural society with three main ethnic groups (Malay, Chinese and Indian). Between the age of 7 and 12 years, children typically attend a government primary school that teaches in one of the three languages according to parents' choice.²³

We conducted our study in the three main types of government primary schools (Malay, Chinese and Indian) to encompass the cultural diversity. The invitations, questionnaires, focus groups and interviews were conducted in the language preferred by the participants.

Identifying and recruiting children with asthma

To identify children diagnosed with asthma, the participating schools sent letters enclosing screening questionnaires to the parents of all pupils

Para citar: Ramdzan SN, Khoo EM, Liew SM, et al. Arch Dis Child 2020;105:819-824.

asking whether their child had been diagnosed with asthma and had received any treatment for asthma in the past 12 months. If the answers were yes to both, we asked parents to complete a questionnaire on asthma control based on their child's symptoms. The completed questionnaires were returned to the schools and we purposively sampled children with asthma from different age groups, ethnicities and degrees of asthma control. We invited parents of the selected children and their child to participate. Parents provided written consent for participation for themselves and their child. In addition, we obtained assent from the children.

Data collection

We arranged focus groups or individual interviews according to participants' preference. Parents and children's participation were paired, but focus groups were carried out separately for parents and children to enable peer interaction. We collected basic sociodemographic data (online supplementary 1), and used a piloted topic guide (online supplementary 2) and pictures of asthma medications and treatments to stimulate discussion. All the interviews and focus groups were moderated by researchers who were native speakers of the language in which the session was conducted, and were carried out either at the child's school or a health centre. The focus groups and interviews were audiorecorded, transcribed verbatim and analysed using NVivo software V.11.

Language and translation

Tamil and Mandarin transcripts were translated to English by experienced bilingual English and native speakers of the source language. Bilingual moderators checked all English transcripts for semantic and contextual equivalence. The Malay transcripts were analysed in the source language, as researchers were fluent in Malay, the national language, and translated into English for publication.

Data analysis

We used a constructivist grounded theory approach, a systematic but flexible technique, to analyse our findings.^{24–26} This uses an inductive, iterative and comparative approach to increase the explanatory and abstract level of emerging themes.^{25 26} The data from children and parents were analysed separately, and then compared between child–parent dyads. Three researchers (SNR, HS and NS) who are Malay native speakers coded the first Malay transcript independently. They read the transcripts word by word, with contextual information from field notes, and created codes to describe the meaning. They met to agree to a coding framework, which was then discussed with the team. SNR paired with one of the authors to code independently the remaining transcripts, guided by the framework. Any new codes were added to the framework in discussion with the team. SNR compared the codes, proceeded with focus and axial coding, and developed a schema by linking codes, subthemes and themes.²⁵ To facilitate interpretation, we adopted the learning development categorisation used in the educational system²⁷: children 7–9 years old are described as 'young'; children^{10–12} years old are 'older' children.

Reflexivity and interpretation

The researchers most closely involved in data collection and coding were SNR (a Malay primary care physician, mother of a child with asthma), HS (a primary care physician) and NS (a Master's student in health service research). All three are involved in research related to implementing supported self-management and, as long-term residents of Malaysia, are familiar with the local cultural beliefs, practices and parenting styles that could influence the self-management beliefs or practices of the participants. We remained aware of the importance of reflexivity, and interpretation involved regular discussions with

Table 1 Characteristics of participants

Demographic characteristics of children	Malay n=16	Chinese n=10	Indian n=27
Age range (years)	10–12	9–12	7–12
Female	8	5	7
Male	8	5	20
Demographic characteristics of parents	Malay n=16	Chinese n=9	Indian n=21
Age range (years)	33–51	31–62	30–68
Female	16	9	17
Male	0	0	4
Educational background			
Primary	1	2	3
Secondary	9	7	9
Tertiary	6	0	1
Missing	0	0	8
Carer relationship with children			
Parents	16	8	19
Grandparents	0	1	2

a wider research team including primary care physicians and paediatricians from UK and Malaysia, and a social scientist, who was able to provide additional perspectives.

RESULTS

Between April and December 2016, 53 children participated in 12 focus groups (up to 9 participants; duration up to 100min) and 5 individual interviews (duration up to 24min). Parents (n=46) participated in 12 focus groups (up to 6 participants; duration up to 60min) and 1 individual interview (duration 29min). Two parents and two children were re-interviewed to clarify points from their first focus groups. Table 1 shows the characteristics of the participants.

Summary of findings

Figure 1 summarises our findings on transition to selfmanagement among children with asthma. Additional illustrative quotes are in tables 2–4.

Transfer of control

Acceptance of parents' views and actions

Parents were the main source of information for asthma and asthma management; their influence was notably stronger among younger children than older children (table 2). Younger children's understanding of asthma was almost exclusively based on their parents' beliefs and actions. An example was the belief that 'hot and cold' are important as cause, trigger and treatment for asthma.

"Cannot drink ice water, cannot take anything 'cold', cannot eat orange." (SC2_ICh, 9-year-old Indian boy, child of A9) "For my son, cool drinks and oranges. He started to have flu and then it became phlegm and eventually asthma. All because of taking ice water." (A9_FGD 9_IC, Indian mother)

Children who believed in the use of warm water for the treatment of asthma had parents who gave warm water to prevent and reduce asthma symptoms. Similarly, children used evidence based medicine for self-management of asthma if their parents believed and practised self-management as recommended by healthcare professionals.

"First you need to use the inhaler (if you have asthma symptoms) and if you do not get better, you need to go and get nebuliser." (P1_FGD1MCh, 10-year-old Malay girl)

"I will give the inhaler first but if this is still not working, I will go (to seek medical attention) even if it is 1, 2 or 3 am..." (M1_FGD-1MC, Malay, mother of P1)

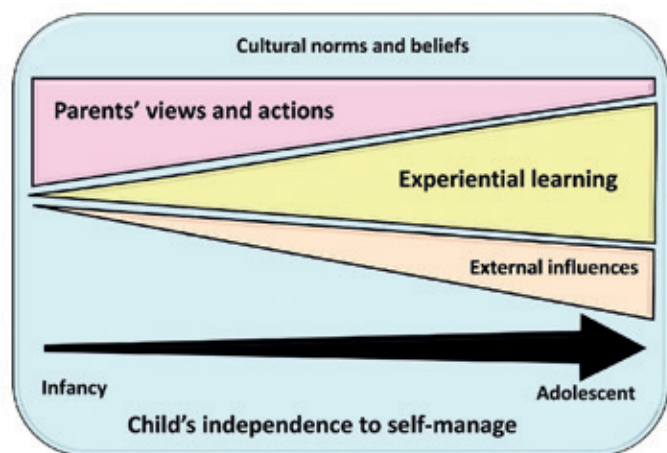


Figure 1 Schema of transition to independent self-management of care among children with asthma.

Parents influenced their child's self-management by imposing 'rules', for example, not allowing their child to participate in sports. Parents based these constraints on their past experiences of coping with their child's asthma (especially if their children had more troublesome symptoms) and their health beliefs.

"After I ran one round, I will make some noise, a little bit." (FF1, FGD1CCh, 12-year-old Chinese girl)

"Don't do strenuous exercise, then she will have less asthma attack." (MS1FGD1CC, Chinese, mother of FF1) Parental confidence in their child's ability to independently self-manage varied. Although the age of the child was a factor in this decision, there were examples of parents of 12-year-old children 'rushing back and forth' to school as well as children as young as 10 years old being trusted to self-medicate.

"I'll pick him from school, bring him home in the middle of his class. If I'm working, I'll have rush back and forth to work and school. (SF2_FGD2_IC, Indian, father of a 12-year-old boy)

"I will remind her to use the inhaler if she is going to play or she feels her chest is tight. Asked her to use the inhaler, she carries it to school." (MA1_FGD1_MC, Malay, mother of a 10-year-old girl)

Experiential learning

Some older children described how they learnt about asthma based on their own experiences, gaining confidence in selfma-

naging their asthma (table 2). Several children developed their own self-management practices by experimenting and gaining experience by 'trial and error'. All children were aware of the constraints imposed by their parents to prevent asthma symptoms and attacks. However, children as young as 9 years old challenged their parents' views and actions, secretly undertaking 'banned' activities that they enjoyed, although sometimes worried that they might be blamed for causing an asthma attack. Some parents were aware that their child did not adhere to the constraints but realised that they were not able to supervise their child all the time.

"P2: My mother usually does not allow us to eat ice cream.

Moderator: Not allowed you to eat ice cream. Why?

P2: Afraid that we will have an asthma attack.

P1: Afraid of asthma attack.

Moderator: So, do you usually eat or do not eat?

P1, P2 and P3: I do.

Moderator: You all have. So, your mother allows you to eat it or you eat it secretly?

P1 and P2: I eat it secretly

Moderator: After eating it, will you have asthma attack?

P1: No

P2: No if you eat a lot then you will have asthma attack."

(FGD1_CCh, P1, 9-year-old Chinese girl; P2, 12-year-old Chinese boy; P3, 10-year-old Chinese girl)

"SC: Drink too much of ice water, wow it's terrible, asthma attack will come immediately.... I'll definitely stop him. But he occasionally will take ice water secretly. My house has a water filter, there are three types: hot, warm, and cold. He will secretly press the cold, then press hot, and then cold again....

SB: Sometimes you cannot monitor your child. She will go and drink ice secretly."

(FGD 3_CC, SC; Chinese, mother of P1 and P2; SB, Chinese, mother of P3)

Cultural norms and beliefs

Cultural norms and beliefs influenced the children's selfmanagement both directly through their parents and indirectly through the child's social network (box 1). Parents imparted cultural norms to their children by sharing their understanding of asthma and administering complementary medicine. Some healthcare personnel supported the parents' cultural beliefs (eg, hot and cold beliefs as the cause/trigger for asthma) which further influenced children self-management of asthma.

Table 2 Quotes illustrating the transfer of control

Acceptance of parents' views and actions

(a) Mirroring parents' beliefs

"Drink hot water... cough will reduce... can breathe and will be better." (D5_FGD5ICh, 10-year-old Indian boy)
"If he continuously drinks the warm water, it can help to prevent getting phlegm (which causes asthma)." (K7_FGD7IC, Indian, mother of D5)

(b) Mirroring parents' actions

"Take a lot of nutritious food like honey, and religiously encouraged food like pomegranate" (W2_FGD2MCh, 11-year-old Malay boy)
"I think it is good to give supplement because I gave his pomegranate juice for quite some time and he did not have any attack." (AM1_FGD1MMC, Malay mother to W2)

(c) Parental 'rules'

"I like cats and dogs. It's fluffy and I like to touch and play with it. But then the fur and dust will be flying. When I breathe it gets into my nose. Will be sneezing a lot. That's when I get asthma." (NG3_FGD3ICh, 11-year-old boy)
"I had dogs in my house. He (my son) had problem and had attacks when we had furry dogs. Now, the dogs will stay outside of the house." (PK4_FGD4IC, Indian mother to NG3)

(d) Parental confidence in child's ability to manage asthma

"I'll drop by the school and give the inhalers. I wouldn't let my child bring it along. I'll just come on time, give the puff using the inhalers and let them go back to their class." (K04_FGD4IC, Indian, mother of a 10-year-old boy)

Experiential learning and growing independence with age

"When I have asthma, I'll scream and call my mum... Mom will drive me to hospital, and they'll give gas." (H6_FGD6_ICh, 7-year-old Indian girl)

Moderator: What do you do when you have asthma? PU1: My mum asks me to use the inhaler. Moderator: Take the inhaler, what do you do after that? PU1: If not better after using the inhaler, will go and get gas (nebuliser)." (FGD1_MCh, 10-year-old Malay girl)

"AM2: Controlled.

Moderator: You said it(asthma) is controlled although it disturbed you? AM2: Because now, I already know how to some breathing technique, no need to use the blue inhaler."

(AM2_FGD2MCh, 12-year-old Malay boy)

"When I was late for school, I ran to school and asthma sometimes occurred. That time, I would slow down and walk slowly, then the breathing discomfort would reduce..."

Sometimes I have to rest for 30 minutes and sometimes even one hour after intense exercises... I will wait by myself. Sometimes I will tell my mother after school if there was still breathing discomfort. Usually at school, I will figure out myself." (C1_IDI4_CCh, 12-year-old Chinese boy)

“For me, my doctor told me that I got asthma when I went to clinic. And then they told me not to drink ice water, not to play in the rain or play in cold water.” (S8, FGD8_ICh, 10-year-old Indian boy)

External influences

Teachers, friends, healthcare professionals and other family members could influence the child's transition to independent self-management (box 2). Negative attitudes (mocking inhaler use, ‘banning’ use of unfamiliar spacers) were potential barriers to confident self-management. In contrast, good support (sharing experience of having asthma with friends) appeared to have a positive influence on the transition.

“She brought it (inhaler and chamber) and her teacher scolded her, saying that she is playing. So, I had to call the school and say, it is not a toy. Maybe her teacher hasn't seen a chamber before.” (MA2_FGD2_MC, Malay, mother of a 10-year-old girl)

School influences

Children and parents viewed school support for asthma self-management as limited. Some children as old as 11 years were dependent on others for decision-making. For example, they would inform their teachers whenever they had symptoms, who in turn contacted the parents to attend and administer an inhaler. In contrast, some younger children carried an inhaler and sought help only if they were unable to get relief themselves.

“Moderator: If at school and your mother is not around, what would you do if you have asthma (symptoms)? AD5: Tell teacher and teacher will call mother and my mother will come.”

(AD5_FGD5_MCh, 11-year-old Malay boy) “AS3: when my asthma is bad, I'll bring the inhaler and spacer, and use it in class.” (AS3_FGD3MCh, 10-year-old Malay girl)

Healthcare influence

Children perceived little direct communication with healthcare professionals as most healthcare interactions were only with their parents. Discussions did not involve the children and no attempt was made to empower them to self-manage their asthma.

“They always talk to mum. I'll be taking nebuliser, they'll (mother and doctor) be talking there. I didn't know what was happening.” (V6, FGD6_TCh, 9-year-old Indian boy)

DISCUSSION

The beginning of the transition to independence was detectable even in the younger children and was clearly apparent in older children. Younger children mirrored their parents' actions and views. However, by the time they reached 10–12 years of age,

Box 1 Quotes illustrating cultural norms and beliefs

- ▶ “They (parents) say not to eat mutton. It causes runny nose and causes (which leads to) asthma. When there is dust, or house cleaning they suggest me to wear mask (so I don't get runny nose).” (NR3, FGD3_ICh, 11-year-old Indian boy)
- ▶ “So, they get runny nose and cough very frequent and it eventually will cause them to have asthma. I tried changing the milk powders for them, but still they'll get runny nose. They get very bad runny nose and later on it led to asthma.” (PK4, FGD4_IC, Indian, mother of NR3)
- ▶ “Doctors do not allow us to do vigorous exercise and advised mom not to give us to drink those icy things.” (P1_FGD2_CCh, 12-year-old Chinese boy)

Box 2 Quotes illustrating external influences

School influences

- ▶ “Moderator: What will happen if you use inhaler in front of your friends?
 - ▶ WA: My friends do not laugh at me. Sometimes they want to try.” (FGD6_MCh, 12-year-old Malay boy)
 - ▶ “If it is too bad, my teacher will call my mom. But if the teacher asked me and I am okay, then I will go back to class.” (FA2_FGD2MCh, 12-year-old Malay girl)
- #### Healthcare influences
- ▶ “Moderator: When you attend the clinic, do you have bad feelings or your feel okay?
 - ▶ SA5: I like
 - ▶ NA5: I don't mind
 - ▶ AD5: I like
 - ▶ Moderator: You like to attend, why do you like it?
 - ▶ AD5: because he has asthma” (FGD5_MC, SA5, 10-year-old Malay boy; NA5, 10-year-old Malay boy; and AD5, 11-year-old Malay boy)
 - ▶ “We went to the clinic few times but I did not understand what the doctor said.” (IDI1_CCh, 9-year-old Chinese boy)

they were learning from their own experiences, challenging parental constraints and gaining confidence to independently self-manage their asthma. All children were aware of their parents' strategies to prevent asthma, but older children experimented and adapted their self-management practices. Cultural norms and beliefs influenced children's transition to independence either directly or indirectly through the child's social network. Schools and healthcare appeared to have a limited role in influencing the transition to independent self-management.

We conclude that self-management education should occur early as children can be expected to learn some degree of self-management once they start primary school, though clearly, young children are not capable of independent self-management. Indeed, even by the age of 15 years, some studies suggest that only three-quarters are capable of self-managing independently.²⁸ There are also cultural differences as Asian parents tend to provide autonomy to their child at later age compared with non-Asians which may delay the transition to independence among Asian children.¹⁸ Healthcare professionals may need to guide parents in this process of transferring the responsibility to their child.^{29 30}

Children's own experiences in self-managing asthma appeared to be an important influencer in the transition to independent self-management. Our study highlighted that the children had different goals and developed different strategies to self-manage asthma compared with their parents, particularly when they were older. This is consistent with the findings of a US study that also found that primary school children and parents were not co-managing, but working independently, to self-manage asthma.³¹ Children frequently experimented to achieve their desired goals, often at school when their parents were not around. Similarly, a UK study identified that ‘trial and error’ was an important component in determining self-management decision-making among children.³² Another US study found that children presented unpleasant personal experiences, for example, bad taste of medicine or perceived lack of effectiveness of medication, as barriers to using treatment.³³ This is contrary to the attitudes of healthcare professionals who tend to underrate children's experience in self-management.³⁴

Echoing the experience related by the children in this study, healthcare professionals typically only engaged with the parents in consultations, particularly when explaining management.^{34,35} International and national asthma guidelines recommended the involvement of children during education of asthma management; however, a child-centred approach in review consultations was not

emphasised.^{4 10} Our finding that even young children are learning to self-manage their asthma suggests it is important for healthcare professionals to listen to children's experiences and enquire about the strategies they used to achieve their desired goals. A more child-centred approach is likely to facilitate the child's emerging self-management skills and improve asthma control.

The reports from our participants suggested that their healthcare professionals rarely communicated directly with the child. Self-management education and shared decision-making (even with adults) are not widely practised in Malaysia,^{11 12} reflecting traditional cultural norms as well as lack of training on communicating with patient/children dyads during clinical consultations.^{36 37} In addition, there are practical challenges in Malaysia (eg, lack of continuity of care) which make it more difficult to establish trusting relationships with children and their families.^{3 38}

Parents are the primary decision-maker on the treatment of a child's asthma,³³ and their involvement in self-management is crucial as young children mirror their parents' views and actions. However, a child-centred approach views care from the perspective of the child,^{39 40} providing developmentally appropriate care tailored to the individual child's capacity, needs and motivation which evolve as the child grows.^{39 41} Clinicians need to work in partnership with parents and children to ensure safe management of asthma.^{29 39} Striking a balance between parental involvement, and re-directing the focus of consultation to the child, is a challenge for healthcare professionals.^{18 40 42}

Support from school (and others in the child's social network)⁴¹ could support transition to independent selfmanagement for children with asthma. School-based interventions, sensitive to local cultural beliefs, could reduce stigma and promote awareness of asthma.^{43–45} School policies for managing asthma symptoms that arise during the school day could expect maturity-appropriate action on the part of the child as well as describing safe response from school staff.^{6 41}

Strengths and limitations of the study

This study explores the early stages of transition to independent self-management among primary school children. A strength is the exploration of the children's perspectives on asthma selfmanagement, matched to that of their parents, enabling triangulation. We involved a large number of participants with different cultural backgrounds conducted in their preferred language enabling cross-cultural comparison of practices and beliefs. A limitation is the identification of children based on parent reported physician-diagnosed asthma without objective confirmation of the diagnosis. However, the participants' perspective remains valid. Only 10 of the participants were between the ages of 7 and 9 years as this age group were more likely to be shy and declined assent to participate.

DISCUSSION

Parents, school and healthcare professionals should be aware that asthma self-management skills emerge as young as 7 years of age in children across different cultures. Recognition that children experiment with their asthma management (sometimes unbeknown to their parents) offers opportunities for child-centred discussion. Healthcare professionals should proactively engage directly with children during consultations and involve them in management decisions from an early age. This has the potential to empower children to use asthma self-management skills that are commensurate with their developmental stage and to promote smooth and supported transition to independent selfmanagement of their asthma.

Acknowledgements We would like to acknowledge all the parents and children who voluntarily took part in this research, and teachers and school authorities for their support during the study. We also like to thank Dr Linda Milnes for her expert opinion, moderators, transcribers and translators for their work.

Collaborators RESPIRE collaborators.

Contributors All authors contributed to study conception. SNR, EMK, NS, JS, PYL and ATC performed the data collection and checking of the transcripts. SNR, EMK, SML, NS, HS, NH, JS, PYL, NSH, ATC, AMA and HP coded and conducted data analysis. All authors contributed to the interpretation of data. SNR drafted the manuscript and all authors provided critical revisions and editing of the manuscript.

Funding International Primary Care Respiratory Group (IF019-2015) and University of Malaya (BKP019-2015) funded this study. SNR is now a PhD student at the University of Edinburgh with the NIHR Global Health Research Unit on Respiratory Health (RESPIRE). RESPIRE is funded by the National Institute of Health Research using Official Development Assistance (ODA) funding.

Disclaimer The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Malaysian Medical Research Ethics Committee, University Malaya Medical Centre (MECID: 20155-1366).

Provenance and peer review Not commissioned; externally peer reviewed.

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Características clínicas e gestão de crianças com discinesia ciliar primária em Inglaterra

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2019-317687>).

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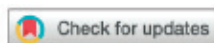
Received 14 June 2019

Revised 26 November 2019

Accepted 3 February 2020

Published Online First

10 March 2020



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RESUMO

Objetivo Em Inglaterra, o Serviço Nacional de Saúde encomendou um Serviço de Gestão Nacional para crianças com discinesia ciliar primária (DCP). Os objetivos deste estudo foram descrever a saúde das crianças observadas neste Serviço e comparar a função pulmonar com a de crianças com fibrose cística (FC).

Desenho Avaliação de serviços multicêntricos do Serviço Nacional de Gestão da DCP de Inglaterra.

Cenário Quatro centros DCP comissionados a nível nacional em Inglaterra.

Doentes 333 crianças com DCP examinadas no Serviço em 2015; os dados de função pulmonar também foram comparados com 2970 crianças com FC.

Resultados A idade mediana no diagnóstico para DCP foi de 2,6 anos, significativamente mais reduzida em crianças com *situs inversus* (1,0 vs. 6,0 anos, $p < 0,001$). Em comparação com os dados nacionais do Registo de FC, a média (DP) do volume expiratório forçado num segundo (FEV₁) previsto foi de 76,8% em DCP ($n=240$) e 85,0% em FC e o FEV₁ foi mais reduzido em crianças com DCP até aos 15 anos de idade. Aproximadamente metade das crianças apresentou alguma deficiência auditiva, com 26% a necessitarem de aparelhos auditivos. As crianças com um índice de massa corporal (IMC) inferior apresentaram um FEV₁ mais reduzido ($p < 0,001$). Um terço das crianças apresentou culturas respiratórias positivas no exame, sendo que 54% destas crianças apresentaram um crescimento de *Haemophilus influenzae*.

Conclusões Proporcionámos evidências de que as crianças com DCP em Inglaterra apresentam pior função pulmonar comparativamente às crianças com FC. O estado nutricional deve ser considerado na gestão da DCP, uma vez que as crianças com um IMC inferior apresentam um FEV₁ significativamente mais reduzido. A deficiência auditiva é comum, mas parece melhorar com a idade. São necessários ensaios aleatorizados controlados e bem desenhados sobre a gestão da DCP de modo a fundamentar as melhores práticas clínicas.

INTRODUCTION

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive condition where abnormal ciliary function leads to impaired mucociliary clearance. This loss of function to the mucociliary escalator leads to recurrent sinopulmonary infection and, ultimately, bronchiectasis. Historically, it has been considered a mild respiratory condition; however, recent data suggest that lung function declines at a similar rate through childhood to children with cystic fibrosis (CF).¹⁻³ In addition, about 80% of patients suffer with persistent otitis media with effusion and associated conductive hearing loss.^{4,5} Half of the patients have *situs inversus totalis*⁶ and up

What is already known on this topic?

- Primary ciliary dyskinesia (PCD) is a rare autosomal recessive condition where abnormal ciliary function leads to impaired mucociliary clearance.
- Historically PCD has been considered a mild respiratory condition.
- There is little evidence to guide the management of children with PCD, with only one randomised controlled trial published to date.

What is already known?

- In England, forced expiratory volume in one second (FEV₁) was lower in children with PCD compared to those with cystic fibrosis, particularly in younger age groups.
- Nutritional status should be considered in PCD management, as those with a lower body mass index have significantly lower FEV₁.
- Hearing impairment is common but seems to improve with age.

to 17% have congenital heart disease (CHD).^{7,8} Many men are infertile due to immotile sperm and women can have reduced fertility.^{9,10} The estimated prevalence is 1 in 10000 live births^{1,11} but this can be significantly higher in certain populations.^{12,13}

In 2012, National Health Service England commissioned a National Children's PCD Management Service to complement the existing diagnostic service.¹⁴ Four PCD centres were commissioned to undertake annual review assessments, to a standardised service specification, by a specialist PCD multi-disciplinary team (MDT) on all children with PCD in England.

Here, we describe the first full set of data collected from children at annual review, in 2015. We compare the lung function of children with PCD to those with CF in England and identify areas of future research that will help to improve patient care.

METHODS

Participants

All children with a diagnosis of PCD who had an annual review assessment between 1 January

Para citar: Rubbo B, Best S, Hirst RA, et al. Arch Dis Child 2020;105:724-729.

and 31 December 2015, in one of the four nationally commissioned PCD centres in England were included in this study. The diagnosis of PCD was confirmed by a specialist PCD diagnostic MDT, in line with European Respiratory Society (ERS) consensus guidelines.^{14 15} Annual reviews were carried out to a standardised service specification.^{14 16} To ensure that children received similar care across centres, national guidelines were developed, teams met regularly to discuss clinical cases and clinical outcome data were audited. The project was reviewed by the Research and Development office at University Hospital Southampton and was deemed to be a service evaluation hence research ethics committee approval was not required.¹⁷

Data collection

Data were extracted from electronic and paper medical records and from annual review reports, using a standardised data sheet, agreed a priori, with variables pre-defined in a coding manual. These included demographics, diagnostic information and a clinical review of the year, focused on respiratory, ear, nose and throat (ENT), and cardiac issues. Also collected were data on treatments, including airway clearance physiotherapy techniques and adjuncts, nebulised mucolytics, antibiotic use (oral and intravenous) both prophylactically and for exacerbations, inhalers and nasal treatments; and anthropometry and investigations, including spirometry, audiometry and collection of an airway microbiology sample. Centres were contacted to clarify any discordant or missing data.

Investigations conducted at annual review assessment

Spirometry data

Equipment was calibrated as per manufacturers' instructions and all measurements were obtained according to the ERS/American Thoracic Society guidelines.¹⁸ Global Lung Initiative (GLI) equations were used to estimate z-scores for forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) from the data, ethnicity-specific equations were used where available.¹⁹ GLI-based FEV₁ z-scores were obtained from the UK CF Registry for all English children in 2015 for direct comparisons with our PCD FEV₁ data.²⁰

Audiology data

Hearing was defined as normal if <20dB, mild loss if 20–40dB, moderate loss if 40–70dB, severe loss if 70–95dB and profound loss if >95dB.

Anthropometric data

Height and weight were performed and recorded in accordance with WHO guidelines.²¹ Body mass index (BMI) z-scores were calculated using the WHO Anthro Plus software V.3.2.2.

Statistical analyses

Data were cleaned, coded and analysed in Stata (V.14.0, Stata Corp, Texas, USA). Continuous variables were presented as mean with SD or median with IQR. Groups were compared using independent t-tests, Mann–Whitney and Kruskal–Wallis tests. Post-hoc for pairwise comparisons were performed for FEV₁ % predicted and age categories, with Tukey's method to adjust for multiple comparisons. Categorical variables were reported as proportions and groups were compared using χ^2 or Fisher's exact test. Multiple regressions were used to model FEV₁ z-score, adjusting for possible covariates. Significant ($p < 0.05$) variables were retained (backward selection) and results from the reduced regression model are reported. Normality of residuals was assessed using kernel density estimations and visual inspection of histograms. Results from the models were presented as number of observations, regression coefficients (r) with 95% CIs and model's goodness-of-fit (adjusted R²). Spearman's rank correlation coefficient was used to compare association between variables

Table 1 Clinical and demographic data on children with PCD who underwent an annual review in 2015 across the four English National Children PCD Management Services

	Mean (SD)	n with available data
Median age in years (IQR)	9.8 (5.5 to 13.8)	333
Male (%)	175 (52.6%)	333
FEV ₁ z-score	1.9 (1.4)	240
FEV ₁ % predicted	76.8% (240)	240
FVC z-score	−1.3 (1.5)	240
FVC % predicted	85.4% (240)	240
BMI z-score	0 (1.4)	307
Weight z-score	−0.1 (1.3)	159*
Height z-score	−0.3 (1.1)	310
Age at diagnosis	2.6 (0.5 to 7.2)†	321

*WHO Weight-for-age reference data are not available beyond age 10 hence n lower than for other anthropometric data.²⁷

†Median (IQR).

BMI, body mass index; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; PCD, primary ciliary dyskinesia.

that were not normally distributed or between continuous and non-continuous variables.

RESULTS

In all, 333 children with PCD underwent an annual review during the study period. Median age at review was 9.8 years, 52.6% of those reviewed were men and the majority were either white British (n=122, 36.6%) or Pakistani and British Pakistani (n=121, 36.3%) (table 1, online supplementary figure 1).

Diagnosis of PCD

Median age at diagnosis of PCD was 2.6 years (IQR: 0.5–7.2 years) (table 1). This was significantly lower in those with dextrocardia (n=172) compared with levocardia (n=151) (1.0 year of age (IQR: 0.3–3.2, range: 0–14.0) vs 6.0 years (IQR: 2.0–9.0, range: 0–16.2), $p < 0.001$). 53.3% of children had dextrocardia with almost all having situs inversus totalis, only 12 patients (3.7%) had dextrocardia in isolation. CHD was reported in 13.1% of children spirometry.

Mean (SD) FEV₁ z-scores for children with PCD were −1.9 (1.4) and FVC z-scores were −1.3 (1.5), mean predicted FEV₁ (SD) was 76.8% (table 1). FEV₁ z-score was significantly lower in older children, with a decrease of 0.6 z-scores for every increase of 10 years in age (n=240, regression coefficient=−0.06, 95%CI −0.11 to −0.02, $p = 0.008$, adjusted R²=2.9%; figure 1a), adjusted for centre of origin, age at diagnosis, sex, cardiac situs and presence of cultured pathogens (online supplementary table 1). Spirometry data from children with CF in 2015 were available as predicted FEV₁ and hence this was used for comparison with our patients with PCD.²⁰ Mean predicted FEV₁ was significantly lower in PCD children compared with CF children up to the age of 15 years ($p = 0.001$), with no difference seen in the 16- to 18-years-old category ($p = 0.7$). The largest difference was in the 5- to 7-year olds, where the mean predicted FEV₁ was 91.3% (SD=15.7%) in CF but was 78.3% (SD=18.6%) in PCD (figure 1b).²⁰ Mean (SD) BMI z-scores in children with PCD were normal (z-score=0 (1.4)) (table 1). However, children with lower BMI also had lower FEV₁ z-scores (n=238, regression coefficient=0.35, 95%CI: 0.22 to 0.47, $p < 0.001$, adjusted R²=10.8%) (figure 1c).

Microbiology

Microbiology data were available for 312 children, of which 67% did not culture a respiratory pathogen at annual review. *Haemophilus influenzae* was the most prevalent pathogen (17.9%, corresponding to 53.9% of those with a positive culture), followed by *Staphylococcus aureus* (5.1%) and *Streptococcus pneumoniae* (4.2%), with *Pseudomonas aeruginosa* cultured in 2.6% of children (online supplementary table 2). No children cultured non-tuberculous *Mycobacterium*. There was no correlation between

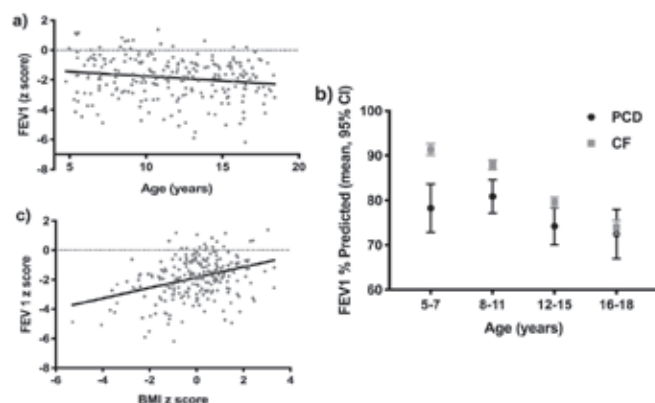


Figure 1 a) Age (years) versus FEV₁ z-score for 240 children with PCD in 2015. (b) Mean (95% CI) % predicted FEV₁ of 240 children with PCD versus 2970 children with CF in England in 2015, stratified by age group (20). (c) BMI z-score versus FEV₁ z-score for children with PCD in 2015. BMI, body mass index; CF, cystic fibrosis; FEV₁, forced expiratory volume in one second; PCD, primary ciliary dyskinesia.

those culturing respiratory pathogens and FEV₁ z-scores and no statistically significant differences were observed in respiratory pathogens when stratified by age category (figure 2).

Audiology

Normal hearing levels were observed in 44.3% of children with audiology results available (n=271; 81.4% of all children), 34% had mild hearing loss and 21.8% had more significant hearing loss. At the time of annual review, 23.6% of children were wearing hearing aids. Moderate to profound hearing loss was seen in 26.4% of children younger than 6 years of age but in only 13.8% of those aged between 16 and 18 years (figure 3). Once the children were under the care of the National Children's PCD Management Service, only two of the 333 children had ventilation tubes inserted.

Physiotherapy and mucolytic nebulisation

All children were trained to perform, and advised to undertake, regular age-appropriate airway clearance physiotherapy. The majority used either oscillating positive expiratory pressure (PEP) (49.2%) or PEP physiotherapy (32.1%) (table 2). Approximately half of children (53.2%) were prescribed nebulised hypertonic saline as a mucolytic agent to aid airway clearance. Children using hypertonic saline had significantly lower FEV₁ z-scores (mean difference -0.4, 95%CI -0.76 to -0.04, p=0.028). Nebulised Dornase Alpha (Pulmozyme, Genentech, San Francisco, USA) was used in only 4.9% of children.

Antibiotics

Thirty per cent of children with PCD had at least one course of intravenous antibiotics over the preceding 12 months. Approximately 10% of the children were prescribed regular

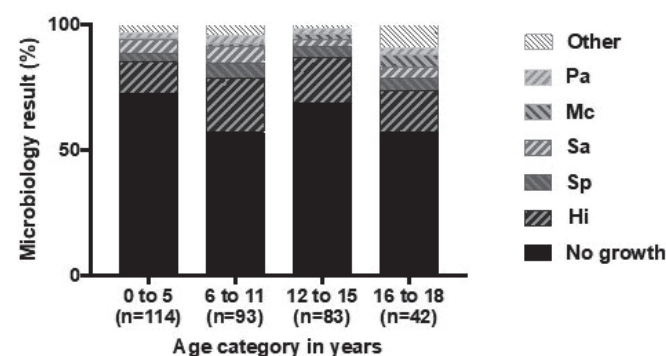


Figure 2 Microbiology results taken at annual review by percentage, stratified by age category. HI, *Haemophilus influenzae*; MC, *Moraxella catarrhalis*; PA, *Pseudomonas aeruginosa*; SA, *Staphylococcus aureus*; SP, *Streptococcus pneumoniae*.

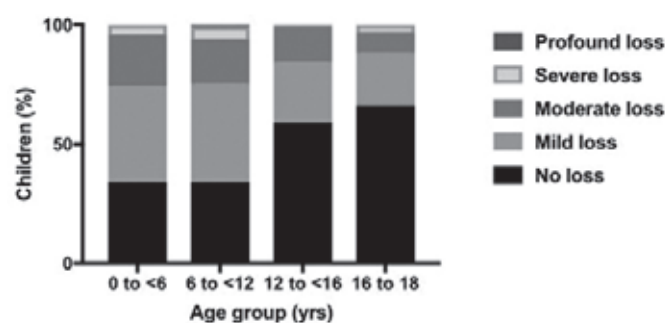


Figure 3 Proportion of children with PCD with varying degrees of hearing loss in different age groups in 2015. PCD, primary ciliary dyskinesia.

intravenous antibiotics (table 2). Those that received intravenous treatment had a lower FEV₁ z-score, adjusted for BMI z-score and age (n=234, regression coefficient=-0.52, 95%CI: -0.88 to -0.16, adjusted R²=17.5%). Children received a median of two courses of oral antibiotics over the preceding year (IQR: 1-3). 59% were prescribed prophylactic antibiotics and of these, over half used Azithromycin (59.8%) (table 2, online supplementary table 3). A significantly lower mean FEV₁ z-score was found in children taking prophylactic antibiotics, adjusted for use of antibiotics in the last year (intravenous or oral) and cultured pathogens (n=162, regression coefficient: -0.66, 95%CI: -1.23 to -0.08, p=0.0008, adjusted R²=8.3%).

DISCUSSION

This study provides detailed characterisation of a large and welldefined group of children with PCD, diagnosed and managed under the unified, specialised National Children's PCD Management Service in England.

Historically, PCD has been considered a mild respiratory condition²²; however, we report a mean FEV₁ of -1.9 z-scores in children with the disease in England. Almost a third of children required admission for intravenous antibiotics over the preceding 12 months with over 10% receiving regular intravenous antibiotics. Further to this, while a recent large international PCD cohort found a similar reduction in lung function between children with PCD and CF, we showed that % predicted FEV₁ was significantly lower in those with PCD compared with those with CF up to the age of 15 years, as was also observed in a smaller Danish cohort study.^{2 3 23} This suggests that in 2015, younger children seen by the National Children's PCD Management Service had lower lung function than their European counterparts. However, lung function decline over time was steeper in patients with CF and, by the age of 16 to 19 years, no statistically significant difference was seen between the two groups.

Table 2 Management of children with PCD in England in 2015

Physiotherapy modality	n (%)	n with available data
Breathing techniques	10 (3.3)	299
Exercise for airway clearance	2 (0.7)	299
Manual techniques	41 (13.7)	299
PEP physiotherapy (mask/Pari)	96 (32.1)	299
Oscillating PEP	147 (49.2)	299
Other	3 (1.0)	299
Antibiotics		
Number of intravenous antibiotic courses in past year	95 (29.7)	320
Median (IQR) courses of oral antibiotics	2 (1 to 3)	254
On regular intravenous treatment (every 3-6 months)	34 (10.6)	320
On antibiotic prophylaxis	189 (58.9)	321
Other treatments		
Inhaled corticosteroids	111 (34.2)	325
Bronchodilators	156 (48.3)	323
Nasal rinsing	123 (38.7)	318

PCD, primary ciliary dyskinesia; PEP, Positive expiratory pressure.

Our children had a median age at diagnosis of 2.6 years. This is considerably younger than previously reported in the literature,²⁴ suggesting that the establishment of National Children's PCD Diagnostic Service in 2006 and Management Service in 2012 might have raised awareness of this rare disease among paediatricians. However, newborn screening for CF was introduced in England in 2007 meaning that CF is generally diagnosed in infancy, allowing for early initiation of treatment. When comparing the spirometry data of our PCD children to those with CF, the largest differences in mean FEV₁ were in younger children (figure 1b). We therefore hypothesise that earlier diagnosis and initiation of treatment for PCD may improve the low values of FEV₁ observed in younger children.

Haemophilus influenzae, as reported in previous studies, was the most frequent respiratory pathogen cultured in our patients.^{25,26} Future studies clarifying the impact of chronic colonisation with this and other pathogens such as *Pseudomonas aeruginosa* in patients with PCD are needed. While these are cross-sectional data, we found no association between any cultured pathogen and FEV₁. Well-powered longitudinal studies will be required to understand the impact of these pathogens on patients and, thereby, inform clinicians as to whether they should persist in attempting to eradicate them. Contrary to previous publications, the prevalence of respiratory pathogen did not vary between age groups, in particular there was no increase seen in the prevalence of *Pseudomonas aeruginosa* in older age groups.²⁷

A recently published large international cohort of children with PCD^{28,29} found that patients with lower BMI z-scores have lower FEV₁ z-scores, which had not been observed previously.³⁰ Our findings support this novel observation and are similar to well-described correlations in children with CF.³¹ However, the majority of patients with CF have pancreatic insufficiency, which is not the case in PCD. This would therefore imply that having suppurative lung disease, independent of pancreatic issues, may impact negatively on nutritional status (or vice versa). These findings lead to the hypothesis that intervening on nutritional status may have a positive benefit on the respiratory health of children with PCD, as is the case in CF,³² and warrants further investigation.

Management of children with PCD is challenging due to the limited evidence base, with only one published randomised control trial (RCT) to date.³³ Management is therefore based on expert opinion, consensus guidelines and extrapolated from the larger evidence base available for patients with CF.^{15,34,35}

All children in the service were advised to undertake regular airway clearance physiotherapy.³⁶ Over half the children used nebulised mucolytics agents, the vast majority using hypertonic saline. A RCT on use of hypertonic saline in PCD did not show improvement on quality of life in patients compared with controls³³; however, the study did not use a disease-specific quality of life questionnaire, was underpowered and the control group received normal saline nebulisation, which might in itself have been beneficial for the patients.³⁷ We found that children on hypertonic saline had a significantly lower FEV₁ than those not. This is likely due to clinicians reserving its use for children with a more severe clinical phenotype; however, further research is needed to exclude the possibility that hypertonic saline has a negative effect on lung function in children with PCD.

The use of prophylactic antibiotics in PCD remains controversial, as the potential decrease in the number of respiratory exacerbations must be balanced against the risk of increasing antimicrobial resistance. Despite this, in 2015, approximately 60% of our children were on prophylactic antibiotics, with over half of these using Azithromycin. These children were noted to have significantly lower FEV₁ than those not on antibiotics. Again, clinicians likely reserved the use of prophylactic antibiotics for more severe, or frequently exacerbating children. Results from a multicentre study assessing the use of prophylactic azithromycin

in PCD should soon be available and will help inform future management.³⁸

Almost a quarter of our children needed hearing aids for moderate to profound hearing loss. Hearing seems to improve with age but the high proportion of patients with some level of hearing loss stresses the importance of regular hearing assessments and ENT follow-up, particularly in early childhood, when hearing is fundamental to speech development. Only 2 out of 333 children in this study had ventilation tubes inserted under the care of the Service. The limited evidence for their use is both inconclusive and conflicting and a well-designed and powered study is needed to investigate this important area of management.^{39–42}

The strength of this work is in the large number of wellcharacterised children with PCD evaluated under a nationally standardised Management Service. However, the data are cross-sectional and therefore do not allow for conclusions to be drawn on, for example, the potential benefits of therapeutic interventions or the detrimental impact of culturing particular pathogens on clinical outcomes. Detailed longitudinal follow-up of these children are therefore required and will help inform both management guidelines and therapies to be evaluated in future RCTs. Comparisons of lung function data between children with PCD and CF were limited to the data provided by the UK CF Registry (ie, GLI-based spirometry measurements) and we were therefore unable to adjust CF data for potential confounders.

CONCLUSIONS

Our data suggest that, far from being a mild respiratory condition, children with PCD have worse lung function than those with CF, particularly at an earlier age. Those with a lower BMI have a significantly lower FEV₁; therefore, nutritional status should be considered in their management. Well-designed and powered RCTs on the management of PCD are needed to inform best clinical practice.

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Acknowledgements We would also like to thank all our shared care centres, our patients and the UK PCD Family Support Group.

Contributors Members of the English National Children's PCD Management Service include: Amanda Harris, Amanda Friend, Victoria Keenan, Hannah Wilkins, Hasnaa Ismail-Koch, Andrea Burgess, Samantha Packham, Patricia Goggin, Gemma Marsh, Laura Baynton, Michael Leshen, Sarah Olsson, Nicola Collins, Peter Rea, Ann-Louise McDermott, Amanda Parsons, Rajinder Kang, Nicola Lloyd, Alison

Truscott, Lynne Schofield, I Knight.

Contributors WW, JSL, SC, CH, PC, EM, MN, PK, CO'C and MW developed the concept and design of the study. WW and BR are responsible for the integrity of the study and data; BR led standardised clinical data collection, data management and statistical analyses; WW and BR drafted the manuscript; SB, BR, SC, PK, PC, EM, RH, AS, PG, MN and WW extracted of clinical data from patient record; WW, JSL, SC, CH, PC, EM, MN, PK, CO'C and MW led the diagnostic service and annual reviews at their respective centres; JSL provided guidance and critically reviewed the manuscript at an early draft. All co-authors critically reviewed and approved the final manuscript.

Funding The National PCD Service is commissioned and funded by NHS England. Research in Southampton is supported by NIHR Southampton Biomedical Research Centre and NIHR Wellcome Trust Clinical Research Facility. Research in Royal Brompton Hospital is supported by the NHLI, Imperial College London. Research in GOSH is supported by the NIHR GOSH BRC. Research in the University Hospitals of Leicester NHS Trust is supported by University of Leicester, Leicester. Research in Birmingham Women's and Children's Hospital NHS Trust is supported by the University of Birmingham and Wellcome Trust Clinical Research Facility.

Disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests JL reports grants, personal fees and non-financial support from Aerocrine/Circassia, grants and personal fees from Vertex, grants from Parion, outside the submitted work.

SC reports grants, personal fees and non-financial support from Vertex Pharmaceuticals, grants and other from Chiesi Pharmaceuticals, other from Pharmaxis Pharmaceuticals, personal fees from Actavis Pharmaceuticals, other from Profile Pharma, outside the submitted work.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data will be made available upon reasonable request by contacting the corresponding author.

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1 VEZ DIA¹

xoterna[®]

breezhaler[®]

Indacaterol/glicopirrônio pó para inalação, cápsulas

Primeira associação fixa LAMA/LABA^{1*}MELHORA OS SINTOMAS DE HOJE^{3**}...... REDUZ FUTURAS EXACERBAÇÕES^{2,5#}Estudo CRYSTAL³

117%

Melhoria da dispneia
vs LABA/ICS³(Medida através do TDI.
Cálculo realizado a partir dos dados
de Melhoria do TDI do Estudo
CRYSTAL ($\Delta = 1,10$ uds;
 $p < 0,0001$ às 12 semanas)

17%

de diminuição
na taxa de exacerbações
moderadas a gravesvs SFC²
(às 52 semanas) $p < 0,001$ Estudo FLAME²

**BREEZHALER, O DISPOSITIVO
COM MENOR TAXA DE ERROS CRÍTICOS**
ASSOCIADOS AO SEU USO^{4§}**

*Informação sobre medicamentos do INFARMED consultada em página da internet do site do Infomed (acessada em 2020/01/15); ¹Indacaterol/glicopirrônio(110/50µg 1x dia) vs Salmeterol/Fluticasona(500/50µg 2x dia), glicopirrônio(50µg 1x dia) e tiotropio(18µg 1x dia); ²Melhoria da dispneia vs LABA/ICS³, LABA e LAMA avaliada através do TDI; ³Breezhaler vs restantes inaladores em estudo (Respimat[®], pMDI[®], Turbuhaler[®], Handihaler[®] e Diskus[®]); ⁴Erro crítico: aquele que pode afetar substancialmente a dose que chega ao pulmão; ⁵LAMA: Antagonista muscarínico de longa duração de ação; ⁶LABA: agonista β2 de longa ação; ⁷ICS: Corticosteroide Inalado; ⁸pMDI: inaladores pressurizados doseáveis; ⁹TDI: Transition Dyspnea Index; ¹⁰SFC: Salmeterol/Fluticasona 50/50µg 2x dia; ¹¹Δ: diferença entre terapêuticas. 1. RCM XOTERNA[®] BREEZHALER[®] 05/2019; 2. Wedzicha JA, Banerji D, Chapman KR. Indacaterol/Glycopyrronium Versus Salmeterol/Fluticasone for COPD Exacerbations. New England Journal of Medicine. 2016;374:2222-2234; 3. Vogelmeier CF, Gaga M, Alamian-Mattheis M, Greulich T, Marin JM, Castellani W, et al. Efficacy and safety of direct switch to indacaterol/glycopyrronium in patients with moderate COPD: the CRYSTAL open-label randomised trial. Respir Res. 2017 Jul 18;18(1):140; 4. Molimard M, Raherson C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. Eur Respir J 2017; 49:1601794; 5. Wedzicha JA, Drecomer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): randomised, double-blind, parallel-group study. Lancet Respir Med. 2013;1:199-209; ⁶População estudo FLAME: Doentes com história de ≥1 exacerbações no ano prévio à inclusão; ⁷População estudo CRYSTAL: Doentes com Doença Pulmonar Obstrutiva Crônica moderada e com ≤1 exacerbação no ano prévio; ⁸População estudo FLAME: Doentes com história de ≥1 exacerbações no ano prévio à inclusão.

Xoterna Breezhaler 85 microgramas/43 microgramas, pó para inalação, cápsulas (indacaterol/glicopirrônio) Nota Importante: Antes de prescrever consulte o Resumo das Características do Medicamento. **APRESENTAÇÃO:** Pó para inalação, cápsulas contendo 143 microgramas de maleato de indacaterol equivalente a 110 microgramas de indacaterol e 63 microgramas de brometo de glicopirrônio equivalente a 50 microgramas de glicopirrônio. Cada dose libertada (a dose libertada do aplicador bucal do inalador) contém 110 microgramas de maleato de indacaterol equivalente a 85 microgramas de indacaterol e 54 microgramas de brometo de glicopirrônio equivalente a 43 microgramas de glicopirrônio. **INDICAÇÕES:** Xoterna Breezhaler é indicado como tratamento broncodilatador de manutenção para alívio dos sintomas em doentes adultos com doença pulmonar obstrutiva crônica (DPOC). **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Adultos: A dose recomendada é a inalação do conteúdo de uma cápsula uma vez por dia, usando o inalador Xoterna Breezhaler. Deve ser utilizado o inalador fornecido com cada nova prescrição. **Populações especiais de doentes:** **Compromisso renal:** pode ser usado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal terminal que necessitem de diálise, este deve ser usado se o benefício esperado superar o risco potencial. **Compromisso hepático:** pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não estão disponíveis dados para a utilização em doentes com compromisso grave da função hepática. **População idosa:** pode ser utilizado na dose recomendada em doentes idosos (idade igual ou superior a 75 anos). **População pediátrica** (<18 anos): a segurança e eficácia não foram estabelecidas. Não existem dados disponíveis. **Modo de administração:** As cápsulas de Xoterna Breezhaler devem ser administradas pela via inalatória oral e apenas com a utilização do inalador Xoterna Breezhaler. As cápsulas não devem ser engolidas. Xoterna Breezhaler deve ser administrado à mesma hora do dia todos os dias. Se for omitida uma dose, esta deve ser tomada assim que possível no mesmo dia. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas devem ser sempre conservadas no blister de origem para proteger da humidade, e apenas retiradas imediatamente antes da utilização. Os doentes devem ser instruídos sobre como administrar o medicamento corretamente. Os doentes que não sentirem melhorias na respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes de Xoterna Breezhaler. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ Xoterna Breezhaler não deve ser administrado concomitantemente com medicamentos contendo agonistas beta-adrenérgicos de longa duração ou antagonistas muscarínicos de longa duração ♦ **asmas:** não deve ser usado no tratamento da asma, os agonistas beta-adrenérgicos de longa duração podem aumentar o risco de acontecimentos adversos graves relacionados com a asma, incluindo mortes relacionadas com a asma, quando utilizados no tratamento da asma ♦ **utilização aguda:** não está indicado para o tratamento de episódios agudos de broncoespasmo ♦ **hipersensibilidade:** se ocorrerem reações de hipersensibilidade, em particular angioedema, urticária ou erupção cutânea, o tratamento com Xoterna Breezhaler deve ser descontinuado e deverá ser instituída terapêutica alternativa ♦ **broncoespasmo paradoxal:** administração de Xoterna Breezhaler pode resultar em broncoespasmo paradoxal, o que pode pôr em risco a vida. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa ♦ **efeitos anticolinérgicos relacionados com glicopirrônio:** utilizar com precaução em doentes com glaucoma de ângulo estreito e retenção urinária ♦ **efeitos sistémicos de beta-agonistas:** tal como com outros agonistas beta-adrenérgicos, deve ser utilizado com precaução em doentes com perturbações cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão); em doentes com perturbações convulsivas ou tirotóxicose, e em doentes com resposta aumentada aos agonistas beta-adrenérgicos ♦ **doentes com compromisso renal grave:** apenas deve ser utilizado se o benefício esperado superar o risco potencial em doentes com compromisso renal grave, incluindo os com doença renal terminal necessitando de diálise ♦ **efeitos cardiovasculares de beta-agonistas:** tal como com outros agonistas beta-adrenérgicos, pode causar efeitos cardiovasculares clinicamente significativos em alguns doentes, evidenciados pelo aumento da frequência cardíaca, pressão arterial e/ou sintomas, alterações no eletrocardiograma (ECG) ♦ **hipocalcémia:** os agonistas beta-adrenérgicos podem produzir hipocalcémia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. A diminuição do potássio sérico é usualmente transitória, não requerendo a suplementação. Em doentes com DPOC grave, a hipocalcémia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas ♦ **hiperglicémia:** A inalação de doses elevadas de agonistas beta-adrenérgicos pode produzir aumento da glicose plasmática. Ao iniciar o tratamento com Xoterna Breezhaler, a glicose plasmática deve ser monitorizada cuidadosamente em doentes diabéticos. Xoterna Breezhaler não foi estudado em doentes com diabetes mellitus inadequadamente controlada, portanto, é recomendada precaução e monitorização apropriada nestes doentes. ♦ Xoterna Breezhaler contém lactose. Doentes com problemas hereditários raros de intolerância à galactose, deficiência total de lactase ou má absorção de glicose-galactose não devem tomar este medicamento. **GRAVIDEZ:** apenas deve ser usado durante a gravidez se os benefícios esperados para o doente compensarem os potenciais riscos para o feto. **TRABALHO DE PARTO:** Informação relacionada com indacaterol – tal como com outros medicamentos contendo agonistas beta-adrenérgicos, Xoterna Breezhaler pode inibir o trabalho de parto devido ao efeito relaxante no músculo liso uterino. **ALEITAMENTO:** apenas deve ser considerado se os benefícios esperados para a mulher compensarem qualquer potencial risco para a criança. **FERTILIDADE:** os estudos de reprodução e outros dados em animais não levantam preocupações no que respeita a fertilidade quer em machos quer em fêmeas. **INTERAÇÕES:** ♦ Não foram conduzidos estudos de interação específicos com Xoterna Breezhaler. A informação sobre o potencial de interações é baseada no potencial para cada uma das suas duas substâncias ativas. ♦ não deve ser administrado conjuntamente com bloqueadores beta-adrenérgicos (incluindo colírios) exceto se existirem razões imperiosas para a sua utilização ♦ os fármacos conhecidos por prolongar o intervalo QT podem aumentar o risco de arritmia ventricular ♦ a administração concomitante de outros agentes simpaticomiméticos pode potenciar os efeitos indesejáveis ♦ o tratamento concomitante com derivados da metilxantina, corticosteroides ou diuréticos não-pouparadores de potássio pode potenciar o possível efeito hipocalcémico dos agonistas beta-adrenérgicos ♦ a inibição dos principais contribuidores para a depuração do indacaterol, CYP3A4 e glicoproteína P (P-gp) não tem impacto na segurança das doses terapêuticas ♦ a coadministração com outros medicamentos que contêm anticolinérgicos não foi estudada e portanto não é recomendada ♦ não se esperam interações medicamentosas relevantes quando glicopirrônio é coadministrado com metidrina ou outros inibidores do transporte de catións orgânicos. **EFEITOS INDESEJÁVEIS:** O perfil de segurança é caracterizado por sintomas beta-adrenérgicos e anticolinérgicos típicos relacionados com os componentes individuais da associação. Outras reações adversas mais frequentes relacionadas com o medicamento foram tosse, nasofaringite e cefaleias. **Reações adversas de Xoterna Breezhaler:** ♦ **Muito frequentes** (≥1/10): infeção do trato respiratório superior. ♦ **Frequentes** (≥1/100, <1/10): nasofaringite, infeção do trato urinário, sinusite, rinite, hipersensibilidade, hiperglicémia e diabetes mellitus, tonturas, cefaleias, tosse, dor orofaríngea incluindo irritação da garganta, dispnéia, cãibras dentárias, obstrução da bexiga e retenção urinária, pirexia¹², dor torácica. ♦ **Pouco frequentes** (≥1/1.000, <1/100): angioedema, insónia, glaucoma¹³, doença cardíaca isquémica, fibrilhação atrial, taquicardia, palpitações, broncoespasmo paradoxal, disfonía, epistaxis, gastroenterite, xerostomia, prurido/exantema, dor musculoesquelética, espasmos musculares, mialgias, dor nas extremidades, edema periférico e fadiga. ♦ **Raros** (≥1/10.000, <1/1.000): parestesias. ¹²Reação adversa observada com Xoterna Breezhaler mas não nos componentes individuais. **TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO:** Novartis Europharm Limited. **REPRESENTANTE LOCAL:** Laboratório Medinfar-Produtos Farmacêuticos, S.A. 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Xoterna Breezhaler 2020-01-FL-08 elaborado em janeiro de 2020

GRUPO

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Preferências de terapêutica de inaladores de manutenção de doentes com asma ou doença pulmonar obstrutiva crónica: uma experiência de escolha discreta

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2019-213974>).

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Received 15 August 2019

Revised 17 April 2020

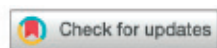
Accepted 7 May 2020

Published Online First

6 July 2020



► (<http://dx.doi.org/10.1136/thoraxjnl-2020-215238>)



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Para citar: Tervonen T, Hawken N, Hanania Na, et al. *Thorax* 2020;75:735–743.

RESUMO

Enquadramento Existe uma variedade de terapias inalatórias de manutenção para tratar a asma e a DPOC. As escolhas de tratamento centradas no doente requerem a compreensão das preferências dos doentes pelas terapias alternativas.

Métodos Foi realizada uma experiência de escolha discreta baseada na internet para obter as preferências dos doentes por dispositivos inaladores e atributos medicinais. A seleção de atributos foi baseada em grupos de foco de doentes e revisão da literatura.

Resultados A experiência de escolha discreta foi completada por 810 doentes com asma e 1147 doentes com DPOC. Os doentes com asma valorizaram mais a diminuição do início de ação de 30 para 5 minutos, seguindo-se a redução das exacerbações anuais de 3 para 1. Os doentes com DPOC valorizaram de modo igual ou superior a diminuição do início de ação de 30 para 5 minutos e a redução das exacerbações anuais de 3 para 1. Tanto os doentes com asma como os doentes com DPOC estavam dispostos a aceitar uma exacerbação adicional em troca de uma diminuição de 15 min no início de ação e um início de ação mais longo em troca de um menor risco de efeitos adversos dos corticosteroides inalados. Os doentes com asma e DPOC valorizaram mais uma dosagem de uma vez por dia em detrimento de duas vezes por dia, inaladores pressurizados sobre inaladores de pó seco e ativação sem cápsula sobre cápsulas de utilização única, embora estes atributos não fossem valorizados tanto como um início de ação mais rápido ou exacerbações reduzidas.

Conclusões Os atributos mais importantes dos inaladores de manutenção para doentes com asma e DPOC foram o rápido início do alívio dos sintomas e uma menor taxa de exacerbações. As preocupações com a segurança dos corticosteroides inalados e a conveniência dos dispositivos também afetaram as preferências dos doentes, mas de forma menos relevante.

INTRODUCTION

Inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) inhalers are routinely used for maintenance therapy in patients with asthma,¹ and long-acting muscarinic antagonist (LAMA)/LABA and ICS/LABA inhalers are used for maintenance therapy in patients with COPD.^{1,2} A variety of inhalers are available, and although they have similar efficacy, their onset of action, adverse effects, dosing regimens, and other attributes differ.^{1,2} Patient-centric drug development and treatment decisions require understanding how patients value the different treatment attributes. Increasingly, decision-makers are promoting formal benefit-risk assessments for this purpose.³ Although qualitative research has provided some general insight into which treatment attributes are important,^{4,5} quantitative methods, especially discrete choice experiments (DCEs), can provide

Mensagens-chave

What is the key question?

► What attributes of maintenance inhalers are most valued by patients with asthma or COPD?

What is the bottom line?

► The most important maintenance inhaler attributes for patients with asthma and COPD were fast onset of symptom relief and a lower rate of exacerbations.

Why read on?

► The findings highlight the importance of considering the patient perspective in selecting maintenance inhalers.

information about the patients' willingness to make trade-offs among the attributes.⁶ In DCEs, respondents complete a series of questions in which they must choose between two treatments where there is a trade-off, for example, between efficacy and safety. In this way, the relative value of each treatment attribute can be discerned. DCEs have indicated that patients with asthma or COPD most value an inhaled therapy's efficacy and safety, in addition to its ability to be used as a reliever medication, its convenience, an accurate dose counter, and low cost.^{7–10}

Choosing an appropriate inhaler for patients has become more complex as the number of maintenance inhalers available has increased. This study used a DCE to establish which attributes of currently available ICS/LABA and LAMA/LABA combination inhalers are most valued by patients with symptomatic asthma or COPD, how willing they are to exchange one attribute for another, and how their choices are influenced by their disease status. It was a priori expected that patients with COPD place more weight on attributes related to treatment effectiveness and patients with asthma place more weight on attributes related to treatment convenience.

METHODS

Overall study design

Following an initial literature review to identify relevant attributes of maintenance inhalers, focus groups were held separately for patients with asthma and COPD, to determine patient-generated positive and negative features of these treatments and to assess the relevance and appropriateness of the identified attributes to the burden of obstructive lung disease. Attributes previously reported in the literature but not spontaneously

brought up by the patients were used to facilitate discussion during focus groups. A qualitative analysis of the information collected from the focus groups, along with consultation with clinical experts, was then used to select eight maintenance inhaler attributes to be included in a DCE. The DCE was pretested in a pilot study to refine the questionnaire and ensure that the selected attributes were meaningful to the patients.

Participants

Patients with asthma or COPD included in a patient database of a recruitment agency (focus groups and pilot interviews) and in eight online access panels (main survey) were invited to participate by email or telephone. All participants had to be living in the USA and be able to speak, read, write, and understand English. Patients with asthma had to be aged ≥ 18 years with self-reported asthma and taking an ICS/LABA inhaler for at least 12 weeks. Patients with COPD had to be aged ≥ 40 years with self-reported COPD and taking a maintenance inhaler to treat COPD for at least 12 weeks. Patients with COPD were required to be symptomatic (COPD Assessment Test (CAT) score ≥ 10) or have had at least two exacerbations or one COPD-related hospitalisation in the past 12 months. Patients with COPD also had to be current or past smokers with a ≥ 10 pack-year history. Participants were excluded if they had a concurrent diagnosis of asthma and COPD. Patients with COPD were excluded from the pilot interviews and main survey if receiving triple therapy (ie, ICS/LABA+LAMA or ICS+LABA/LAMA) because fixed-dose combination triple therapies were not approved for use in the US at the time of this study.

Patients were compensated US\$150 for participating in a focus group and US\$100 for participating in an interview. Patients recruited from the access panels were compensated US\$1.50–US\$7.00 in accordance with a standing agreement with the online access panel.

Focus groups

Separate focus groups for asthma ($n=15$) and COPD ($n=22$) were conducted in person in Dallas, Texas and Chicago, Illinois. Focus groups were conducted with the help of a semi-structured interview guide that focused on patients' experiences with maintenance medications. An audio recording was made for transcription and qualitative analysis. Responses were used to determine which key issues patients were concerned with regarding the benefit, risks and other treatment attributes for maintenance therapy, and which potential attributes were appropriate and relevant. Narrative data were coded by two trained coders using a custom coding dictionary and analysed using ATLAS.ti V.7.5.9 (Scientific Software Development, Berlin, Germany). A third coder was consulted to resolve any disagreements.

Qualitative pilot study

A qualitative pilot study was conducted online and by telephone using a semi-structured interview guide to ensure that patients could understand information in the DCE survey, including the attribute and level definitions, and that the burden of completing the survey was acceptable. An iterative process with two sets of five individual interviews each for asthma and COPD was used to refine the wording and organisation of the DCE questionnaire. Each interview lasted approximately 60 min and was audio recorded.

Main study

At least 800 participants with asthma and 1250 with COPD were to be recruited to complete the DCE. Sample sizes were selected to obtain a sufficient representation of 150 patients using each of the different maintenance inhalers available, included as a recruitment quota. In addition, quotas were included to have $\geq 40\%$ of each sex, $\geq 40\%$ of patients with COPD within each of the <65 and ≥ 65 years age ranges, and $\geq 30\%$ of patients with

asthma in each of the 18–34, 35–64 and ≥ 65 years age ranges. Due to difficulty in meeting all recruitment quotas, the quotas were relaxed towards end of the recruitment period after an investigator review of the sufficient number of patients needed to complete the DCE for the relevant subgroups.

Discrete choice experiments

Two DCEs, one for asthma and one for COPD, were administered as online surveys. Each consisted of 14 questions addressing maintenance inhaler attributes related to efficacy (onset of action and exacerbations per year), safety (5-year risk of osteoporosis) and non-clinical features (device type, dosing frequency, dose counters and priming). The COPD DCE also included an additional safety attribute, 5-year risk of pneumonia, because of concerns about a possible increased risk of pneumonia in patients with COPD treated with ICS.¹¹

Each attribute had two to four levels that were determined based on asthma and COPD treatment product characteristics, clinical expert feedback and a review of clinical data sources, published studies on patient perceptions and preference studies. An example question is shown in figure 1. To assess whether patients understood the discrete choice task presented in the questions and were responding appropriately to the choices, the DCE included a repeated question and a dominated-choice question (online supplementary figure 1), in which one of the medication choices was superior. For each participant, the order of attributes, choices and DCE questions were randomised, although for each participant, the attributes were presented in the same order within their survey.

Eligible participants were provided a brief description of the study's purpose, instructions on how to complete the DCE questions and descriptions of the treatment attributes and levels. Patients with asthma completed the Asthma Control Questionnaire (ACQ),¹² and patients with COPD completed the CAT.¹³ Before starting the online survey, participants completed a practice question. After completing the DCE, participants responded to a three-item subjective self-reported questionnaire to assess health literacy (Chew's Set of Brief Screening Questions)¹⁴ and responded to a subset of items from the Numeracy Scale¹⁵ to ensure that they would be able to understand medical information and probabilities presented in the survey.

DCE data were analysed by estimating marginal utility values, which express preferences for changes in attributes using multinomial logit models (see online supplementary material). Given the ordinal nature of attributes, the interpretation of marginal utilities should be limited to significance and direction of the effect (ie, positive valuation vs negative valuation). To provide more detailed insight into patient preferences, three

	Treatment A	Treatment B
Priming	Need to discharge test doses on first use. 1 simple step to get dose ready	1 or 2 simple steps to get dose ready
5-year risk of pneumonia	10% (10 out of 100 patients)	20% (20 out of 100 patients)
Dose counter	Every 10 doses	Metered dose counter
Onset of action	5 minutes	20 minutes
Device type	Pressurised inhaler	Soft mist inhaler
Number of exacerbations	3 exacerbations in a year	2 exacerbations in a year
5-year risk of osteoporosis	5% (5 out of 100 patients)	6% (6 out of 100 patients)
Dosing frequency	Twice daily	Once daily

Figure 1 Example discrete choice experiment question.

behavioural output measures were derived from the estimated marginal utilities: (i) relative attribute importance (RI) scores, which measure the share of variation in utility that can be explained by each attribute; (ii) maximum acceptable onset (MAO) of action, which measures trade-offs that patients are willing to make between improvements in other attributes and slower onset of action; and (iii) maximum acceptable exacerbations (MAE), which measures trade-offs that patients are willing to make between improvements in other attributes and average increase in yearly number of exacerbations.

Data were analysed separately according to patient diagnosis (asthma or COPD) and severity category ($ACQ \leq 0.75$, >0.75 to <1.5 , and ≥ 1.5 for asthma; $CAT \leq 20$, >20 to ≤ 30 , and >30 for COPD). Additional analyses were conducted to understand effects of age, sex and education level on patient preferences, while controlling for disease severity. Only fully completed surveys were included in the analysis. Stata V.15 (StataCorp, College Station, Texas, USA), R V.3.4 (R Foundation for Statistical Computing, Vienna, Austria) and Matlab V.R2017b (MathWorks, Natick, Massachusetts, USA) were used for the analyses. All statistical tests were two-sided and used a significance level of 0.05. SEs of RI, MAE and MAO were estimated using the delta method.

The internal validity of the DCE was assessed by measuring the time to complete the survey and the proportions of participants correctly answering the dominance test, correctly answering the repeated question, always choosing option A or B and always choosing the better alternative on one attribute (see online supplementary material). To avoid selection bias, no participants were excluded from the analysis based on their answers to internal validity assessments.^{16 17}

RESULTS

Participants

The DCEs were completed by 810 patients with asthma and 1147 patients with COPD between May 30 and October 1, 2018 (figure 2). This includes the last seven patients who completed the qualitative pilot interviews because no significant changes were made to the survey afterwards. In both the asthma and COPD patient groups, most respondents were female (62% asthma, 57% COPD ($p=0.06$ for sex)) and white (76% for asthma, 87% for COPD), although patients with asthma were more often non-white than patients with COPD ($p<0.0001$) (table 1). The median age was 47 years for patients with asthma and 59 years for patients with COPD ($p<0.0001$ for mean age and age category). Compared with patients with COPD, patients with asthma more often were employed (34% vs 57%; $p<0.0001$ for overall employment status), had college education (72% vs 80%; $p<0.0001$ for overall educational status) and were married or living with a significant other (59% vs 62% asthma; $p<0.0001$ for overall current living/domestic situation). Most participants had high literacy (85% ($n=1662$)) and numeracy (88% ($n=1729$)) (online supplementary table 2).

Only 27% of patients with asthma were considered wellcontrolled (ACQ score ≤ 0.75)¹² (table 2). Most patients with COPD (99%) had a CAT score ≥ 10 (median, 26), indicating at least a medium impact of symptoms.¹³ All patients with asthma were taking an ICS/LABA maintenance inhaler. For patients with COPD, the most common maintenance inhaler type was ICS/ LABA (52%), followed by LAMA or LABA (29%) and LAMA/LABA (21%).

Patient preferences for treatment attributes

Patients with asthma most valued a decrease in medication onset of action from 30 to 5 min ($RI=0.33$), followed by a reduction in yearly exacerbations from 3 to 1 ($RI=0.21$), whereas patients with COPD most and equally valued a decrease in medication onset of action from 30 to 5 min ($RI=0.28$) and a reduction in yearly exacerbations from 3 to 1 ($RI=0.27$) (figure 3, online supplementary table 3). Overall, a faster onset of action and a reduction in yearly

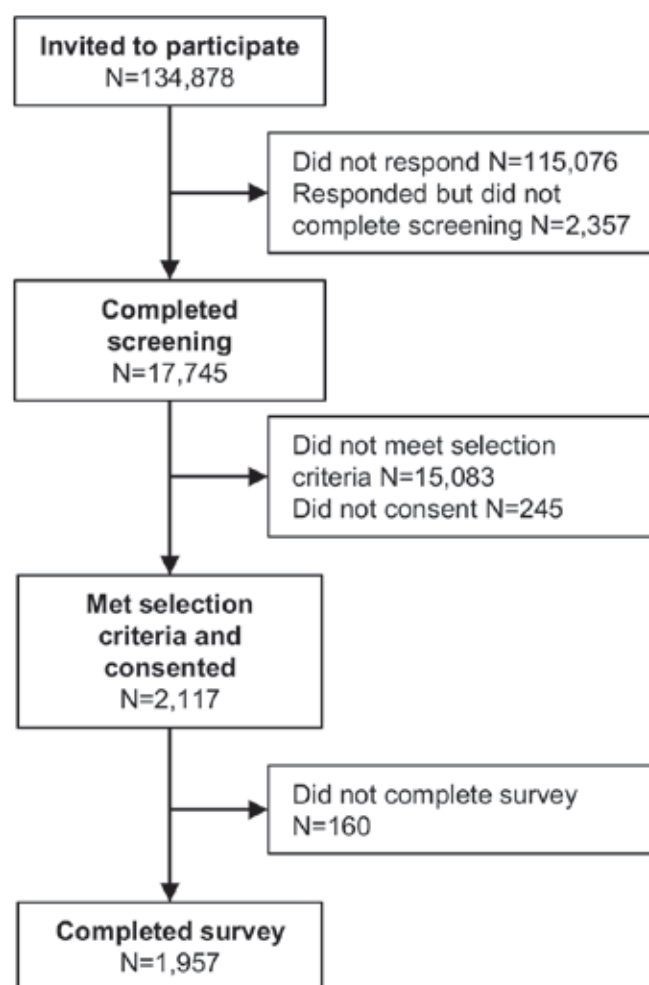


Figure 2 Disposition of participants in the main study.

exacerbations were more highly valued than all other attributes. Both patients with asthma and patients with COPD also valued a decrease in the risk of treatment side effects (for asthma, marginal utility=0.21 (95% CI 0.15 to 0.27) for decreasing 5-year risk of osteoporosis from 6% to 5%; for COPD, marginal utility=0.21 (95% CI 0.15 to 0.26) for decreasing 5-year risk of osteoporosis from 6% to 5%; for COPD, marginal utility=0.27 (95% CI 0.21 to 0.32) for decreasing 5-year risk of pneumonia from 20% to 15%). In addition, patients with asthma and COPD valued pressurised inhalers over dry powder inhalers (marginal utility=0.34 (95% CI 0.28 to 0.41) for asthma and 0.16 (95% CI 0.11 to 0.21) for COPD), once-daily over twice-daily dosing (marginal utility=0.15 (95% CI 0.10 to 0.20) for asthma and 0.21 (95% CI 0.16 to 0.25) for COPD), and non-capsule priming methods over single-use capsules (marginal utility range, 0.36–0.40 for asthma and 0.20–0.32 for COPD). Most patients valued a dose counter that counts every dose over a metered dose counter (marginal utility=0.08 (95% CI 0.02 to 0.15) for asthma and 0.07 (95% CI 0.02 to 0.13) for COPD). Patients with COPD valued a metered dose counter over one that counts every 10 doses (marginal utility=−0.13 (95% CI −0.18 to −0.08)), whereas patients with asthma did not distinguish between the two dose counter types (marginal utility=0.03 (95% CI −0.03 to 0.10)).

Willingness of patients to make trade-offs between attributes

Patient willingness to make trade-offs was assessed by estimating maximal acceptable time to onset of action and maximal acceptable yearly exacerbations (table 3, online supplementary tables 3 and 4), the two most valued inhaler attributes. Both patients with asthma and patients with COPD were willing to accept one extra exacerbation per year in exchange for a 15

Table 1 Demographic characteristics of participants

Characteristic	Asthma (n=810)	COPD (n=1147)	P value*
Sex, n (%)			0.0600
Male	310 (38)	488 (43)	
Female	500 (62)	659 (57)	
Age (years), median (IQR)	47 (35 to 61)	59 (52 to 67)	<0.0001
Age group (years), n (%)			<0.0001
18–34	201 (25)	0 (0)	
35–64	441 (54)	780 (68)	
≥65	168 (21)	367 (32)	
Racial background, n (%)			<0.0001
White	618 (76)	996 (87)	
Black	100 (12)	90 (8)	
Asian	21 (3)	15 (1)	
Hispanic	25 (3)	22 (2)	
Other	46 (6)	24 (2)	
Employment status, n (%)			<0.0001
Employed, full-time	384 (47)	330 (29)	
Employed, part-time	80 (10)	61 (5)	
Homemaker	73 (9)	73 (6)	
Student	13 (2)	1 (0)	
Unemployed	31 (4)	35 (3)	
Retired	169 (21)	415 (36)	
Disabled	58 (7)	222 (19)	
Other	2 (0)	10 (1)	
Education, n (%)			<0.0001
Elementary/primary school	12 (1)	6 (1)	
Secondary/high school	140 (17)	308 (27)	
Some college	244 (30)	380 (33)	
College degree	264 (33)	314 (27)	
Postgraduate degree	144 (18)	128 (11)	
Other	6 (1)	11 (1)	
Current living/domestic situation, n (%)			<0.0001
Married/living with significant other	504 (62)	680 (59)	
Divorced/separated	108 (13)	215 (19)	
Widow	29 (4)	129 (11)	
Single	166 (20)	119 (10)	
Other	3 (0)	4 (0)	

*P values were calculated by χ^2 test for categorical variables and by analysis of variance for continuous variables.

min faster onset of action. For example, for a decrease in onset from 30 to 15 min, patients with asthma were willing to accept on average 1.8 more exacerbations per year and patients with COPD were willing to accept on average 1.4 more exacerbations per year. In exchange for decreasing the onset of action from 30 to 5 min, patients with asthma were willing to accept a greater increase in the yearly rate of exacerbations (on average 3.1 per year) than patients with COPD (on average 2.1 per year).

Patients with asthma were more willing than patients with COPD to accept a slower onset of action (10.8 min for asthma vs 7.1 min for COPD) in exchange for a reduced 5-year risk of osteoporosis from 6% to 4%, and they were willing to accept one extra exacerbation for a similar reduction in 5-year risk of osteoporosis. Patients with COPD were willing to accept a 13.5 min slower onset of action to reduce the 5-year risk of pneumonia from 20% to 10%. They were also willing to accept one extra exacerbation per year in exchange for this 10% reduction in the 5-year risk of pneumonia.

To obtain a pressurised inhaler instead of a dry powder inhaler, patients with asthma were more willing than patients with COPD to accept slower onset of action (8.1 min for asthma vs 3.6 min for COPD). In exchange for once-daily instead of twice-daily dosing, patients with asthma were willing to accept a 3.6 min slower onset of action, whereas patients with COPD were willing to accept a 4.6 min slower onset.

Impact of disease status on patient preferences

Patients with inadequately controlled asthma (ACQ score ≥ 1.5) considered faster onset of action (RI=0.39) to be more impor-

Table 2 Disease severity and current medications

Characteristic	Asthma (n=810)	COPD (n=1147)
ACQ score median, n (%)	1.3 (1.0 to 2.0)	
ACQ score category†, n (%)		
≤0.75 (well-controlled)	219 (27)	
0.75–1.5	195 (24)	
≥1.5 (inadequately controlled)	396 (49)	
CAT score‡, median (IQR)	-	26 (20 to 32)
CAT score category§, n (%)		
1–9 (low impact)	-	11 (1)
10–20 (medium impact)	-	323 (28)
21–30 (high impact)	-	476 (4)
31–40 (very high impact)	-	337 (29)
Current asthma medication, n (%)		
Budesonide/formoterol (Symbicort) (any dose)	263 (32)	
80/4.5 HFA	136 (17)	
160/4.5 HFA	127 (16)	
Fluticasone/salmeterol (Advair HFA or Advair Diskus) (any dose)	429 (53)	
115/21 HFA	113 (14)	
230/21 HFA	80 (10)	
250/50 Diskus	203 (25)	
500/50 Diskus	33 (4)	
Mometasone/formoterol (Dulera) (any dose)	48 (6)	
100/25 HFA	26 (3)	
200/25 HFA	22 (3)	
Fluticasone/vilanterol (Breo) (any dose)	136 (17)	
100/25 Ellipta	70 (9)	
200/25 Ellipta	66 (8)	
Current COPD medication, n (%)		
LAMA or LABA	-	337 (29)
Umeclidinium (Incruse Ellipta)	-	31 (3)
Tiotropium (Spiriva)	-	274 (24)
Olodaterol (Striverdi Respimat)	-	11 (1)
Acclidinium (Tudorza Pressair)	-	19 (2)
ICS/LABA	-	593 (52)
Budesonide/formoterol (Symbicort HFA)	-	263 (23)
Fluticasone/salmeterol (Advair Diskus)	-	295 (26)
Fluticasone/vilanterol (Breo Ellipta)	-	87 (8)
LAMA/LABA	-	236 (21)
Glycopyrrolate/formoterol (Bevespi Aerosphere)	-	34 (3)
Umeclidinium/vilanterol (Anoro Ellipta)	-	134 (12)
Tiotropium/olodaterol (Stiolto Respimat)	-	65 (6)
Glycopyrrolate/indacaterol (Utibron Neohaler)	-	17 (1)

*Average from seven questions, each scored from 0 (no impairment) to 6 (maximum impairment).

†ACQ categories were defined as described by Juniper *et al.*¹²

‡Sum of eight items scored from 0 (least severe impact on the patient's life) to 5 (most severe impact), resulting in a total score of 0 to 40.

§CAT scores categories were defined as described by Jones *et al.*¹³

ACQ, Asthma Control Questionnaire; CAT, COPD Assessment Test; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

tant than reduced exacerbations (RI=0.19) (figure 4, online supplementary tables 6 and 7). The difference in importance of faster onset of action and reduced exacerbations decreased as asthma control improved. Similarly, patients with COPD whose symptoms had the greatest impact on their health (CAT score >30) considered faster onset of action (RI=0.32) to be more important than a reduction in exacerbations (RI=0.27), whereas patients with the least symptom impact (CAT ≤ 20) considered a reduction in exacerbations (RI=0.27) more important than a faster onset of action (RI=0.20).

Reducing the risk of potential ICS adverse events was more important to patients with better disease status than to patients with worse disease status (for asthma, RI for 5-year risk of osteoporosis=0.18 for ACQ ≤ 0.75 , 0.10 for 0.75<ACQ ≤ 1.5 and 0.13 for ACQ ≥ 1.5 ; for COPD, RI for 5-year risk of pneumonia=0.24 for CAT ≤ 20 , 0.21 for 20<CAT <30 and 0.16 for CAT ≥ 30). Disease status affected preferences of patients with COPD for dosing frequency (marginal utility=0.34 (95% CI 0.25 to 0.43) for CAT ≤ 20 , 0.20 (95% CI 0.13 to 0.27) for 20<CAT <30 and 0.09 (95% CI 0.00 to 0.17) for CAT ≥ 30).

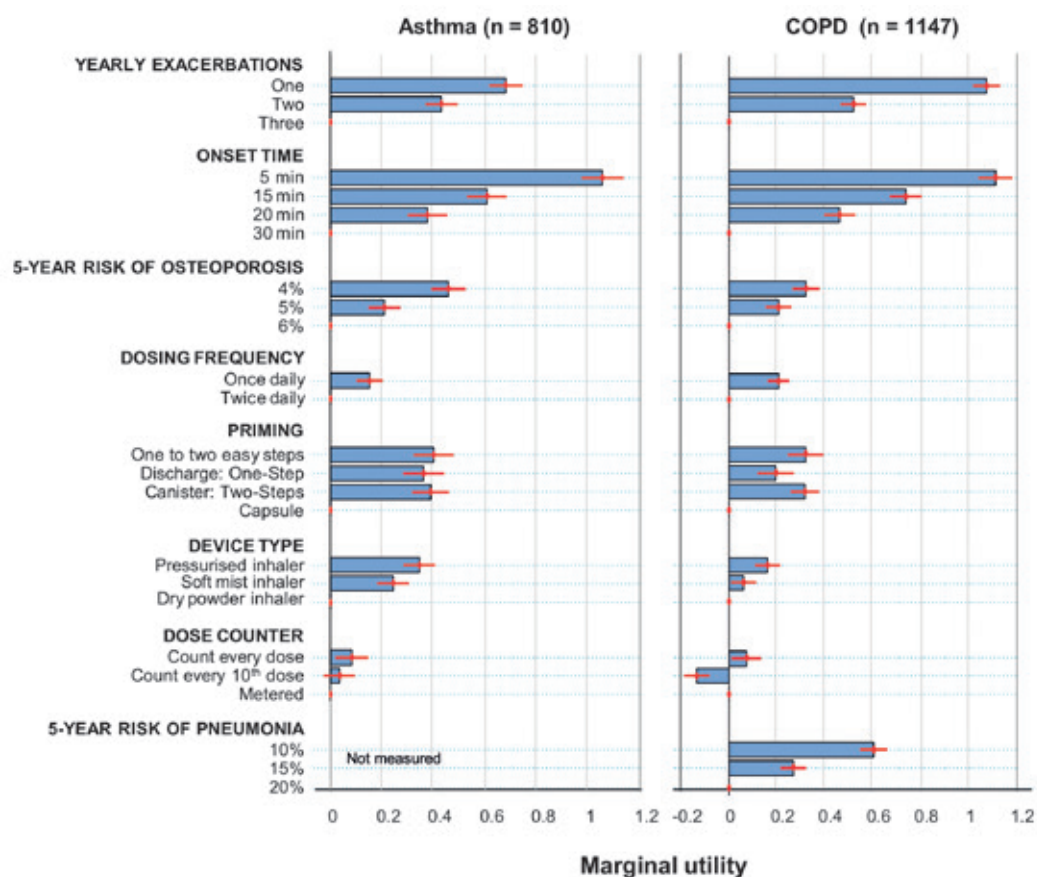


Figure 3 Overall preferences for inhaler attributes. Patient preferences were assessed by calculating marginal utilities, which measure how sensitive the respondents' treatment preference is to changes between reference and non-reference levels of an attribute (see online supplementary table 3 for calculations). Values are means $\pm$ 95% CIs.

Patient preferences were affected by age, sex and education (online supplementary tables 8 and 9). Key findings were that patients with college or postgraduate degrees valued exacerbation reduction and faster onset of action more than patients with less education; females placed more value on exacerbation reduction than males; and patients with asthma aged ≥ 65 years valued a dose counter that counts every dose more than those aged < 65 years.

Internal validity of the DCE

Of the 1957 participants, 88% (n=1731) answered the dominated choice question correctly and 79% (n=1547) answered the repeated question correctly (online supplementary table 2). The dominated-choice question was incorrectly answered by 8% (n=93) of patients with COPD and 16% (n=133) of patients with asthma. Fewer than one in five participants (19% (n=364)) always chose the treatment for which one specific attribute had the most desirable level (eg, they always chose the treatment with the faster onset of action). The dominated-choice question was answered incorrectly by 33% of participants with low literacy and 41% with low numeracy but by only 8% of participants with high literacy and 8% with high numeracy.

DISCUSSION

DCE experiments conducted over the last decade have provided some information about which maintenance inhaler attributes are most valued by patients. Key inhaler attributes have included more symptom-free days,⁹ fewer adverse events,⁹ one-step dose preparation,¹⁸ ability to be used during breathing difficulties,¹⁸ dose counter accuracy,¹⁸ symptom control/not being disturbed during sleep,^{10,18} and low cost.¹⁰ However, the availability of new inhaled therapies and inhaler devices has made choosing an appropriate inhaler for patients more complicated. Furthermore, these studies have not examined the willingness of patients to

trade-off between longer onset of action or additional exacerbations and improvements in other inhaler attributes.

This study, conducted in the USA in 2018, examined the relative importance of eight key maintenance inhaler attributes, including medication time to onset of action, number of exacerbations per year, risk of osteoporosis, risk of pneumonia (for COPD), dosing frequency, priming, device type, and dose counter. To capture the patient perspective, these attributes were selected from a previous patient focus group, coupled with a literature search and expert clinical advice.

Of the attributes examined, patients with symptomatic asthma or COPD most valued faster onset of action and reduced number of exacerbations. Both patients with asthma and patients with COPD were willing to accept increases in the rate of exacerbations in exchange for a faster onset of action, although patients with asthma appeared more willing than patients with COPD to make this exchange. Although patients valued these less than a faster onset of action and reduced exacerbations, both patients with asthma and patients with COPD valued a decrease in the risk of treatment side effects, pressurised over dry powder inhalers, once-daily over twice-daily dosing, more precise dose counters and non-capsule priming methods over single-use capsules. The study further found that disease status strongly influenced patient preferences: patients with more severe disease placed increased importance on a faster onset over a reduction in exacerbations.

Several assessments indicated internal validity of the data and adequate attention to the questions. In addition, efforts were made to include patients using all types of maintenance inhalers and with all relevant disease severities. Furthermore, the study was built to specifically capture patient preferences rather than healthcare providers' expectations. Nonetheless, the study had some important limitations. Patient choices in hypothetical settings may not fully correspond to choices in real

Table 3 Maximum acceptable exacerbations and maximal acceptable onset time by disease

Attribute		Maximum acceptable exacerbations		Maximum acceptable onset time	
		Mean (95% CI)*		Mean (95% CI)†	
		Asthma (n=810)	COPD (n=1147)	Asthma (n=810)	COPD (n=1147)
Number of exacerbations	3 per year	—	—	Reference	Reference
	2 per year	—	—	10.1 (8.6 to 11.7) min	11.6 (10.3 to 12.9) min
	1 per year	—	—	16.0 (14.2 to 17.7) min	24.0 (22.3 to 25.7) min
Onset of action	30 min	Reference	Reference	—	—
	20 min	1.1 (0.85 to 1.3) per year	0.9 (0.7 to 1.0) per year	—	—
	15 min	1.8 (1.5 to 2.0) per year	1.4 (1.2 to 1.5) per year	—	—
	5 min	3.1 (2.7 to 3.4) per year	2.1 (1.9 to 2.2) per year	—	—
5-year risk of osteoporosis	6%	Reference	Reference	Reference	Reference
	5%	0.6 (0.4 to 0.8) per year	0.4 (0.3 to 0.5) per year	4.9 (3.5 to 6.4) min	4.5 (3.4 to 5.7) min
	4%	1.3 (1.1 to 1.5) per year	0.6 (0.5 to 0.7) per year	10.8 (9.2 to 12.4) min	7.1 (5.9 to 8.4) min
Dosing frequency	Twice daily	Reference	Reference	Reference	Reference
	Once daily	0.4 (0.3 to 0.6) per year	0.4 (0.3 to 0.5) per year	3.6 (2.4 to 4.8) min	4.6 (3.6 to 5.6) min
Priming	New capsule each time	Reference	Reference	Reference	Reference
	New canister+one step	1.1 (0.9 to 1.4) per year	0.6 (0.5 to 0.7) per year	9.2 (7.4 to 11.0) min	7.1 (5.7 to 8.4) min
	Discharge+one step	1.05 (0.8 to 1.3) per year	0.4 (0.2 to 0.5) per year	8.5 (6.6 to 10.4) min	4.4 (2.8 to 6.1) min
	One or two simple steps	1.2 (0.9 to 1.4) per year	0.6 (0.5 to 0.7) per year	9.4 (7.5 to 11.3) min	7.2 (5.6 to 8.9) min
Device type	Dry powder inhaler	Reference	Reference	Reference	Reference
	Soft mist inhaler	0.7 (0.5 to 0.9) per year	0.1 (0.0 to 0.2) per year	5.6 (4.1 to 7.1) min	1.4 (0.2 to 2.6) min
	Pressurised inhaler	1.0 (0.8 to 1.2) per year	0.3 (0.2 to 0.4) per year	8.1 (6.5 to 9.6) min	3.6 (2.4 to 4.8) min
Dose counter	Metered dose counter	Reference	Reference	Reference	Reference
	Every 10 doses	0.1 (−0.1 to 0.3) per year	−0.2 (−0.3 to −0.1) per year	0.7 (−0.7 to 2.2) min	−3.0 (−4.2 to −1.8) min
	Every dose	0.2 (0.1 to 0.4) per year	0.1 (0.0 to 0.2) per year	1.9 (0.4 to 3.4) min	1.6 (0.3 to 2.8) min
5-year risk of pneumonia	20%	—	Reference	—	Reference
	15%	—	0.5 (0.4 to 0.6) per year	—	6.0 (4.8 to 7.2) min
	10%	—	1.1 (1.0 to 1.2) per year	—	13.5 (12.2 to 14.9) min

*How many additional exacerbations a respondent was willing to accept for each of the attribute levels, relative to their respective reference level (see online supplementary table 4 for calculations).

†How many extra minutes of onset of action patients were willing to accept for each of the attribute levels, relative to their respective reference level (see online supplementary table 5 for calculations).

life, although recent research has shown that DCEs are able to predict choices.¹⁹ As with all surveys, DCEs are subject to framing and presentation effects.²⁰ The study therefore followed conventional presentation formats and adhered to design guidelines, and the framing and presentation format of the DCE were tested in a qualitative pilot.²¹ Like other patient preference studies, we did not examine the relationship between patient preferences and treatment adherence.²² Another limitation is that clinical and sociodemographic characteristics were self-reported, although this is not expected to affect the conclusions. To limit the duration of the survey, we did not collect information on all possible variables, for example, we did not include questions on exacerbation history or LAMA add-on use in the asthma survey. Furthermore, the DCE study was limited to US patients registered in online access panels; the results may not be transferrable to patient populations in other countries or with different ethnical compositions. The asthma and COPD patient samples in this study were representative of US patient populations in terms of sex,²³ and the COPD patient sample was representative in terms of ICS use,^{24 25} although 43% had a college degree, which is higher than the US average of 33.4% in 2016.²⁶ Finally, to provide results relevant to prescribing clinicians, this study did not analyse the role of factors other than disease status in preference heterogeneity. Future analyses should address whether disease status is a key driver of differences and whether other factors such as pneumonia history, use of psychoanaleptics or experience with different inhalers independently affect preferences in these patient populations.

The current findings add substantially to the evidence on the preferences of patients with asthma and COPD for treatment attributes. Initial qualitative research indicated that safety and treatment costs are important to patients with asthma or COPD,^{4 5} and more recently, DCEs have indicated that patients with asthma and COPD highly value efficacy and safety and other attributes of inhaled treatments, such as use as rescue medication, convenience, rapid onset of action, accuracy of dose counter, and low cost.^{8–10 18} The current study was the largest DCE to date to explore preferences of patients with asthma

and COPD for attributes of inhaled therapies, the first to consider adverse events due to long-term ICS use and one of the few to examine the influence of disease severity on preferences. The study also assessed device characteristics in greater detail than previous DCEs.

A potential limitation of this study is that it did not include nebulisers because most of the inhaler device attributes are difficult to measure for nebulisers. Thus, understanding why some patients prefer nebulisers over inhalers would require a different study design. Also, as per GINA¹ and GOLD,² nebulisers are not the preferred choice for the general obstructive lung disease population. Another potential limitation is that cost was not included as an attribute in the DCE. Although focus group interviews indicated that patients care about out-of-pocket costs, cost was not included as an attribute because the study focused on clinical and inhaler attributes of maintenance medications and because out-of-pocket costs in the USA vary according to each patient's insurance scheme.

The current study suggested that patients with asthma or COPD would prefer treatments with a faster onset of action, greater exacerbation reduction and containing an ICS with a lower risk of osteoporosis and pneumonia. This information can be helpful to payers and policy makers who must decide which maintenance inhalers to recommend and reimburse. Many prescription plans in the USA already offer patients a choice, and practising providers have options for peer-to-peer conversations with insurers to ensure that medical provider and patient views are considered in coverage decisions. The results also highlight the importance of considering the patient perspective in selecting maintenance inhalers, a recommendation also made in treatment guidelines^{1 2} and in a recent review of maintenance inhalers for asthma and COPD.²²

Acknowledgements The authors would like to thank Phillip Ieventhal (evidera) for medical writing; ariane Kawata, nancy leidy and Kevin Marsh (evidera) for helpful suggestions on study design; Jaemin seo (evidera) for support in visualising results; robyn cyr and caitlin Thomas (evidera) for data management; Jill Davis (astraZeneca) for early phase protocol development; Durgesh Bhandary (astraZeneca) for helpful comments on the manuscript and carrie Iancos (astraZeneca) and Kawthar nakayima (evidera) for editorial support. The authors also would like to thank the study participants from the various study phases.

Contributors TT participated in design, planning, conduct, conception and design of the study and in design, analysis and interpretation of data. sh participated in reporting, analysis and interpretation of data. ig participated in planning,

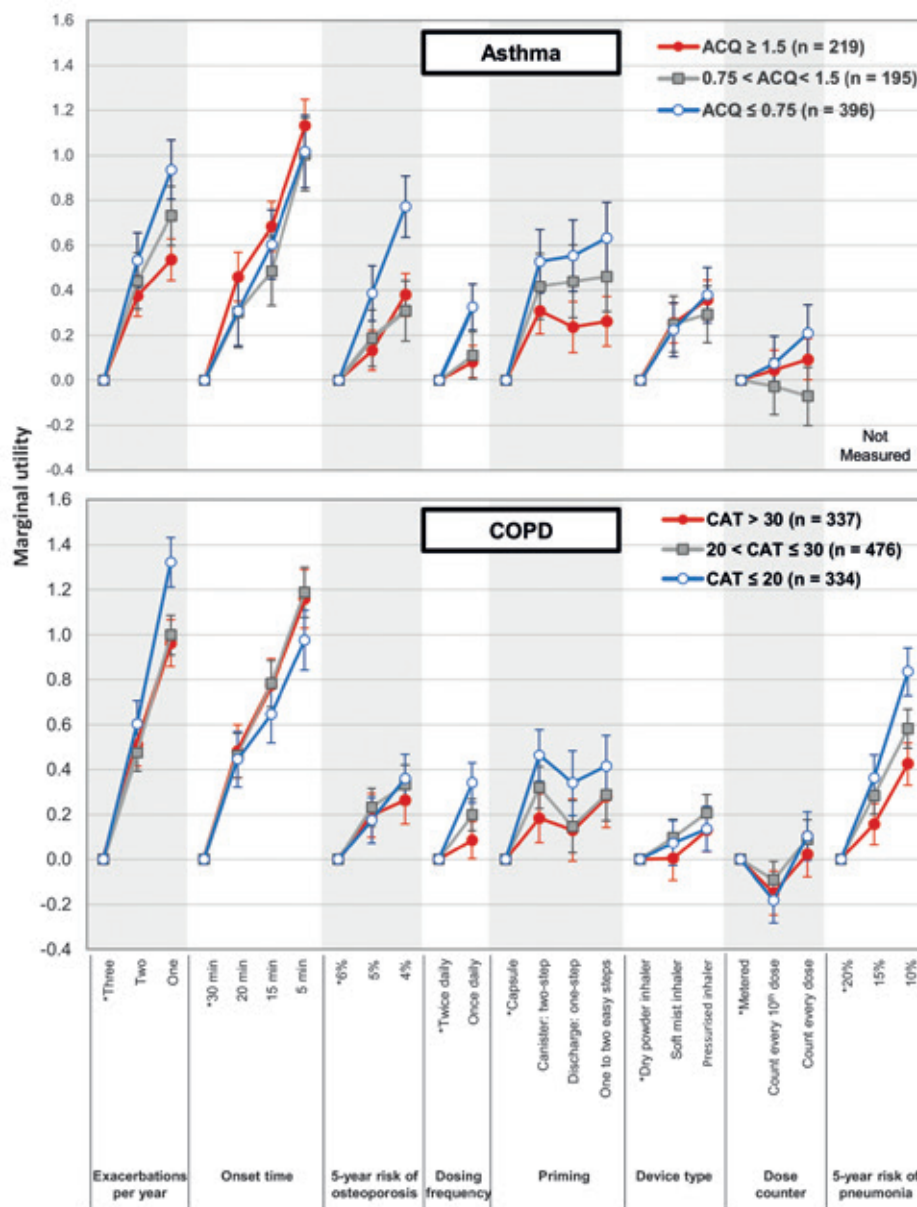


Figure 4 Impact of disease status on patient preferences. Patient preferences were assessed by calculating marginal utilities, which measure how sensitive the respondents' treatment preference is to changes between reference and non-reference levels of an attribute (see online supplementary tables 6 and 7 for calculations). Values are means $\pm$ 95% CIs. Asterisk indicates reference level. ACQ, Asthma Control Questionnaire; CAT, COPD Assessment Test.

conception, design and conduct of the study and in reporting and interpretation of data. nh participated in planning, conduct, design and conception of the study and reporting of data. FJM and nah participated in conception and design of the study and interpretation of data. In addition, all authors wrote, edited or provided significant comments on the manuscript; approved the final version of the manuscript and agreed to be accountable for the manuscript's contents. TT takes responsibility for the content of the manuscript, included the data and analysis.

Funding

AstraZeneca.

Competing interests ig is an employee of astraZeneca, the study sponsor. TT, nh and sh are employees of evidera, which was contracted by astraZeneca to complete work related to this study. nah has received honoraria for serving as an advisor/consultant and research funds (to his institution) from astraZeneca. FJM reports personal fees from adept, afferent, amgen, astraZeneca, axon, axon communication, Boehringer Ingelheim, clarion, concert, Forest, genentech, glaxosmithKline, ikaria/Bellerophon, informa, Janssen, Kadmon, lucid, Methodist hospital, novartis, nycomed/Takeda, Pearl Therapeutics, Pfizer, Prime, roche, sunovion, Theravance, Unity Biotechnology, Veracety and WebMD; royalty fees from informa and has spoken on behalf of astraZeneca and nycomed/Takeda.

Patient consent for publication not required.

Ethics approval astraZeneca institutional review Board (columbia, MD, USA) granted exemption from institutional review board oversight based on Department of health and human services regulations. all participants provided written informed consent in all study phases.

Provenance and peer review not commissioned; externally peer reviewed. data availability statement no data are available. Data not available as no consent was sought from patients to allow sharing of data with third parties.

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Aplicações da inteligência artificial e aprendizagem de máquina na medicina respiratória

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Received 14 January 2020

Revised 19 April 2020

Accepted 22 April 2020

Published Online First

14 May 2020

RESUMO

Nos últimos 5 anos, assistiu-se a uma explosão do interesse na utilização de inteligência artificial (IA) e de técnicas de aprendizagem automática na medicina. Isto tem sido impulsionado pelo desenvolvimento de redes neurais profundas (RNP) - redes complexas in silico, mas vagamente modeladas no cérebro humano - que podem processar dados de entrada complexos, como uma radiografia do tórax, e produzir uma classificação como 'normal' ou 'anormal'. As RNP são 'treinadas' com recurso a extensos bancos de imagens ou outros dados de entrada que receberam a classificação correta. As RNP demonstraram a capacidade de igualar ou mesmo ultrapassar a precisão dos especialistas humanos em tarefas de reconhecimento de padrões, tais como a interpretação de imagens médicas ou sinais biológicos. No âmbito da medicina respiratória, as principais aplicações de IA e de aprendizagem automática até ao momento têm sido a interpretação de imagens torácicas, lâminas de patologia pulmonar e dados fisiológicos, como os testes de função pulmonar. Este artigo analisa o progresso nesta área ao longo dos últimos 5 anos, salientando também as atuais limitações da IA e da aprendizagem automática e o potencial de desenvolvimentos futuros.

INTRODUCTION

'Artificial intelligence (AI)' may be defined as 'the theory and development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages'.¹ Machine learning is a subfield of AI in which statistical models are used to learn patterns from data in order to accomplish a specific task. Machine learning techniques range from simple linear models such as logistic regression and naïve Bayes classifiers to complex neural network models with many thousands of parameters.

The explosion of interest in medical applications of AI during the past 5 years may be attributed to the confluence of two key factors:

1. Deep neural networks (DNNs)

Artificial neural networks (ANNs) are loosely modelled on the human brain and consist of multiple layers of 'neurons' that successively process input data until the output layer is reached. DNNs are a recently developed variant of ANNs that have a large number of intermediate layers (often greater than 10) and process input data in a hierarchical manner, with the first few layers responding to simple low-level features (such as straight lines) and successive layers responding to more abstract high-level features (such as the shape of specific objects).² DNNs are typically used to classify the input data into a number of categories. For instance, a chest radiograph image may be classified as 'normal' or 'abnormal'. DNNs have been accom-

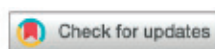
panied by a paradigm shift in AI. In the early years of AI research, the goal was to encode the knowledge of human experts into rule-based 'expert systems' that would be explicitly programmed to look for certain hand-crafted features in the data. However, DNNs are developed using large training datasets and learn in an autonomous manner the features which most discriminate between categories. DNNs therefore have the potential to surpass human experts in classification tasks. Although their accuracy is impressive, a drawback of DNNs is their lack of interpretability. The features that are used to distinguish between data categories are not readily translated into verbal or visual 'rules' that a human can understand.

2. Big data and faster computation

The success of DNNs has been dependent on the availability of large training datasets that have been correctly labelled with the categories to be distinguished, as well as faster computation to train the DNNs within a reasonable timeframe. For example, a system that can distinguish handwritten numerals requires thousands of examples of each numeral to achieve reasonable accuracy. The widespread use of Electronic Health Records (EHR) and Picture Archiving and Communication Systems has resulted in the availability of large training datasets for healthcare applications, subject to appropriate ethical and information governance safeguards.

DNNs have shown equivalent diagnostic accuracy to expert dermatologists at distinguishing between the macroscopic appearance of malignant and benign skin lesions³ and to expert pathologists at detecting breast cancer nodal metastases on histological slides.⁴ DNNs have been successfully applied to retinal images for the detection of diabetic retinopathy and other retinal pathologies,⁵⁻⁸ CT images for the detection of acute intracranial events,⁹ ECGs for the diagnosis of arrhythmias¹⁰ and cardiac contractile dysfunction,¹¹ identification of the facial phenotypes of genetic disorders¹² and interpretation of screening mammography.¹³ Significant progress has also been made in the analysis of EHRs for medical diagnosis¹⁴ and predicting future events such as acute kidney injury.¹⁵ DNNs have shown an ability to detect subtle features that are undetectable by human observers even in hindsight. For instance, Attia *et al*¹⁶ developed a DNN that accurately predicted the presence of atrial fibrillation occurring previously or in the near future using ECGs recorded during sinus rhythm.

This review will focus on the advances that have been made in AI and machine learning as applied to respiratory medicine in the past 5 years. The inputs that have been subjected to machine learning techniques may be broadly categorised into:



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Para citar: Gonem S, Janssens W, Das N, *et al*. Thorax 2020;75:695-701.

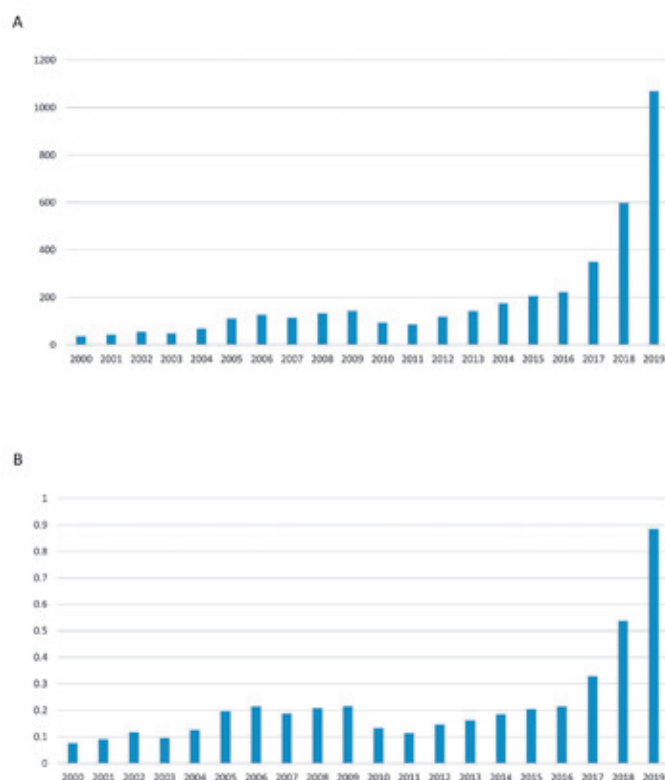


Figure 1 Published articles on artificial intelligence and machine learning in respiratory medicine shown as raw numbers (panel A) and as a percentage of all articles on respiratory medicine (panel B) from 2000 to 2019. Panel A shows the number of retrieved articles on the PubMed database published from 2000 to 2019 using the search terms specified for this review (artificial intelligence related term and respiratory-related term). Panel B shows this number expressed as a percentage of all articles retrieved using just the respiratory-related search terms.

- i. Thoracic imaging.
- ii. Histopathology or cytology.
- iii. Physiological measurements and biosignals.

Search strategy:

The following search was performed on the PubMed database on 19 March 2020: ('artificial intelligence'[All Fields] OR 'machine learning'[All Fields] OR 'deep learning'[All Fields] OR 'neural network'[All Fields]) AND ('chest'[All Fields] OR 'lung'[All Fields] OR 'pulmonary'[All Fields] OR 'respiratory'[All Fields] OR 'thorax'[All Fields] OR 'thoracic'[All Fields] OR 'pneumonia'[All Fields] OR 'pneumonitis'[All Fields] OR 'bronchiectasis'[All Fields] OR 'bronchiolitis'[All Fields] OR 'cystic fibrosis'[All Fields] OR 'tuberculosis'[All Fields] OR 'mycobacteria'[All Fields] OR 'asthma'[All Fields] OR 'copd'[All Fields] OR 'pleural'[All Fields] OR 'sarcoidosis'[All Fields] OR 'sleep'[All Fields] OR 'ventilation'[All Fields]).

A total of 4610 results were returned. All abstracts were reviewed by the first author (SG), and full-text articles were retrieved for papers that described a clinically relevant advance in the field. These papers were reviewed in detail, and examples representing the state of the art in each subfield were selected for inclusion in this narrative review. It was observed that there has been an exponential increase in published papers on this topic starting from 2016 (figure 1).

THORACIC IMAGING

The application of DNNs to chest radiographs and CT scans has resulted in a step change in diagnostic accuracy compared with qualitative semantic features such as tumour spiculation and quantitative features such as shape and texture derived using image analysis software (often referred to as radiomics). The advantage of DNNs is that they derive features directly from the data, resulting in greater accuracy than hand-crafted qualita-

tive or quantitative analyses but with the disadvantage of reduced interpretability. However, some progress has been made towards correlating 'deep features' derived from DNNs with semantic features that are detectable by human radiologists.¹⁷

A number of algorithms have been developed for automated reporting or triage of plain chest radiographs, in many cases exceeding the accuracy of expert thoracic radiologists. Annarumma *et al*¹⁸ trained a DNN to triage chest radiographs as 'normal', 'non-urgent', 'urgent' and 'critical' using a training dataset of 329698 images. The AI system detected normal radiographs with a sensitivity of 71%, specificity of 95% and a positive predictive value of 73% in the test dataset. In a simulated radiology reporting pipeline in which the AI was used to prioritise urgent and critical radiographs for reporting by a radiologist, there was an approximately fourfold reduction in the delay to report radiographs with critical findings and a twofold reduction in the delay to report urgent findings. A similar chest radiograph triage system using a binary classification of 'normal' or 'abnormal' was developed by Yates *et al*,¹⁹ with a final model accuracy of 94.6% in the test dataset. These findings suggest a potentially important role for AI in prioritising cases for review by a radiologist, in order to expedite the reporting of cases with critical abnormalities. This could be particularly relevant in resource-poor settings in which there is a shortage of trained radiologists. AI assessment of chest imaging may also have prognostic significance: Lu *et al*²⁰ developed a DNN that accurately predicted all-cause mortality over a follow-up period of 12 years based on a single plain chest radiograph, even after adjusting for radiologists' diagnostic findings and standard risk factors for mortality.

DNNs have been trained to recognise specific pathologies on chest radiographs including tuberculosis,^{21–24} malignant pulmonary nodules,²⁵ congestive cardiac failure²⁶ and pneumothorax.²⁷ Hwang *et al*²⁸ developed a DNN that could recognise lung cancer, tuberculosis, pneumonia and pneumothorax on chest radiographs as well as providing visual localisation of the abnormality. In a head-to-head comparison using the same test dataset, the DNN achieved an area under the receiver operating curve (AUC; a measure of the accuracy of a diagnostic test) of 0.983, exceeding that of thoracic radiologists (0.932), general radiologists (0.896) and non-radiology physicians (0.614). The same research group subsequently tested this DNN algorithm in an emergency department setting and found that it improved the sensitivity of radiology residents in the detection of clinically significant abnormalities when used as a second reader.²⁹ However, the DNN was not trained to interpret radiographs with multiple pathologies, nor to interpret images in the context of background clinical information. Therefore, while current DNNs cannot replace radiologist reporting of chest radiographs, they may act as a competent second reader to reduce perceptual errors. Prospective studies incorporating DNNs as a second reader in routine clinical practice are warranted to determine whether they can reduce the rate of reporting errors.

Evidence that lung cancer screening can reduce mortality is steadily accumulating, and a recent European Union position statement has concluded that implementation of low-dose CT screening should start throughout Europe as soon as possible.³⁰

An important limiting factor in this implementation is the availability of radiologists to report the large volume of screening CT scans. There has therefore been substantial interest in developing AI systems that can detect and accurately diagnose malignant pulmonary nodules on CT imaging.^{31–35} Ardila *et al*³¹ trained a DNN to predict the risk of lung cancer based on current and previous chest CT scans using cases from the National Lung Cancer Screening Trial. The DNN achieved an AUC of 0.944 for predicting biopsy-proven cancer in the test dataset. The accuracy of the DNN was higher than that of six board-certified radiologists when only the current CT scan was available and was equivalent to the radiologists when both current and

previous CT scans were available for review. Similarly, Baldwin *et al* developed a DNN to predict malignancy in incidentally detected pulmonary nodules measuring 5–15mm and achieved an AUC of 0.896 in the test dataset, which was significantly higher than that of the Brock model currently recommended in UK guidelines.³² In order to improve the interpretability and clinical acceptability of DNN predictions, Shen *et al*³³ merged deep learning techniques with more traditional semantic features such as nodule calcification and margin definition. Incorporating semantic features into DNN predictions did not significantly affect model accuracy but may have improved interpretability of the model output. A number of investigators have taken a hybrid approach, in which radiomic features are entered into machine learning models in order to derive the best combination of features to optimise classification accuracy.^{34,35} Delzell *et al*³⁴ measured 416 quantitative imaging biomarkers in CT scans of pulmonary nodules from 200 patients and entered these radiomic features into a variety of machine learning models. The best performing models were elastic net and support vector machine, which achieved an AUC of 0.72 for distinguishing benign from malignant nodules.

Beyond lung cancer diagnosis, there is evidence that DNNs can be used to predict prognosis and tumour type based on CT images. Hosny *et al*³⁶ trained a DNN to predict survival based on CT appearances in patients with non-small cell lung cancer undergoing surgery or radiotherapy. The DNN distinguished between early (<2 years) and late (≥2 years) mortality with an AUC of 0.71 and 0.70 in patients undergoing surgery and radiotherapy, respectively. Wang *et al*³⁷ found that a DNN could predict epithelial growth factor receptor mutation status in patients with lung adenocarcinoma based on CT images, with an AUC of 0.81 in the validation dataset. The accuracy of the DNN significantly exceeded that of predictive models using clinical features alone, semantic features or radiomics features.

Machine learning techniques have also been used for the diagnosis of interstitial lung disease.^{38,39} Walsh *et al*³⁸ trained a DNN using a total of 420096 montages each consisting of four transverse CT images. These were derived from full high-resolution CT scans of 210 patients with usual interstitial pneumonia (UIP), 392 with possible UIP and 327 whose scans were considered inconsistent with UIP. The reference standard for each CT scan was determined by an experienced thoracic radiologist with a specialist interest in interstitial lung disease. In a test set of 68093 montages derived from 139 separate patients, the algorithm achieved an accuracy of 76.4%. A second test set consisted of 150 four-slice montages from CT scans that had been previously evaluated by 91 thoracic radiologists, with the reference standard being the majority opinion of the radiologists. The algorithm achieved an accuracy of 73.3% in this test set that was comparable with the median accuracy of the individual radiologists (70.7%). Moreover, in a Cox regression analysis, an algorithm diagnosis of UIP was associated with a HR for mortality of 2.88, compared with a diagnosis of 'not UIP', with the equivalent HR for a majority radiologist opinion diagnosis of UIP being 2.74.

González *et al*⁴⁰ trained a DNN using four-slice CT montages from 7983 smokers who took part in the COPDGene study and found that the algorithm could accurately diagnose COPD, with an AUC of 0.856. A subsequent study using the same dataset found that the staging of emphysema from 'absent' to 'advanced destructive' using a DNN was highly predictive of survival and lung function.⁴¹ DNNs have also been developed to diagnose and evaluate the burden of thrombus in acute pulmonary embolism. The algorithm developed by Liu *et al*⁴² achieved an AUC of 0.926 for the diagnosis of pulmonary embolism, and the clot burden measured by the DNN correlated significantly with manual (Qanadli and Mastora) scores and with measures of right ventricular function.

HISTOPATHOLOGY AND CYTOLOGY

Deep learning techniques have been successfully applied to digital histology images, particularly in the field of lung cancer. Coudray *et al*⁴³ found that a DNN could distinguish between adenocarcinoma and squamous cell carcinoma of the lung with comparable accuracy with expert pathologists (AUC of 0.97). This significantly exceeded the performance of traditional image-processing techniques with hand-crafted features, which achieved an AUC of approximately 0.75 for the same task.⁴⁴ Moreover, the DNN could also predict the presence or absence of six common gene mutations of therapeutic significance (STK11, EGFR, FAT1, SETBP1, KRAS and TP53) with AUC values ranging from 0.73 to 0.86. Similarly, Sha *et al*⁴⁵ trained a DNN to predict programmed death-ligand 1 status in non-small cell lung cancer based on morphological appearances on standard H&E stained tumour sections, with an AUC of 0.80. DNNs have also been trained to accurately differentiate between lung adenocarcinoma growth patterns (acinar, micropapillary, solid, lepidic and cribriform),^{46,47} as well as to detect lung cancer metastases in lymph node slides.⁴⁸ Courtiol *et al*⁴⁹ trained a DNN (MesoNet) to accurately predict overall survival of patients with malignant mesothelioma based on whole slide digitised images. The predictions made by MesoNet cut across traditional histological boundaries (such as epithelioid, sarcomatoid and biphasic) and moreover identified the specific regions within the slides that most contributed to patient outcome prediction.

Kim *et al*⁵⁰ used machine learning methods (support vector machines and penalised logistic regression) to develop classifiers for interstitial lung diseases based on high-dimensional transcriptional data from surgical lung biopsies. In a subsequent prospective study, the investigators found that the molecular classifier they developed could accurately distinguish between UIP and non-UIP in less invasive transbronchial biopsy samples, suggesting that the technique could avoid the need for surgical biopsy in some cases.⁵¹

Xiong *et al*⁵² trained a DNN to recognise acid fast-stained *Mycobacterium tuberculosis* bacilli on digital cytology slides. The small size of the bacilli (20×4 pixels) and the loss of resolution when scanning the digital images resulted in some technical challenges. Although good sensitivity of 98% was achieved following modifications to the algorithm, there were a number of false positive results due to contaminant bacilli and slide artefacts, resulting in a specificity of 84%.

PHYSIOLOGICAL MEASUREMENTS AND BIOSIGNALS

Interpretation of pulmonary function tests including spirometry, body plethysmography and measurement of diffusing capacity has traditionally been considered an important aspect of the expertise of respiratory physicians. Topalovic *et al*⁵³ developed a random forest machine learning model using 1430 historical cases that could accurately differentiate between eight categories of respiratory disease. In a head-to-head comparison using 50 test cases, the model displayed an accuracy of 82% and outperformed 120 European pulmonologists by a wide margin.

Machine learning approaches have also been applied to the forced oscillation technique (FOT), which measures respiratory impedance non-invasively using sound waves, with minimal effort from the subject.⁵⁴ Amaral *et al*⁵⁵ applied a variety of machine learning models (including K nearest neighbour, decision trees, ANNs and support vector machines) to FOT measurements to detect COPD (AUC >0.95) to discriminate between different Global initiative for Obstructive Lung Disease stages of airflow obstruction⁵⁶ and to identify early smoking-induced changes in healthy subjects,⁵⁷ as well as to identify airflow obstruction in patients with asthma.⁵⁸

Breath analysis offers excellent potential to phenotype respiratory disorders because exhaled breath contains a mixture of gases and traces of many volatile organic compounds (VOCs)

that emanate from the respiratory tract itself. Several techniques exist to measure VOCs in the breath, such as gas chromatography–mass spectroscopy, electronic nose and chemical sensors, each of which require advanced pattern recognition methods to identify abnormal signatures in measured VOCs.⁵⁹ Machine learning methods such as decision trees and support vector machines on VOC data have been used to discriminate COPD and healthy individuals⁶⁰ and to detect lung cancer.⁶¹ Brinkman *et al*⁶² used an electronic nose to classify inflammatory asthma phenotypes using K-means and Ward clustering. These unsupervised learning techniques do not rely on prelabelling but instead group the cases into novel categories or clusters based on similarity of exhaled breath metabolites.

Computerised lung sound analysis involves discriminating between normal and adventitious lung sounds obtained during auscultation. Although machine learning has become a standard method to classify adventitious sounds, these sound events are intermittent and highly variable from one person to another presenting a challenge in generalising these algorithms to a general population.⁶³ Machine learning approaches (including ANNs and support vector machines) have been applied to classify adventitious sounds associated with asthma,⁶⁴ COPD⁶⁵ and interstitial lung disease⁶⁶ and to detect common respiratory disorders in children using cough sounds.⁶⁷ Bardou *et al*⁶⁸ found that DNNs outperformed traditional machine learning techniques in the classification of lung sounds into seven categories (normal, coarse crackle, fine crackle, monophonic wheeze, polyphonic wheeze, squawk and stridor).

Analysis of biosignals using machine learning may permit a superior understanding of the dynamics of physiological regulation in health and disease. Examples of biosignal monitoring in the respiratory sphere include polysomnography, which is used to diagnose obstructive sleep apnoea and other sleep disorders. Nikkonen *et al*⁶⁹ developed an ANN that accurately determined the oxygen desaturation index (ODI) and apnoea–hypopnoea index (AHI) using only the oxygen saturation signal as input. The median absolute error was 0.78 events/hour for AHI and 0.68 events/hour for ODI, using manual scoring of events as the gold standard. Allocca *et al*⁷⁰ developed an automated sleep-stage classification programme that achieved high accuracy against a gold standard of manual visual scoring in human, rodent and pigeon polysomnography data. Mousavi *et al*⁷¹ developed a DNN to annotate various sleep stages using an openly accessible electroencephalogram (EEG) dataset, achieving an accuracy of 84%. Automated monitoring of biosignals has also been proposed as a solution to patient-ventilator asynchrony, which is a mismatch between ventilator delivery and patient demand. Gholami *et al*⁷² developed a random forest machine learning model to detect cycling asynchrony based on waveform analysis with positive and negative predictive values above 90%.

As the use of smartphones, sensors and wearables proliferates, telemedicine may become an important tool for the self-management of respiratory disorders. By monitoring clinical outcomes at an individual level, such technologies facilitate preventive and pre-emptive care while providing medical expertise remotely. Machine learning offers a powerful solution to analyse patterns associated with respiratory outcomes in data collected by telemonitoring devices.⁷³ Machine learning methods such as naïve Bayes classifiers and support vector machines have been applied to home peak expiratory flow measurements and symptom scores to predict exacerbations a week early in adults⁷⁴ and children⁷⁵ with asthma. Similar studies have also been published to predict exacerbations in patients with COPD.^{76–77}

CONCLUSION AND FUTURE DEVELOPMENTS

Research into AI in medicine has accelerated markedly since 2015, with the field of respiratory medicine being well represented. DNNs are emerging as a key tool to develop imaging biomarkers for diagnosis, prognosis and prediction of res-

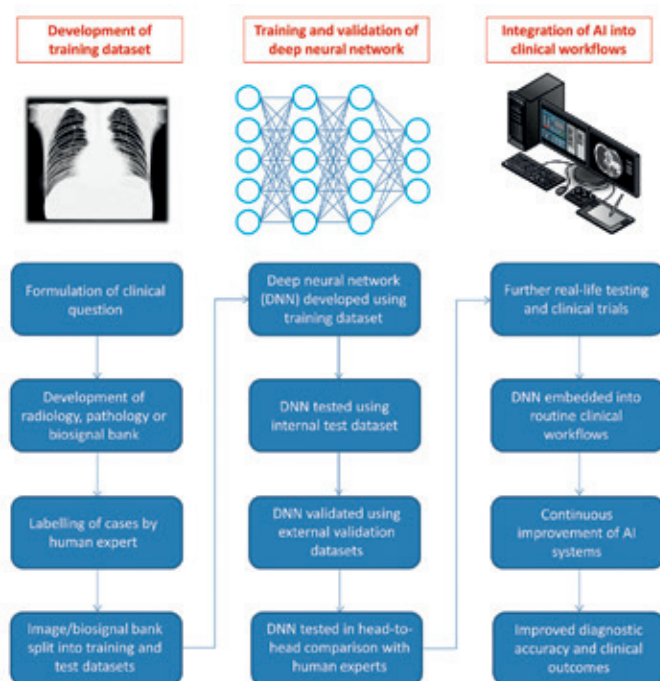


Figure 2 Typical path for the development of a machine learning model and its incorporation into clinical practice. Chest radiograph and imaging workstation images are from www.shutterstock.com (reproduced under licence). Contributing artists were sfam_photo and Zern Liew, respectively.

ponse to therapy. Figure 2 summarises the process by which machine learning models may be developed and incorporated into routine clinical practice in the near future. There remains an enormous potential for DNNs to embrace domains outside of imaging such as pulmonary function tests and physiological biosignals. However, a major limitation for such computational approaches is a shortage of sufficiently large medical training datasets. Overcoming this will require large-scale collaborations such as the recently formed Open-Source Imaging Consortium (<https://www.osicild.org/>), a collaboration between academia and industry to develop imaging biomarkers for idiopathic pulmonary fibrosis and other interstitial lung diseases using AI.

Large clinical databases from multicentre randomised controlled trials are another underexplored domain. Applying DNNs to these detailed datasets, potentially including merged data from multiple similar trials, carries the potential to predict treatment effects for individual patients, ushering in a new era of personalised medicine. The benefits of sharing and reuse of individual participant data from clinical trials are increasingly recognised but will require a robust internationally recognised ethical and legal framework to gain wider adoption and acceptance.⁷⁸ Similarly, data collected during the course of routine clinical practice has great potential for training AI algorithms for patient benefit. However, clear legal and ethical guidelines are needed to maximise the benefit of such datasets while preserving the confidentiality of individual patients.⁷⁹

Natural language processing (NLP) is still at an early stage of development but in future may be deployed to extract clinical insights from the vast pool of unstructured EHR⁸⁰ or to extract relationships between concepts from the rapidly expanding body of medical research.⁸¹ NLP may also be used to accelerate the development of AI algorithms for interpreting radiological or histological images, by automatically converting free-text radiology or pathology reports into a structured format suitable for training DNNs, potentially obviating the need for manual labelling of cases.^{82–84}

While the advances made over the past 5 years have been impressive, a number of challenges must still be overcome before AI can be widely adopted into routine clinical practice.^{79,85–86} These include intrinsic problems with the machine learning algorithms themselves, logistical difficulties and social or cultural barriers.

It is known that DNNs have the potential to misclassify examples that have been subtly altered, even by the addition of a few extra pixels.⁸⁷ In a clinical setting, this could manifest as a lack of generalisability; for instance, a DNN model trained on imaging data from the latest scanner at an advanced care facility may not function properly at a hospital that has older machines. Similarly, machine learning models are prone to perpetuating biases that may exist in the training dataset, as well as spurious associations in which confounding factors are used as predictors.⁸⁶ A related problem with DNNs and other complex machine learning algorithms is their lack of interpretability, which may be defined as an ability to provide reasons for their output. DNNs often act like 'black boxes' with the reasons for their output remaining opaque, even to their developers. In the medical sphere, interpretability is critical for gaining trust, particularly if important management decisions are being made based on the evaluation of a DNN. Fortunately, progress is now being made towards more interpretable AI. Several techniques have been developed that can generate explanations by estimating how the input features or different regions within an input image contributed to the output.⁸⁵ These techniques should allow a closer inspection of DNN outputs by clinicians so that decisions based on faulty or biased explanations can be over-ruled.

In conclusion, AI and machine learning have the power to transform many aspects of respiratory medicine. The emergence of DNNs developed using big training datasets has resulted in a number of novel applications, particularly in the field of thoracic imaging. However, DNN models still suffer from problems with interpretability, generalisability and potential bias. Rigorous validation strategies combined with the development of new standards for reporting machine learning models are required to address these issues before AI can take its place in the clinic.⁸⁸

Contributors SG conceived the idea for the manuscript, undertook literature search, co-wrote the first draft, and prepared the final draft and figures; WJ, ND and MT undertook literature search, co-wrote the first draft and critically appraised the final draft.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SG has received speaker's fees from Teva and consultancy fees from Anaxsys and 3M. WJ has received grants from AstraZeneca, Chiesi and GSK. WJ and MT are co-founders of ArtiQ, a spinoff company of KU Leuven. ND has no competing interests to declare.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Acompanhamento respiratório de doentes com pneumonia COVID-19

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2020-215314>).

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Received 18 May 2020

Revised 16 June 2020

Accepted 3 July 2020

Published Online First

24 August 2020

RESUMO

A pandemia COVID-19 levou a um surto sem precedentes em doentes hospitalizados com pneumonia viral. Os doentes mais gravemente afetados são homens mais velhos, indivíduos das minorias étnicas negra e asiática e indivíduos com comorbidades. A COVID-19 também está associada a um risco acrescido de hipercoagulabilidade e de tromboembolismo venoso. A esmagadora maioria dos doentes admitidos em hospital apresenta insuficiência respiratória e, embora a maioria seja tratada em enfermarias gerais, uma proporção considerável requer apoio de cuidados intensivos. As complicações a longo prazo da pneumonia COVID-19 começam a surgir, mas os dados de surtos anteriores de coronavírus, tais como a síndrome respiratória aguda grave (SARS) e a síndrome respiratória do Médio Oriente (MERS) sugerem que alguns doentes irão sofrer de complicações respiratórias a longo prazo resultantes da infeção.

Com o padrão de anomalias na imagiologia torácica e a crescente experiência clínica, considera-se que a doença pulmonar intersticial e a doença vascular pulmonar são, provavelmente, as complicações respiratórias mais importantes. Verifica-se a necessidade de uma via unificada para o acompanhamento respiratório dos doentes COVID-19, equilibrando a prestação de cuidados clínicos de alta qualidade com os recursos sobrecarregados do Serviço Nacional de Saúde (SNS). Neste documento orientador, sugerimos uma estrutura para o acompanhamento respiratório de doentes com confirmação clínico-radiológica da pneumonia COVID-19. Definimos dois algoritmos separados que integram a gravidade da doença, a probabilidade de complicações respiratórias a longo prazo e a capacidade funcional na alta hospitalar. Para mitigar as pressões do SNS, foram incorporadas soluções virtuais dentro da via, tal como a rede de segurança dos doentes cuja trajetória clínica se afaste da via. Para todos os doentes, sugerimos um pacote holístico de cuidados para lidar com a falta de ar, a ansiedade, a necessidade de oxigénio, os cuidados paliativos e a reabilitação.

INTRODUCTION

The first reports of a novel respiratory virus which was subsequently shown to be a coronavirus, severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), emerged from Wuhan, China in December 2019.¹ The highly transmissible virus spread rapidly and on 11 March 2020, coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organisation. By 10 May 2020, there were over 4 million confirmed cases worldwide with over 280 000 deaths. In the UK alone by this date, there were over 215 000 confirmed cases and over 30 000 deaths.

The clinical manifestations of SARS-Cov-2 infection vary, ranging from asymptomatic car-

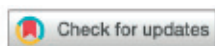
riage to atypical pneumonia, a hyperinflammatory phenotype, respiratory failure and acute respiratory distress syndrome (ARDS).²⁻⁵ An unexpectedly high prevalence of venous thromboembolic (VTE) disease and pulmonary embolism (PE) has become apparent⁶ and this is an important consideration for acute management and subsequent follow-up. Those most severely affected by COVID-19 are older men, individuals of black, Asian and minority ethnicity and those with comorbidities such as obesity, hypertension and diabetes.^{2-4 7-9} By far, the most common indication for admission to hospital is viral pneumonia and over 80% of hospitalised patients are cared for in general medical wards.¹⁰ A smaller proportion of patients with more severe disease require additional ventilatory support and are admitted to high dependency and intensive care units (ICUs). In a Chinese study of 1099 hospitalised COVID-19 patients, 173 patients (16%) had severe disease based on American Thoracic Society (ATS) community-acquired pneumonia guidelines¹¹ and 55 (5%) required ICU admission.² The mortality associated with COVID-19 is considerable—in a large UK study, in-hospital mortality was 26% for patients on general wards rising to 32% in those requiring ICU care.¹⁰ Depending on the series, COVID-19-related ICU mortality has been reported to be between 16% and 78%.^{3 4 8 10 12-15}

As effective vaccines and treatments for SARS-Cov-2 emerge, a key objective will be to identify and proactively manage complications from the infection and support patients through the recovery phase with the goal of preserving their health status. In this guidance document, we provide a suggested structure to achieve these aims with a focus on the respiratory follow-up of patients with clinicoradiological confirmation of COVID-19 pneumonia.

This guidance has been adopted by the British Thoracic Society (BTS) and the British Society of Thoracic Imaging (BSTI) after wide consultation and peer review. It is available online (<https://britthoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community/>).

COVID-19 PNEUMONIA IMAGING AND SPECIFIC RESPIRATORY COMPLICATIONS FOR CONSIDERATION

In typical cases of COVID-19 pneumonia, the chest X-ray (CXR) shows multiple bilateral peripheral opacities (figure 1A). In some patients, the morphological pattern of lung disease on CT scan with regions of ground-glass opacification and consolidation, which variably comprise foci of oedema, organising pneumonia and diffuse



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Para citar: George PM, Barratt SL, Condliffe R, et al. *Thorax* 2020;75:1009-1016.

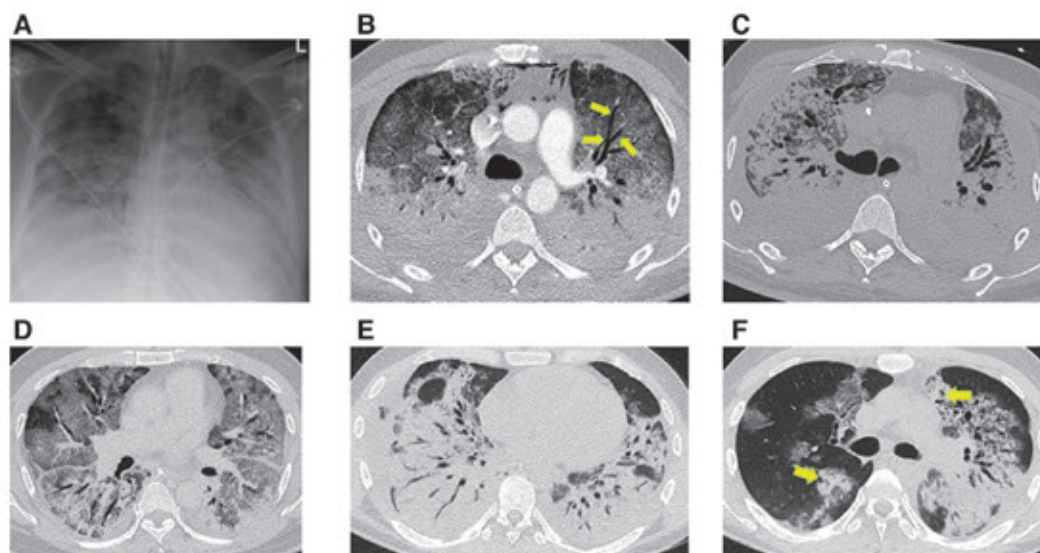


Figure 1 (A) Plain chest radiograph in a male patient with COVID-19 pneumonia referred for extracorporeal membrane oxygenation support. (B) CT images showing broadly symmetrical air space opacification with dependent dense parenchymal opacification and extensive ground-glass opacification with thickened interlobular and intralobular septa (the 'crazy-paving' pattern) in the non-dependent lung. Note that the airways are conspicuous against the ground-glass opacification but, importantly, taper normally (arrows) and have smooth walls. (C) CT performed 10 days later again showing widespread air space opacification but now with 'varicose' dilatation (non-tapering) of airways in the left upper lobe indicative of developing pulmonary fibrosis. (D) Classical 'crazy-paving' appearance in COVID-19. There is patchy but very extensive ground-glass opacification with superimposed fine thickening of interlobular and intralobular septa throughout both lungs. Relatively limited dense parenchymal opacification is present in the dependent lung bilaterally, likely to reflect variable combinations of the consolidated and atelectatic lung. (E) A patient with COVID-19-related acute respiratory distress syndrome (ARDS) with image section through the lower zones showing characteristic findings of ARDS with symmetrical air space opacification but with a gradient of increasing density from the ventral to the dorsal lung. (F) Image just below the carina demonstrating foci of non-dependent consolidation (arrows), conceivably denoting areas of organising pneumonia.

alveolar damage, are not too far removed from those in patients with an acute inflammatory pneumonitis (figure 1B–F). The radiological changes in COVID-19 pneumonia do not appear to resolve fully in all patients and in some, inflammation matures to form residual pulmonary fibrosis (figure 2).

Predicting the likely respiratory consequences of COVID-19 is challenging but reviewing data from this and other coronavirus infections provides insights. There may be important parallels from the severe acute respiratory syndrome (SARS) outbreak of 2002–2003 caused by SARS-CoV and Middle East respiratory syndrome (MERS) first identified in 2012.^{16–20} In a longitudinal CT study of 90 patients with COVID-19, 94% of individuals had residual changes on CT at discharge (median duration of 24 days after symptom onset) with ground-glass opacity the most common pattern.²¹ At discharge, in a study of 110 patients with COVID-19, 91 (83%) of whom had a mild–

moderate disease and 19 (17%) of whom had severe disease, almost half had impairment of the transfer factor of the lung for carbon monoxide (TLco).²² The duration between onset of illness and pulmonary function testing ranged from an average of 20 days in mild cases to an average of 34 days in severe pneumonia. The TLco was lower in patients with severe disease and was more sensitive to disease severity than other lung function measures such as forced vital capacity (FVC) and total lung capacity (TLC). Interestingly in this study, and although still largely within normal ranges at an average of 83% predicted, the TLco/alveolar volume (Kco) was significantly lower in those with severe disease than those with mild to moderate COVID-19 possibly implying a degree of pulmonary vasculopathy.

In a study of SARS survivors, 12 weeks after discharge, 36% of patients had residual CXR abnormalities and at 6 months, these were still present in 30% of the entire cohort, with airspace opacification and reticulation the predominant abnormalities.²³ CXR abnormalities were correlated with lung function test parameters including FVC, TLco and TLC but not with measures of respiratory muscle strength. Six months from hospital discharge, 16% of patients had persistent impairment of TLco with the preservation of the Kco.²³ The implication, therefore, is that these CXR imaging abnormalities were physiologically relevant and related to parenchymal lung disease. Similarly, in MERS survivors, at a median follow-up point of 6 weeks (range 32–230 days), 36% of patients had residual CXR changes, the vast majority of which were due to pulmonary fibrosis.¹⁶

These data suggest that the majority of patients infected with coronaviruses are discharged from hospital with persisting radiological change but that (at least in SARS²³ and MERS¹⁶) by 12 weeks, approximately two-thirds of patients have full CXR resolution. The optimal time for follow-up imaging to assess for radiological clearance in COVID-19 is unknown. Current BTS guidelines recommend a repeat CXR 6 weeks after a (bacterial or viral) community-acquired pneumonia²⁴, the rationale being to exclude primary bronchial neoplasms that can contribute to lobar or segmental pneumonia. The ATS does not recommend routine follow-up imaging for patients recovering satisfactorily from community-acquired

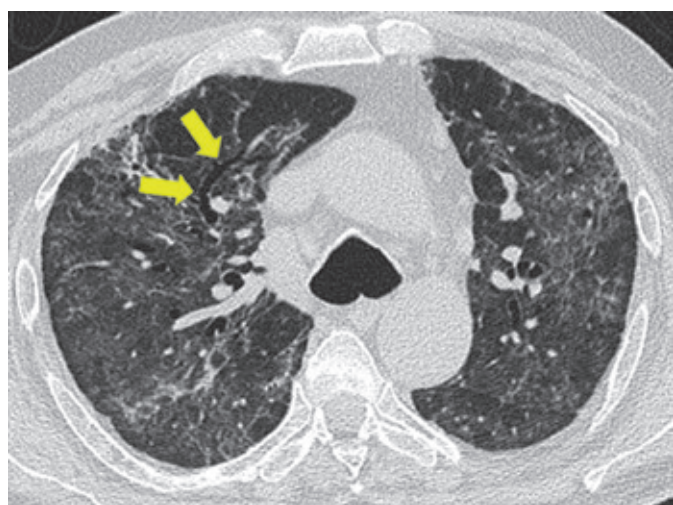


Figure 2 CT in COVID-19 extubated survivor: a study performed during recovery (26 days after onset of COVID-19 pneumonia). Image section at the level of the carina demonstrating widespread groundglass opacification and considerable architectural distortion. There is definite CT evidence of fibrosis—note the varicose dilatation ('traction bronchiectasis') of the anterior segmental bronchus in the right upper lobe (arrows).

pneumonia.¹¹ The patchy groundglass opacification classically observed in COVID-19 pneumonia (figure 1A–F) is, however, much less suspicious of harbouring a malignancy, particularly in the context of a pandemic. A 6-week follow-up CXR is, therefore, not advised and the 12-week time point is considered to be optimal in providing sufficient time for imaging resolution while also ensuring that non-resolving changes are addressed sufficiently early. Given that persisting imaging abnormalities correlate with physiological impairment, it is likely that these patients are at a greater risk of long-term parenchymal lung disease and are the group in whom closer follow-up and further investigation are indicated.

Unlike the MERS and SARS outbreaks, acute COVID-19 infection is associated with a high prevalence of VTE disease^{25–27} and in situ thrombosis. Indeed, patients remain hypercoagulable for a variable period of time and prolonged immobility in the most severely affected patients represents an additional VTE risk factor. It is increasingly appreciated that a number of patients are diagnosed with acute PE and deep vein thromboses *de novo* during the pneumonia recovery phase. Although the follow-up of COVID-19 pneumonia may hinge on the radiological resolution, it is crucial to be mindful of the high risk of PE in this group; this follow-up guidance should highlight to clinicians the need for prompt identification and treatment of acute PE and post-PE complications such as chronic thromboembolic disease and pulmonary hypertension (PH).

AIMS AND SCOPE OF GUIDANCE

Given the large numbers of patients admitted to hospital in a short period of time, the aims of this guidance are to ensure that patients are followed-up in a timely but practical manner, ensuring the early identification of respiratory complications integrating factors such as disease severity, likelihood of long-term respiratory sequelae and functional disability (box 1).

In this document, we provide a suggested structure for the respiratory follow-up of patients with clinoradiological confirmation of COVID-19 pneumonia. We do not recommend routine imaging or respiratory follow-up for patients without pneumonia on imaging nor those in whom CXR changes have fully resolved on follow-up imaging during hospitalisation. Given that the risk of subsequent post-infectious complications in this patient group is unknown, we do however advise that such patients consult their general practitioner (GP) should they experience persistent, new or progressive respiratory symptoms that do not recover over the 6–12 weeks following their acute illness. The lack of a robust evidence base for this new disease means that in consultation with their patient, an individual clinician can and should choose to deviate from the pathway when required.

On discharge from hospital, all patients should be advised that if they develop progressive or new respiratory symptoms prior to their intended review date, they should seek advice either from their GP surgery or if appropriate by presenting to emergency services. Frail patients or those with a performance status of 3–4 who have made a good clinical recovery post-COVID-19 pneumonia may understandably decline to reattend for a follow-up CXR. Where patients do not wish to attend for a follow-up CXR, teams should review the case notes and consider a remote clinic consultation to establish patient wishes and individual needs for further follow-up.

Use of this follow-up guidance may lead to the detection of incidental lung cancers and if detected these should be actioned. If any imaging is suspicious for lung malignancy, patients should either have an early repeat CXR 6 weeks after hospital discharge or a thoracic CT scan as appropriate to check for resolution with referral to local cancer services for further assessment as clinically indicated.

Box 1 Specific aims of COVID-19 pneumonia followup

- ▶ The early, medium and long-term respiratory complications of COVID-19 pneumonia are identified and affected patients are then followed-up by appropriate services.
- ▶ The most serious and potentially life-limiting complications of COVID-19 such as pulmonary fibrosis and pulmonary vascular disease are identified at the earliest possible stage without overinvestigating those patients who will make a full recovery.
- ▶ Acute patients' needs such as breathlessness, oxygen requirements, rehabilitation, palliative care/symptom management and psychosocial needs are identified and addressed at the earliest possible stage.
- ▶ Patients diagnosed with COVID-19 pneumonia who have made a full recovery are appropriately reassured that their chest X-ray changes have resolved.
- ▶ Respiratory, radiology and physiology resources are coordinated and used optimally and efficiently using virtual systems where feasible.
- ▶ Patients with hitherto undiagnosed pre-existing respiratory disease are opportunistically identified and managed as appropriate.
- ▶ At all points of patient contact, teams are reminded to undertake a 'post-COVID-19 holistic assessment' (box 3) of patient needs.

FOLLOW-UP ALGORITHMS

With the intention of addressing these aims (box 1), we have defined two follow-up algorithms (figures 3 and 4) that integrate disease severity as well as the functional capacity of patients on discharge.

1. Patients admitted for hospital care with a clinoradiological diagnosis of COVID-19 pneumonia who required ICU or high dependency unit (HDU) admission or were cared for in the ward with severe pneumonia (figure 3)

Patients with severe COVID-19 pneumonia and those discharged with acute care needs including the elderly, those with multiple comorbidities and those with a lower performance status are also likely to be the most vulnerable and in need of more intensive medical, nursing, rehabilitation, psychological and social input. They are more likely to benefit from an earlier clinical review which in this algorithm is 4–6 weeks after discharge.

Severe disease is also associated with a higher likelihood of longer-term disability. During the SARS outbreak, patients requiring ICU admission experienced poorer longer-term outcomes with persisting radiological change and physiological impairment as compared with those cared for on general wards.²³ Although there was persistent lung function impairment, a prospective cohort study showed that the interstitial changes did not progress over time.²⁸

Severe COVID-19 leads to ARDS.²⁹ The majority of patients with ARDS develop histopathological evidence of pulmonary fibrosis³⁰ and in survivors of ARDS, a significant proportion not only have CT evidence of residual pulmonary fibrosis but also functional impairment.^{31 32} It is possible that some COVID-19 ICU survivors will experience persistent physiological impairment and radiological abnormalities although whether these are progressive remains to be seen.³³ There is some debate as to whether SARS-CoV-2-associated ARDS is phenotypically distinct from conventional ARDS, being characterised by profound hypoxaemia, relatively preserved lung compliance and significant ventilation/perfusion mismatch.³⁴ There is, however, a clearly emerging signal for endothelial dysfunction³⁵ with a high pre-

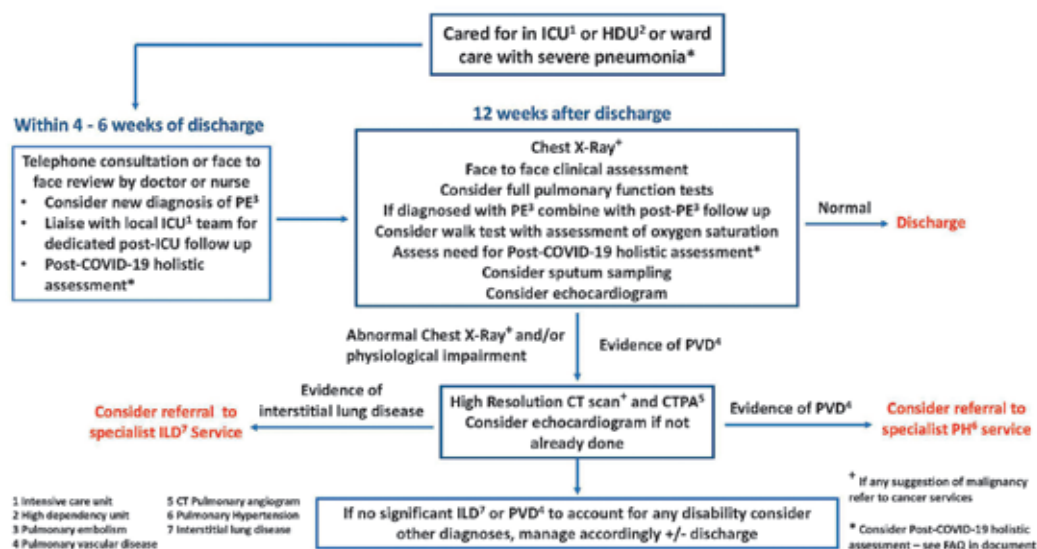


Figure 3 Respiratory follow-up algorithm for patients with COVID-19 pneumonia cared for in the ICU, HDU or those cared for on the ward with severe disease.

valence of pulmonary vascular dysfunction, thrombotic disease with PE and acute PH in the most severely affected patients. Some patients will be initiated on pulmonary vasodilators during the acute illness and will be discharged on therapy. These patients will require dedicated PH follow-up. Patients with organising pneumonia features and those in whom pulmonary fibrosis has started to develop may have been treated with corticosteroids with a plan for weaning of the dose as an outpatient. These patients should be assessed by specialist interstitial lung disease (ILD) teams where possible.

We recommend that patients cared for in ICU or those with severe COVID-19 pneumonia (box 2) should undergo an early follow-up assessment at 4–6 weeks after discharge.

This should ideally take the form of a remote or virtual clinic consultation by either a respiratory doctor or nurse. A face-to-face clinical assessment by either a respiratory doctor, a nurse or a suitably trained allied healthcare professional can then be arranged should a virtual consultation not be deemed sufficient or suitable to assess specific patients. This appointment should include a post-COVID-19 holistic assessment (box 3).

Patients should then undergo a full clinical assessment at 12 weeks with a repeat CXR which should be compared with previous CXRs performed during the patient's hospitalisation. If the CXR changes have fully resolved by this point (or if there are only minor insignificant changes such as small areas of atelectasis) and the patient is asymptomatic having made a full recovery, then they

can be considered for discharge. In some cases, a patient will be clinically improving but the CXR may still have persisting changes that require further assessment. In this scenario, clinicians should consider arranging a further CXR in 6–8 weeks to assess for clearance with remote or virtual follow-up assessment by a doctor or a nurse prior to discharge if progress remains satisfactory.

If the CXR changes have not satisfactorily resolved and/or the patient has ongoing respiratory symptoms, consider the following:

- ▶ Full pulmonary function testing.
- ▶ Walk test with an assessment of oxygen saturation.
- ▶ Echocardiogram.
- ▶ Sputum sample if expectorating for microbiological analysis.
- ▶ Referral to rehabilitation services if not already done.
- ▶ A new diagnosis of PE or post-PE complications if diagnosed during the acute illness.

Patients with persistent significant radiological abnormalities on plain imaging or with any clinically significant functional deficit or respiratory symptoms should then proceed to a precontrast thin section volumetric high-resolution CT (HRCT) scan and a CT pulmonary angiogram (CTPA) to assess for the presence of ILD and PE. If there is evidence of clinically significant ILD such as organising pneumonia or pulmonary fibrosis, patients should be considered for referral to regional specialist ILD services.

Patients diagnosed with PE de novo during follow-up should be treated as per standard protocols and followed-up in local

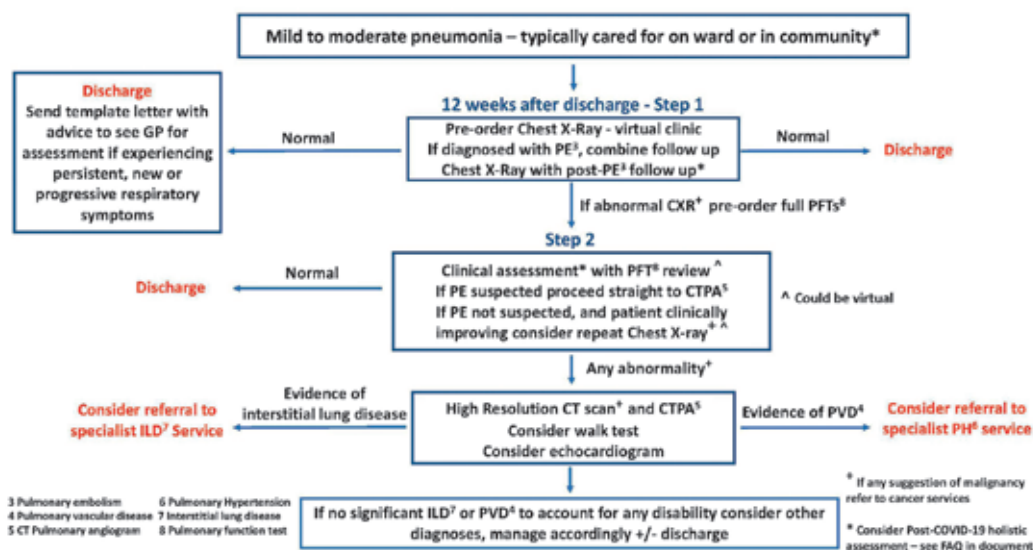


Figure 4 Respiratory follow-up algorithm for patients with mild to moderate COVID-19 pneumonia—typically cared for on the ward or in the community. GP, general practitioner.

Box 2 Patients at highest risk of COVID-19 pneumonia complications

- ▶ All patients managed on intensive care unit or high-dependency unit.
- ▶ All patients discharged with a new oxygen prescription.
- ▶ All patients with protracted dependency on high inspired fractions of oxygen, continued positive pressure ventilation and bi-level non-invasive ventilation.
- ▶ Any other patient the discharging team has significant concerns about.

services. If there is evidence of significant PH during follow-up, patients should be considered for referral to a specialist PH service. Patients diagnosed with PE during the acute illness should, where possible, be followed-up in local clinics 12 weeks after discharge as per usual protocols. If there is no suspicion of residual thromboembolic disease or evidence of significant PH, patients should be considered for discharge from PE follow-up with clear advice to primary care teams about the intended length of anticoagulation treatment. Patients with evidence of significant PH or evidence of significant chronic thromboembolic disease with or without PH should be considered for referral to specialist PH services.

If there is evidence of physiological or functional impairment but no evidence of significant ILD or pulmonary vascular disease, other diagnoses should be considered and managed appropriately. Specifically, there may be a high prevalence of dysfunctional breathing and breathing pattern disorder—if this is suspected, consider referral to specialist physiotherapy services.

2. Patients with a mild to moderate clinicoradiological diagnosis of COVID-19 pneumonia who did not require ICU or HDU care—typically cared for on the ward or in the community (figure 4)

This group includes those discharged directly from the emergency department or medical assessment unit and not admitted to hospital despite a diagnosis of COVID-19 pneumonia. These patients should have a routine follow-up CXR at 12 weeks from hospital discharge ideally in a virtual clinic. The CXR should be compared with previous CXRs performed during the patient's hospitalisation. If the 12-week follow-up CXR demonstrates complete resolution (or minor insignificant changes such as atelectasis), the patient should be discharged from further follow-up. Patients in this group who experience persistent or progressive respiratory symptoms such as breathlessness, chest pain or cough should seek medical attention promptly in advance of the scheduled CXR review, as early acute post-COVID-19 complications

Box 3 Post-COVID-19 holistic assessment

- ▶ Symptom or palliative care management where required.
- ▶ Assessment and management of oxygen requirements.
- ▶ Consideration of rehabilitation needs and onward referral where required.
- ▶ Psychosocial assessment and onward referral where required.
- ▶ Assessment and management of anxiety.
- ▶ Assessment and management of fatigue.
- ▶ Assessment and management of dysfunctional breathing.
- ▶ Assessment and management of postviral cough.
- ▶ Consideration of a new diagnosis of venous thromboembolic disease.
- ▶ Consideration of specific post-intensive care unit complications such as sarcopaenia, cognitive impairment and post-traumatic stress disorder.

such as PE, interstitial lung disease or secondary infection will require more urgent medical attention. It is expected that respiratory follow-up for a significant number of post-COVID-19 pneumonia will end at this point.

For patients with significant persisting CXR abnormalities at 12 weeks;

▶ Arrange to see the patient at a face-to-face outpatient clinic setting.

▶ Organise full pulmonary function tests.

▶ If more than 6 weeks have passed since the first CXR, consider repeating the CXR on arrival to the outpatient setting as in some patients the abnormalities may have resolved between these two time points.

If the second CXR has cleared or has non-significant findings, radiological follow-up ends and the patient can be considered for discharge if they have recovered satisfactorily. Patients with persistent significant abnormalities on the second CXR and/or abnormal pulmonary function tests and/or significant unexplained breathlessness will require further investigations which may include the following:

▶ Precontrast thin section volumetric HRCT and CTPA to assess for the presence of ILD and PE.

▶ Walk test with an assessment of oxygen saturation.

▶ Echocardiogram if PH is suspected following pulmonary function testing and CT.

In the event that specific abnormalities such as ILD or PH are identified, patients should be considered for referral to regional specialist services. Patients diagnosed with PE de novo during follow-up should be treated as per usual protocols and followed-up in local services. Patients diagnosed with PE during the acute illness should be followed-up where possible in local clinics 12 weeks after discharge. If there is no residual thromboembolic disease or evidence of PH, patients should be discharged. Patients with evidence of PH or evidence of significant chronic thromboembolic disease with or without PH should be referred to specialist PH services. Any patient with post-COVID-19 pneumonia who is attending a post PE follow-up should have that visit coordinated with their pneumonia follow-up review where possible. A CXR should be offered on arrival to assess for resolution. If the CXR continues to show significant nonresolution, further investigations as before should be considered. If there is evidence of physiological or functional impairment but no evidence of significant ILD or pulmonary vascular disease, other diagnoses should be considered. As previously, if dysfunctional breathing is suspected, then consider referral to specialist physiotherapy services.

PE AND POST-PE FOLLOW-UP

Patients diagnosed with PE during the acute illness should have post-PE follow-up as per local protocols. Patients should be considered for referral to specialist PH services where appropriate if PH is suspected or significant chronic thromboembolic disease demonstrated. If there is no evidence of chronic thromboembolic PH or significant residual thromboembolic disease, in light of the strongly provoked nature of the PE, discontinuation of anticoagulation after 3 months of therapy can be considered.³⁶ Further details are provided in the BTS VTE guidance (<https://brit-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community>). Patients may remain hypercoagulable for some time after the acute illness and so extended thromboprophylaxis on discharge should be considered and there should be a high index of suspicion for the diagnosis of acute PE during the follow-up period. In those with PE who remain symptomatic, echocardiography and pulmonary vascular imaging modalities such as ventilation/perfusion (V/Q) scanning and CTPA form the mainstay of assessment for post-PE complications. It should be noted that V/Q scanning has limitations for patients with structural lung disease, which may be more likely in the aftermath of mechanical ventilation.

D-Dimer is a non-specific acute phase reactant that may be elevated in acute inflammatory illnesses, pneumonia and other causes of sepsis. Elevated levels are common in acute COVID-19 and are associated with poorer outcomes. Guan *et al* observed elevated D-dimer levels in 46% of patients in a series of 1099 patients,² whereas in a study of 183 patients with COVID-19 pneumonia, Tang *et al* observed higher D-dimer levels (median 2120 µg/L vs 610 µg/L) in non-survivors compared with survivors.³⁷ Although significantly elevated levels are more likely to be associated with VTE than more modestly elevated levels,^{25,38} it is not possible to identify a threshold that can be used to non-invasively diagnose thrombus and a decision to proceed to diagnostic imaging should be based on overall clinical assessment. Acute thrombus can be excluded, however, in patients with normal D-dimer levels who do not have a high clinical probability of VTE.³⁹ There is no role for the routine measurement of D-dimer in patients being followed-up post-discharge. D-dimer may be useful in the investigation of possible acute PE in patients who develop acute new or worsening breathlessness. It should not be used to exclude suspected chronic thromboembolic disease and PH. Although there is some limited utility, outwith of COVID-19, in measuring convalescent D-dimer levels to refine decision-making regarding duration anticoagulation, there are no data to support this approach in patients following COVID-19 infection.⁴⁰

GENERAL ISSUES TO CONSIDER DURING FOLLOW-UP

COVID-19, particularly severe disease, often leads to a wide range of sequelae that require dedicated follow-up. Renal dysfunction is common³ and acute cardiac presentations of COVID-19 including myocarditis are well recognised.^{41–42} Screening questionnaires utilising the Hospital Anxiety and Depression Scale may identify those in whom referral for psychological support is required.⁴³ Cognitive, psychiatric and physical complications including critical care neuromyopathy and post-tracheostomy care, collectively termed post intensive care syndrome⁴⁴ are often addressed in dedicated post-ICU clinics, which were first developed in the UK.⁴⁵ Other countries have recently started to replicate this approach to post-ICU care but it is estimated that in the UK, the country in which these clinics are most widely adopted, only approximately 30% of patients discharged from ICU are currently followed-up in this way.⁴⁶ Furthermore, patients requiring extracorporeal membrane oxygenation support are seen in dedicated follow-up clinics and so it will be important for respiratory and critical care teams to liaise closely ensuring that follow-up clinics are rationalised to avoid duplication of work.

Experience from the SARS outbreak suggested definitive evidence of coinfection with other microorganisms in a subset of patients, including disseminated invasive aspergillus infection and cytomegalovirus, with a prevalence as high as 15% in one postmortem cohort.^{47–48} Systemic corticosteroid treatment was speculated to have contributed to some of these cases. In critically ill patients with COVID-19, it has been suggested that the prevalence of invasive aspergillosis is as high as 25%.⁴⁹ We recommend, therefore, that clinicians have a high index of suspicion for bacterial and fungal coinfection. Careful microbiological sampling and analysis are required to ensure that infective complications are addressed as early as possible.

Pulmonary rehabilitation is already established as a key management strategy in those with chronic respiratory disease, designed to optimise patients' exercise capacity, breathlessness, health status and psychological well-being.⁵⁰ A study investigating the pulmonary function and exercise capacity in a group of SARS survivors showed that although residual mild pulmonary function defects were detected in over half of recovered SARS patients at 3 months after hospital discharge, 41% had impaired exercise capacity that could

not be accounted for by ventilatory limitation.⁵¹ Critical illness muscle weakness and deconditioning are likely to be contributing factors.⁵² Rehabilitation services are currently under national review after the COVID-19 outbreak and are expected to offer comprehensive assessments, including psychosocial assessments where appropriate, for patients who prefer web-based, self-directed rehabilitation at home (<https://www.bts-thoracic.org.uk/about-us/covid-19-information-for-the-respiratory-community/>). Respiratory teams are advised to seek additional resources to support the delivery of post-COVID-19 follow-up work. Respiratory services have in most places already shouldered much of the responsibility for the care of patients with acute COVID-19. They will be key in delivering ongoing acute care with further surges predicted against a backdrop of 'chronic COVID-19 activity' as the infection persists within the population at a lower incidence level. Like other medical specialities, they also have a backlog of outpatient activity to address in a new working environment that is 'COVID-19 safe' but 'COVID-19 slow', for example, when considering access to imaging, physiology and bronchoscopy. With an appreciation that models of care will by necessity evolve to adapt to the post-COVID era, possible virtual solutions have been embedded within this guidance at multiple points. Respiratory community teams will play an important part in the early and indeed longer-term care of patients discharged from hospital, for example, when considering ongoing oxygen requirements, identification of rehabilitation needs, management of dysfunctional breathing and mental health assessment.

Summary

COVID-19 is a unique and novel infection that has already demonstrated a range of perplexing clinical syndromes—it's legacy will be felt long after the pandemic has passed. It is vital that the respiratory community is primed to detect and manage the long-term consequences of the infection and has sufficient resources to deliver it. This clinical guidance has been developed through expert consensus and then extensive peer review by a number of specialist advisory groups and experts at the BTS and the BSTI. Coordinated national guidance will facilitate data collection, research and audit, allowing the respiratory community to learn more about COVID-19 as well as ensuring that the clinical follow-up pathway can be iterated where required for future peaks of the infection. The use of the standardised BSTI CXR and CT reporting codes will facilitate data collection for audit and research purposes (online supplementary appendix 1 and 2). As the National Health Service starts to recover from the first peak of the COVID-19 pandemic and with high-quality patient care as a central principle, we envisage that this guidance will help to protect precious resources whilst minimising the long-term health effects related to the respiratory complications of this devastating disease.

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Contributors PMG and LGS wrote the first draft. All authors contributed to the literature search, writing of the manuscript and approval of the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests PMG reports grants, personal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Roche Pharmaceuticals, personal fees from Teva, outside the submitted work. SLB reports personal fees from Boehringer Ingelheim, outside the submitted work. RC reports he has received honoraria for advisory boards and lecturing from Bayer pharmaceuticals. SRD reports personal fees from Boehringer Ingelheim, personal fees from GSK, outside the submitted work. AD reports personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from Galapagos, personal fees from Galeto Biotech, outside the submitted work.

IF reports personal fees from Boehringer Ingelheim, from Roche Ltd, outside the submitted work. MAG has nothing to disclose. NH reports unrestricted grants from Philips and Resmed outside the area of work commented on here with the funds held and managed by Guy's & St Thomas' NHS Foundation Trust; financial support from Philips for development of the MYOTRACE technology that has patent approved in Europe and US outside the area of work commented on here; personal fees for lecturing from PhilipsRespiroics, Philips, Resmed, Fisher-Paykel outside the area of work commented on here; NH is on the Pulmonary Research Advisory Board for Philips outside the area of work commented on here with the funds for this role held by Guy's & St Thomas' NHS Foundation Trust. GJ reports grants from Astra Zeneca, grants from Biogen, personal fees from Boehringer Ingelheim, personal fees from Daewoong, personal fees from Galapagos, grants from Galacto, grants from GlaxoSmithKline, personal fees from Heptares, non-financial support from NuMedi, grants and personal fees from Pliant, personal fees from Promedior, non-financial support from Redx, personal fees from Roche, other from Action for Pulmonary Fibrosis, outside the submitted work. Outside the submitted work, DFM reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim and Bayer, Outside the submitted work, his institution has received funds from grants from the UK NIHR, Wellcome Trust and others. In addition, DFM is one of the four named inventors on a patent US8962032 covering the use of sialic acid-bearing nanoparticles as anti-inflammatory agents issued to his institution, The Queen's University of Belfast <http://www.google.com/patents/US8962032>. This has no direct impact on the contents of the manuscript. BP reports personal fees from GSK, grants from Mermaid Care A/C, grants from ESICM, grants from Royal Brompton & Harefield Charity, grants from European Commission, grants from Academy of Medical Sciences, outside the submitted work. LGS reports personal fees from Roche and Boehringer Ingelheim, other from Roche and Boehringer Ingelheim, other from Boehringer Ingelheim, outside the submitted work.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Pneumonite por hipersensibilidade potencialmente fatal associada ao uso de cigarros eletrônicos

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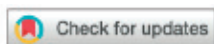
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Published Online First 11 November 2019



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Para citar: Nair N, Hurley M, Gates S, et al. *Thorax* 2020;75:1114–1116.

RESUMO

Relatamos um caso de pneumonite por hipersensibilidade (PH) num jovem indivíduo associada ao uso de produtos de vaping. Apresentou um diagnóstico putativo de asma e necessitou de oxigenação por membrana extracorporeal devido a insuficiência respiratória intratável. O doente desenvolveu uma doença crítica e miopatia esteroide, o que exigiu uma reabilitação prolongada. O nosso doente preenche os critérios de diagnóstico para PH associada ao uso de cigarros eletrônicos com um histórico de exposição positivo, deterioração após teste cutâneo de alergia, anticorpos IgM específicos séricos contra o líquido implicado, aumentando a possibilidade de o antigénio relevante estar presente nesse líquido, e características radiológicas e histopatológicas compatíveis com PH aguda. Resultam duas aprendizagens. A primeira é considerar sempre uma reação aos cigarros eletrônicos em alguém que apresente uma doença respiratória atípica. A segunda é que consideramos os cigarros eletrônicos “muito mais seguros do que o tabaco” por nossa conta e risco.

INTRODUCTION

Hypersensitivity pneumonitis (HP) is an immunemediated reaction that follows the inhalation of antigens or chemicals and mainly affects the alveoli, interstitium and bronchioles. There are two main categories of HP: acute/inflammatory and chronic/fibrotic.¹ Putative antigen triggers are diverse, and the list is ever increasing. Pathogenesis is attributed to a combination of type III (immune complex mediated) and type IV (delayed) hypersensitivity reactions. Though any environment with sufficient amount of antigen can cause HP, there is evidence that a second hit such as viral infection or endotoxin exposure may be needed to induce the disease.

Flavoured e-cigarettes liquids contain airway irritants and toxicants such as propylene glycol (PG), vegetable glycerine (VG) and many different flavouring chemicals that have been implicated in the pathogenesis and worsening of lung diseases and that likely induce respiratory effects not seen in tobacco smokers. Additionally thermal decomposition of PG and VG, the base constituents of e-liquids, produces reactive carbonyls, including acrolein, formaldehyde and acetaldehyde, which have known respiratory toxicities.² It is possible that the pulmonary manifestations associated with vaping represent a range of disease processes. What is important however is that clinicians should consider the possibility of pulmonary disease associated with vaping when patients report recent use, especially when other causes are not identified as the recent epidemic highlights.³

CASE

A previously healthy 16-year-old boy presented to the emergency department with a 7-day history of fever, cough and increasing difficulty breathing despite oral antibiotics and inhaled salbutamol. There was no previous confirmed diagnosis of asthma, and he was not on any regular controller treatment with inhaled corticosteroids. He deteriorated rapidly and required non-invasive, conventional and then high frequency oscillation ventilation and finally transferred for ECMO because of intractable respiratory failure. He had 3 days of venovenous ECMO and treatment with broad spectrum intravenous antibiotics, intravenous hydrocortisone, a macrolide and antifungals. He was stepped down to the paediatric respiratory ward 10 days after his admission on 4L/min nasal cannula oxygen and inhaled bronchodilators and oral corticosteroids for a putative diagnosis of asthma. He developed a critical illness and steroid myopathy and required prolonged rehabilitation.

Further questioning revealed that he had recently started to use e-cigarettes fairly frequently, using two different liquids, purchased over the counter. During his convalescence, he mentioned that at some point he had used both the liquids in question though was unable to recollect the exact sequence of use and in particular which one he had used immediately prior to becoming unwell. The listed ingredients of both the liquids were identical except for the un-named flavourings (see figure 1).

He had smoked cannabis a year previously but not recently. He had no recent bird or farm animal exposure or any recent travel. The results of the investigations during his acute illness were:

- ▶ A CT chest 6 days after admission (figure 1) showed bilateral ground glass changes in the upper and mid-zones with perihilar bronchial wall thickening and retained secretions in the dependant airways.
- ▶ Bronchoalveolar lavage (BAL) in paediatric intensive care unit (PICU) and a later expectorated sputum sample both showed moderate numbers of macrophages, neutrophils and eosinophils (20%) consistent with active inflammation.
- ▶ First spirometry 22 days after admission showed forced expiratory volume in 1s (FEV₁) was 3.52L, z score –1.91 and forced vital capacity (FVC) 3.68L, z score –2.73. Total lung capacity (helium dilution) was 5.91L, z score –0.82 and transfer factor (TLCOc SB) (mmol/min/kPa) was 9.02, z score –0.92.
- ▶ The only evidence of infection was a nasopharyngeal aspirate positive for rhinovirus.
- ▶ He had a raised C reactive protein but negative tests for autoimmune disease, vasculitis and avian precipitins.

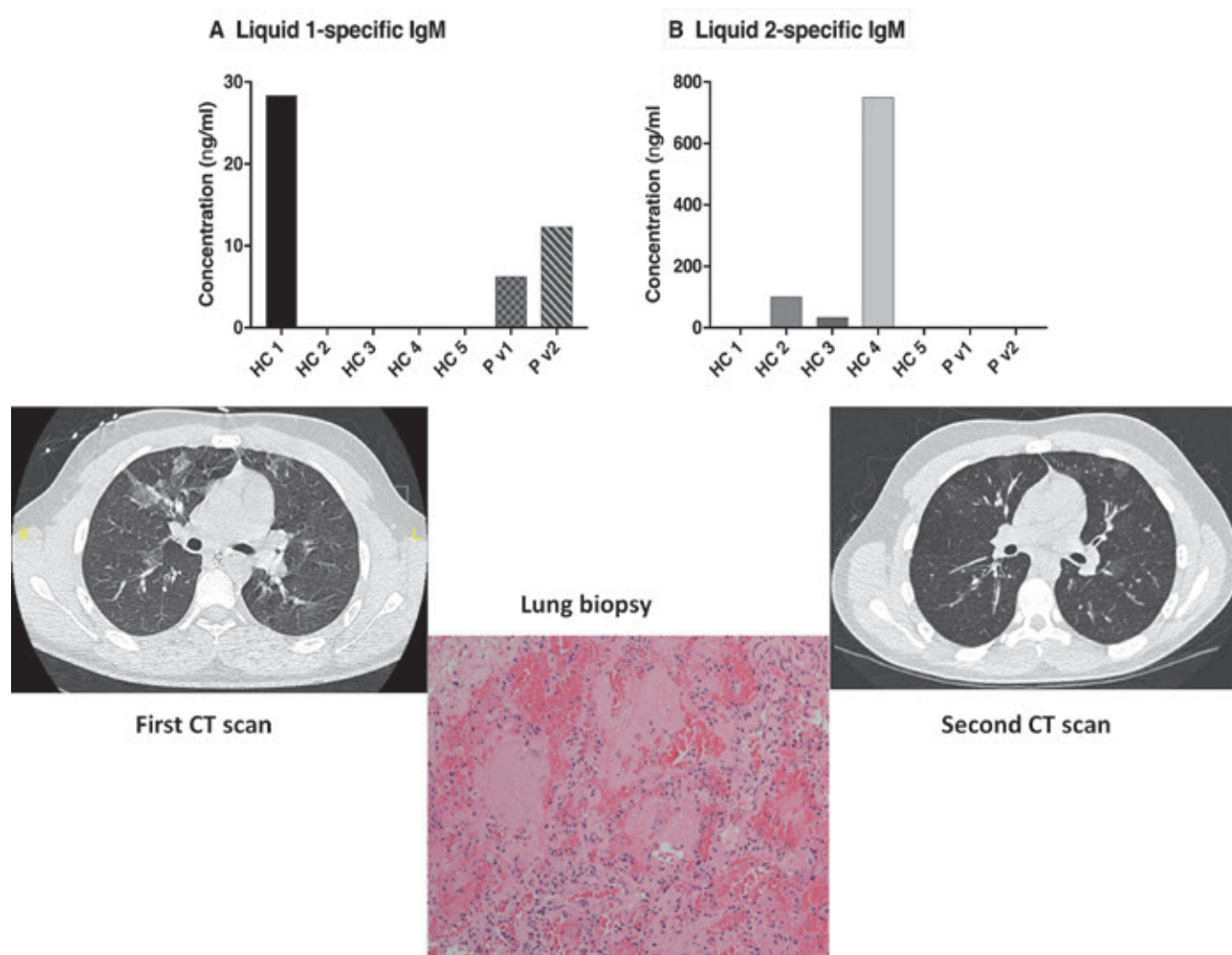


Figure 1 Radiology—immunology—histopathology correlation in a case of hypersensitivity pneumonitis: concentration of liquid 1 specific IgM. Concentration of liquid 2 specific IgM. First CT scan: day 6 from first presentation. Second CT scan: day 44 from first presentation. Lung biopsy showing inflammation and hyaline membrane formation.

► He had a negative skin prick test (SPT) to e-cigarettes liquid 1 and liquid 2 (with identical ingredients but different flavourings: 0.3% nicotine, VG, mono-PG, flavourings; neither had a comprehensive list of ingredients); the positive control was 5mm, so the clinical picture was not that of IgE-mediated reaction. However, this does not exclude an adverse reaction to e-cigarettes. Indeed, 8 hours after SPT, he deteriorated with chest tightness, difficulty breathing and widespread wheeze requiring oxygen, intravenous and nebulised salbutamol and an increased dose of oral steroids. We postulated that this exacerbation of symptoms occurred due to antigen re-exposure in the setting of his pre-existing acute HP4 with the eliciting antigen in either or both of the e-cigarette liquids.

He was discharged home 35 days after admission with a plan to slowly taper oral steroids. This led to worsening respiratory status, and he returned to the emergency department on one occasion and was admitted on other requiring intensive treatment for respiratory distress and wheeze. He was categorical that he had not used any more e-cigarettes, and there were no other obvious triggers in the environment; however, we did not specifically test him for any respiratory viruses, and the clinical worsening was attributed to a too rapid taper of steroids. He had a repeat CT chest 44 days after presentation (figure 1), which showed patchy areas of ground glass opacification throughout both lungs that had improved considerably since the previous scan, but there were ground glass appearances in new areas including the right lower lobe.

A surgical lung biopsy was obtained 50 days after his first presentation as he continued to be symptomatic, and

further treatment with pulsed methylprednisolone was contemplated.

The biopsy showed (figure 1) alveolar spaces containing macrophages and evidence of haemorrhage. A few alveolar spaces lined by fibrin suggesting early hyaline membrane formation. No granulomas were identified. Of note, the lung biopsy and the CT appearances are likely to have been modified by the very significant ventilation and high doses of steroids.

The presence of an eliciting antigen in either or both of the e-cigarette liquids was further investigated by developing an in-house ELISA to detect antibodies specific to the e-cigarette liquid constituents. Serum samples were obtained from the patient on day 50 (no serum was available for analysis of the immunological assay in the academic department prior to day 50) and 112 days from first presentation, the latter following treatment with high dose pulsed methylprednisolone and abstinence from e-cigarettes. Sera were also obtained from five healthy donors (median age 21 years old, range 20–23; three men and two women) who had never smoked tobacco or used e-cigarettes.

IgG antibodies binding to both e-cigarette liquids were detected at similar levels in all serum samples (from both the patient and the controls), suggesting the presence of cross-reactive antibodies in all individuals. As shown in figure 1, fewer samples were positive for specific IgM antibodies, and the patient had IgM specific for liquid 1, but not liquid 2, raising the possibility that the eliciting antigen was present in liquid 1. Healthy control 1 also had IgM antibodies specific for liquid 1, again suggesting the occurrence of cross-reactive antibodies in

some non-exposed individuals. Fourteen months after the initial presentation, he was asymptomatic with normal spirometry (FEV₁ 4.35L, z score -0.65 and FVC 5.12L, z score -0.16).

DISCUSSION

This previously well young person presented with a catastrophic respiratory illness. For such to be the very first presentation of asthma would be virtually unheard of.

Our patient fulfils diagnostic criteria for HP secondary to e-cigarettes. There was a positive exposure history and, importantly, deterioration after SPT. We detected serum IgM antibodies against the implicated liquid raising the possibility that the eliciting antigen was present in the vaping liquid; however, we acknowledge these are not specific, being present in a control; a previous patient had no supportive immunological evidence.⁵ Antibodies associated with HP are usually of IgG class; IgM class antibodies can also be involved.⁶

The CT pattern was typical for acute HP with ground glass opacities predominantly in upper and middle lobes and mosaic attenuation; other features such as centrilobular diffuse micronodular pattern were not seen, likely because of previous corticosteroid therapy. The histopathology was compatible, but the pathological features of acute HP are poorly characterised because patients are rarely (if ever) biopsied. Findings include intra-alveolar fibrin, neutrophil accumulation with or without findings of acute lung injury and possible small vessel vasculitis; poorly formed, non-necrotising, granulomas may be seen.^{4,7} Our patient had evidence of inflammation (BAL and biopsy) and hyaline membrane formation.

CONCLUSIONS

There are two important lessons here. The first is always to consider a reaction to e-cigarettes in someone presenting with an atypical respiratory illness. The second is that we consider e-cigarettes as 'much safer than tobacco' at our peril.

Contributors NN: reviewed case notes and wrote parts of case (as indicated). MH, SG and PD: contributed to clinical management. LF and IT: consultant immunologists supervised I-LC to develop the immunologic assay and wrote part of the case (as indicated). AB: professor of paediatric respiratory reviewed drafts and suggested major improvements and agreed on the final draft. JMB: consultant respiratory paediatrician in charge of the patient's respiratory care, suggested writing case report for this patient, collated contributions from the other authors, obtained images, obtained informed consent from the patient, wrote substantial parts of case (as indicated), reviewed drafts and suggested improvements and agreed on the final draft and is the corresponding author.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed. data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Mecanismo de desenvolvimento pulmonar na etiologia das malformações congénitas das vias respiratórias pulmonares adultas

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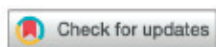
Received 3 March 2020

Revised 27 June 2020

Accepted 2 July 2020

Published Online First

30 July 2020



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Para citar: Taylor B, Rice A, Nicholson AG, *et al.* Thorax 2020;75:1001-1003.

RESUMO

As malformações congénitas das vias respiratórias pulmonares adultas (MCVRP) são anomalias pulmonares raras que resultam na formação de quistos e que estão associadas à dificuldade respiratória em crianças e a um potencial maligno em adultos. A patogénese das MCVRP permanece desconhecida, mas os dados sugerem uma perturbação do programa próximo-distal normal da ramificação e diferenciação das vias respiratórias. Aqui, demonstramos que as MCVRP de adultos humanos são revestidas com epitélio que retém SOX-2 e marcadores imunohistoquímicos do fator de transcrição da tireóide-1, característicos de pulmão em desenvolvimento. No entanto, o RALDH-1, outro marcador essencial, está ausente. Isto sugere uma etiologia mais complexa para as MACVRP do que uma paragem focal completa do desenvolvimento pulmonar e pode permitir conhecer melhor o risco associado de malignidade.

INTRODUCTION

The three-dimensional network of conducting airways is formed during the pseudoglandular phase of lung development, by branching morphogenesis. This process is controlled by temporal and spatial localisation of key genes and signalling molecules that co-ordinate to drive organ formation. The fundamental pathways used during development also have key roles in tissue homeostasis and repair once the adult lung is formed; dysregulation of these same developmental pathways contributes to the pathogenesis of many adult diseases including emphysema,^{1,2} fibrosis³ and lung cancer.⁴

Congenital pulmonary airway malformations (CPAMs) comprise a spectrum of lung abnormalities estimated to affect between: 1:11 000 and 1:35 000 live births.⁵ CPAMs are associated with neonatal respiratory distress, recurrent childhood pulmonary infection and, without resection, malignant potential in adults.^{6,7} CPAMs have traditionally been classified into types 0–4 depending on size and location of lesions present. The most common sub-types are 1 (60%–70%), characterised by large (>2 cm) intercommunicating cysts, and 2 (15%–20%), consisting of small (<2 cm) cysts and solid tissue⁸

The high mobility group box transcription factor SOX-2, early embryonic transcription factor thyroid transcription factor-1 (TTF-1) and the retinoic acid synthesising enzyme RALDH-1 are necessary for normal patterning and development of airway branching in the mouse lung.⁹ In addition, SOX-2 overexpression in mouse has been previously found to result in cystic lesions resembling those observed in human CPAM.¹⁰ It is therefore hypothesised that alterations in signalling during branching morphogenesis underlie CPAM pathogenesis. In these experimental pathology studies, we examine localisation of the proteins TTF-1, SOX-2 and RALDH-1 in lung tissue from 14 cases of type 1 and 2 cases of type 2 adult CPAM compared to normal adult lung parenchyma and embryonic (fetal) human lung.

METHODS

Fourteen type 1 and 2 two type 2 CPAM resection specimens were obtained from the diagnostic archive of

the Royal Brompton Hospital (ethics reference number 10/H0504/9). Normal adult lung tissue was obtained from the International Institute for the Advancement of Medicine (USA). Human fetal lung sections (14 weeks post conception, WPC) were provided by the Joint MRC/Wellcome Trust (099175/Z/12/Z) Human Developmental Biology Resource (www.hdbi.org). Sections of adult normal resected, CPAM and fetal human lung tissue underwent immunohistochemical (IHC) staining for SOX-2, TTF-1 and RALDH-1. Sections were incubated with primary antibody at optimised concentrations (Dako TTF clone 8G7G3/1 (M3575) at 1:500, Immune Systems. SOX-2 (GT15098) at 1:500 and Sigma ALDH1A1 (HPA002123) at 1:250) overnight at 4°C. Sections were then incubated with biotinylated antibody (1:50) from the VectaStain ABC kit followed by ABC reagent (1:50) and DAB substrate application. Sections were mounted in DPX and digital images were captured at 20× magnification using Leica Application Suite software (Leica microsystems, Milton Keynes, UK) for qualitative comparison of lung tissue sections.

RESULTS

SOX-2

Control embryonic lung section with primary antibody omitted shows no positive staining (figure 1A). In comparison, embryonic lung tissue shows positive SOX-2 immunostaining localised to airway epithelial cells with strong staining present in the large, proximal airways (figure 1B). SOX-2 was absent in normal adult epithelium (figure 1C) whereas positive SOX-2 staining was observed in CPAM lung tissue sections, localised to cyst-lining epithelial cells (figure 1D).

TTF-1

Control embryonic lung section with primary antibody omitted shows no positive staining (figure 2A). TTF-1 was localised to airway epithelial cells in embryonic lung tissue (figure 2B), but in adult sections was present in a sub-set of alveolar cells (figure 2C). In CPAM lung tissue sections, all cyst lining epithelial cells stained positively for TTF-1 (figure 2D).

RALDH-1

Control embryonic lung section with primary antibody omitted shows no positive staining (figure 3A). Positive staining was localised to the airway epithelium in embryonic lung tissue (figure 3B). RALDH1 staining was absent in normal adult lung tissue (3K). Similarly, RALDH1 staining was absent, or only very weakly positive in CPAM lung tissue sections (figure 3C).

DISCUSSION

This study shows that the embryonic airway epithelial cell markers SOX-2 and TTF-1 are retained in the cyst-lining epithelial cells of CPAM human lung tissue. However, localisation of another key development protein, RALDH1, reported here for the first time, is similar to that of adult lungs. This suggests that the phenotype of CPAM epithelial cells may be more complex than complete focal arrest in development.

SOX-2, TTF-1 and RALDH1 expression in normal adult and embryonic lung tissue sections, as

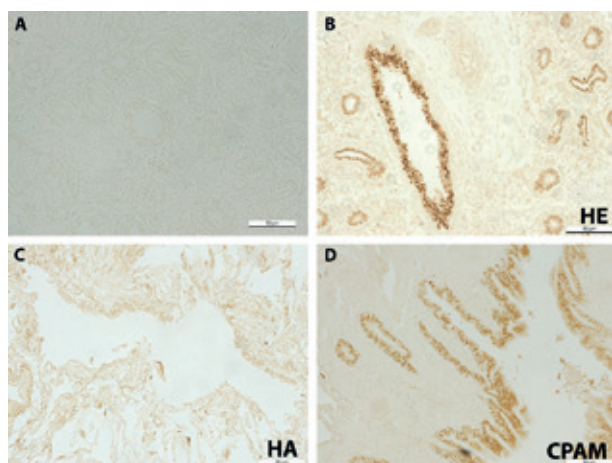


Figure 1 Fourteen WPC normal human embryonic lung with primary antibody omitted (negative control) (A); SOX-2 immunostaining in 14 WPC normal HE lung (B); normal HA lung (C) and CPAM HA lung (D). Scale bar, 50 µm. CPAM, congenital pulmonary airway malformation; HA, human adult; HE, human embryonic; WPC, weeks post conception.

represented by positive IHC staining, was consistent with previous studies.^{10–11} SOX-2 is critical to cell pluripotency and self-renewal, with principal embryonic expression in the proximal airway epithelium during bronchiole development. In pseudoglandular human lungs, SOX-2 levels are high in proximal stalk epithelium (differentiating bronchioles), with low levels of SOX-2 present in the distal tip epithelium. Tip expression of SOX-2 disappears completely by 20 WPC and, as a result, involvement in peripheral alveolar development is minimal, and SOX-2 protein is absent in the adult lung.¹² However, expression was present in the cyst-lining epithelial cells of adult CPAM sections, suggesting cystic regions retain a proximal embryonic phenotype. This is supportive of previous studies by Ochieng *et al* demonstrating the likely role of SOX-2 overexpression in CPAM cyst development.¹⁰

TTF-1 expression in adult human lung tissue was localised to a sub-set of alveolar epithelial cells, presumably type II pneumocytes and absent from airway epithelium. TTF-1 is localised to all airway epithelial cells in human embryonic lungs but unlike SOX-2, there is no difference between proximal and distal airways. TTF-1 staining in cyst-lining epithelium of CPAM lung tissue more closely resembled the generalised epithelial expression of embryonic lung tissue. RALDH1 expression was prominent in airway epithelial cells of pseudoglandular lung, whereas no staining was present in the adult lung. In CPAM lung tissue sections, some extremely weak

RALDH1 staining was observed when compared with normal adult tissue but the pattern of staining did not resemble that seen in embryonic sections, suggesting that the phenotype of cyst-lining epithelium in CPAM differs from that of embryonic lung epithelium.

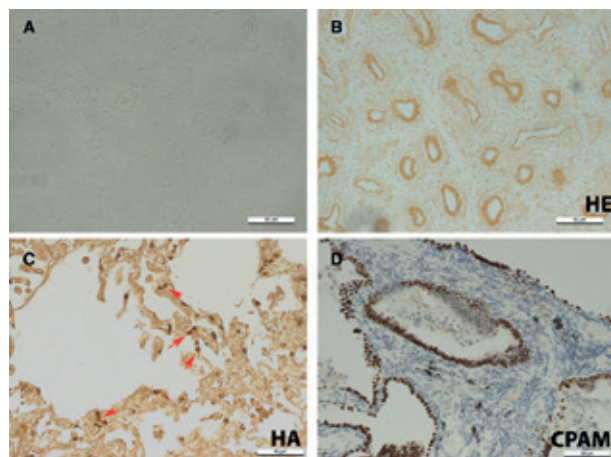


Figure 2 Fourteen WPC normal human embryonic lung with primary antibody omitted (negative control) (A); TTF-1 immunostaining in 14 WPC normal HE lung (B); normal HA lung (C) and CPAM HA lung (D); counterstained with haematoxylin (D). Red arrows in (D) indicate positive cells. Scale bar, 50 µm. CPAM, congenital pulmonary airway malformation; HA, human adult; HE, human embryonic; WPC, weeks post conception.

These findings may also be relevant to the unusual association of lung cancer developing in some CPAMs, mainly type 1 and rarely type 2.^{5,13} Both SOX-2 and TTF-1 (NK2X-1) genes are associated with tumour plasticity¹⁴ and a decrease in expression of genes that regulate retinoid metabolism and signalling, including RALDH1, has also been reported in non-small cell lung cancers.¹⁵ Although most cancers associated with type 1 CPAMs are mucinous adenocarcinomas^{5,13} and therefore negative for TTF-1, persistence of SOX-2 expression and loss of RALDH1 in the epithelial cells may have some bearing on tumour development and warrant further study.

We recognise that this paper has limitations, in that our cohort is limited to types 1 and 2 CPAMs. However, current thinking is that there are greater similarities between large cyst type (Stocker type 1) and the small cyst type (Stocker type 2) CPAMs, with the remaining three morphologic types believed to be different pathogenetic processes, namely acinar dysplasia (type 0), pulmonary hyperplasia (type 3) and low-grade cystic pleuropulmonary blastoma (type 4).¹⁶

In conclusion, our data show novel variations in embryonic airway epithelial cell markers that will hopefully lead to improved understanding of CPAM development.

Contributors BT, CD and MH conceived and designed the study. BT, AR and CD conducted the study and acquired data. BT and CD prepared figures. BT, CD, MH and AN wrote the manuscript. All authors discussed the findings and reviewed and approved the manuscript.

Funding This work was funded by a Wellcome Trust Vacation Scholarship to BT, grant #WT20437/Z/16/Z and by The Royal Brompton and Harefield Hospitals charity through funding from Mr and Mrs Youssef Mansour, grant B1064.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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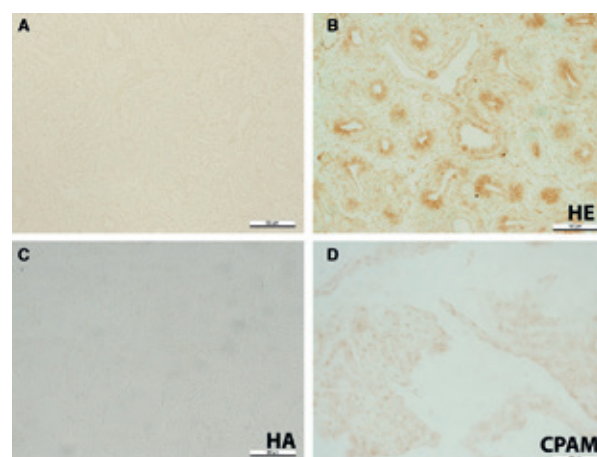


Figure 3 Fourteen weeks post conception (WPC) normal human embryonic lung with primary antibody omitted (negative control) (A); RALDH-1 expression in 14 WPC normal HE lung (B); normal HA lung (C) and CPAM human adult (HA) lung (D). Scale bar, 50 µm. CPAM, congenital pulmonary airway malformation; HA, human adult; HE, human embryonic; WPC, weeks post conception.

Oxigenoterapia com cânula nasal de alto fluxo para o tratamento de doentes com insuficiência respiratória aguda hipoxêmica resultante de infecção com SARS-CoV-2

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Received 14 April 2020

Revised 26 June 2020

Accepted 27 June 2020

Published Online First

23 July 2020



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RESUMO

O presente estudo observacional tem como objetivo avaliar os resultados e a segurança da oxigenoterapia por cânula nasal de alto fluxo (CNAF) em 28 doentes consecutivos com insuficiência respiratória aguda hipoxêmica (IRAH) resultante de infecção com SARS-CoV-2, não respondentes a terapia convencional com O₂. Dezanove doentes apresentaram uma resposta positiva. Nove doentes necessitaram de uma escalada do tratamento para ventilação não invasiva (cinco foram subsequentemente entubados). Nenhum dos profissionais de saúde teve um teste de esfregaço positivo durante o período do estudo nem nos 14 dias subsequentes. A gravidade da hipoxemia e o nível de proteína C reativa estiveram correlacionados com a insuficiência da CNAF. Estes dados sugerem que a CNAF é um tratamento seguro para doentes menos graves com IRAH por SARS-CoV-2 e a eficácia terá de ser avaliada como parte de um ensaio clínico.

Patients with Coronavirus 2 (SARS-CoV-2) infection may experience severe hypoxemic acute respiratory failure (hARF) requiring supportive respiratory therapy.¹

O₂-therapy by high-flow nasal cannula (HFNC), which allows delivering heated, humidified inspired gas at a high flow rate and precise fraction of inspired oxygen (FiO₂), has been increasingly used in patients with severe hARF.² Recent guidelines for the management of SARS-CoV-2 infection suggest HFNC also for treatment of SARS-CoV-2 hARF unresponsive to conventional O₂-therapy.³ However, data on the efficacy of HFNC in these patients are scarce and there are major concerns on the possibility of spreading infection among healthcare personnel caring for patients in SARS-CoV-2 dedicated areas.

We report the outcomes of 28 consecutive unselected patients with hARF admitted to the SARS-CoV-2 Respiratory Intensive Care Unit (RICU) of the University Hospital of Padua between 13 and 23 March 2020 who underwent HFNC. The criterion for patients' admission to our RICU was failure of conventional O₂-therapy to maintain SaO₂ ≥92%. Study ethical approval was waived by the local Ethics Committee in view of the fact that all the procedures being performed were part of the routine care.

Study inclusion criteria were (1) laboratoryconfirmed COVID-19 infection⁴; (2) PaO₂/FIO₂ ratio <300mmHg, FIO₂ being determined as previously described⁵; (3) failure of conventional O₂-therapy delivered through a non-rebreathing mask with a reservoir bag to maintain SaO₂ ≥92%. Exclusion criteria were need for immediate endotracheal intubation (ETI) and haemodynamic instability.

A treatment algorithm from the hospital internal protocol based on a stepwise utilisation of HFNC, non-invasive ventilation (NIV) and ETI

was used in the effort to reverse hypoxemia in these patients (figure 1). HFNC oxygen therapy was delivered using an AIRVO2 respiratory humidifier (Fisher & Paykel Healthcare, Auckland, New Zealand), with an integrated flow generator able to adjust FIO₂ (between 0.21 and 1.0) and to deliver an air/oxygen mixture at flow rates of up to 60L/min. The gas mixture (at 37°C) is routed through a circuit via large-bore bi-nasal prongs.

HFNC was initially used at a 60L/min gas flow rate and a FIO₂ of 1.0; it was then adjusted to provide the minimum FIO₂ necessary to maintain a SaO₂ ≥92%. To reduce the risk of viral transmission, the patient wore a surgical mask and was instructed to breathe through a closed mouth as long as possible.

The patients were divided into two groups depending on their outcome: the first (success group) included patients who had a successful outcome, as defined by reversal of hypoxemia (SaO₂ ≥92%), no need for NIV and/or invasive mechanical ventilation (IMV), discharge from RICU, with the patient alive and conscious for at least 48hours after discharge. The second group (failure group) included patients who had an unsuccessful outcome, defined as the need for NIV or IMV by ETI and/or death while on HFNC support.

The patients' baseline demographic and clinical features and clinical and laboratory data at RICU admission (also including SOFA score⁶) are outlined in table 1. Arterial blood gases were obtained while patients were receiving supplemental oxygen therapy via non-rebreathing mask with a reservoir bag.

The male:female ratio was 3 to 1 (21 vs 7). The patients were classified, in accordance with the WHO criteria,⁴ as showing moderate (17 cases) or severe (11 cases) acute respiratory distress at the time they were admitted to the RICU.

Nineteen (67.8%) succeeded HFNC as hypoxemia was reversed and they were discharged from the RICU and were still alive on day 15 after discharge. Nine patients (32.2%) failed HFNC and received NIV. Five of them (17.8%) subsequently required IMV, of whom three died. All nine failing patients had lower PaO₂/FIO₂ (76 (53–190) vs 126 (52–296) mmHg; p=0.0194) and higher serum C reactive protein level (130 (110–270) vs 110 (29–180); p=0.01277) with respect to their counterparts. Exact logistic regression following multivariate analysis indicated PaO₂/FIO₂ to be significantly associated with treatment failure (p=0.0314). Patients with PaO₂/FIO₂ at RICU admission ≤100mmHg showed a greater rate of treatment failure (7/9 (77.8%)), as opposed to those with PaO₂/FIO₂ >100mmHg (6/21 (31.6%); p=0.0246), with an OR of failure of 7.6 (95% CI 1.2 to 48.1).

Seventy-three healthcare workers (HCWs) (20 physicians, including residents, 40 nurses and 13 healthcare assistants) were exposed to confirmed

Para citar: Vianello A, Arcaro G, Molena B, *et al.* Thorax 2020;75:998–1000.

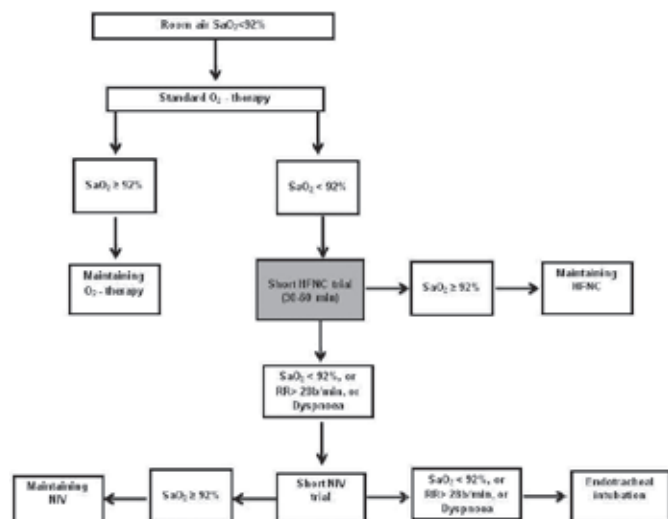


Figure 1 Treatment algorithm. HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; RR, respiratory rate; SaO₂, arterial oxygen saturation.

cases of SARS-CoV-2 during the study period. Exposure duration was 48 (44–52) hours per person. All HCWs wore appropriate personal protective equipment, including gowns, hair covers, gloves, eye and face shields, and filtering face-piece respirator class 2 (FFP2) or 3 (FFP3), depending on the kind of manoeuvre performed, FFP3 being reserved for intubation, suctioning and bronchoscopy. All HCWs underwent nasopharyngeal swab on a weekly basis. HCWs who had fever or other COVID-19 signs and symptoms were immediately tested. COVID-19 swab PCR testing was negative in all our staff members during the study period and the following 14 days.

Our data suggest that HFNC played an important role in reversing hypoxemia in approximately two-thirds of the patients with SARS-CoV-2 with severe hARF unable to achieve SaO₂ ≥ 92% under standard oxygen therapy. This improvement in oxygenation might depend on varied mechanisms, such as matching of delivered flow with increased ventilatory demand, achievement of high and stable FIO₂ (up to 100%), upper airway washout, generation of positive pressure at end-expiration, and delivery of air heated and humidified.⁷ Noteworthy, PaO₂/FIO₂ at RICU admission had prognostic relevance. In fact, in keeping with previous work,¹ patients with PaO₂/FIO₂ values ≤ 100 mmHg had an increased risk of treatment failure.

Despite the use of HFNC as a means of respiratory support raises concerns for the increased risk of viral transmission,⁸ COVID-19 swab PCR testing resulted to be negative in all our staff members throughout the whole study period and in the following 14 days. In support of a limited risk of airborne transmission, recent data demonstrated the dispersion distance of exhaled gases during HFNC treatment to be quite limited.⁹ Worth remarking, we always applied a surgical mask over the nose and mouth of patients receiving HFNC.

Our study has limitations, such as the low number of patients enrolled and its retrospective nature, which may have caused a significant bias.

Despite these clear limitations, our data show that HFNC can be considered an effective and safe means to improve oxygenation in less severe forms of hARF secondary to COVID-19 not responding to conventional oxygen therapy.

Contributors AV: study design, manuscript preparation. BM: data collection and analysis. CT: data collection and analysis. GA: data collection, conduction of the study. AS: conduction of the study. GG: data collection, conduction of the study. FL: data collection, conduction of the study. GS: study design, data analysis. PN: manuscript preparation, revision of the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Table 1 Patients' baseline demographic and clinical characteristics, and clinical and laboratory data at RICU admission

	All cases (n=28)	Success group (n=19)	Failure group (n=9)	P value
Clinical and demographic features				
Age (years), median (min–max)	69 (42–87)	67 (42–84)	80 (64–87)	0.0543
Gender (males/females)	21/7	13/6	8/1	0.2513
No of smokers	6 (21.4%)	3 (15.7%)	3 (33.3%)	0.2995
No of patients with comorbidities	20 (71.4%)	13 (68.4%)	7 (77.8%)	0.5286
No of comorbidities per patient, median (min–max)	1 (0–4)	1 (0–4)	2 (0–4)	0.3922
Clinical and laboratory data at RICU admission				
Respiratory rate (breaths/min), median (min–max)	26 (12–40)	24 (12–40)	26 (15–36)	0.6950
Heart rate (beats/min), median (min–max)	77 (59–105)	77 (59–89)	77.5 (62–150)	0.6362
No of patients with fever (temperature >38°C)	11 (21.4%)	6 (31.6%)	5 (55.6%)	0.2770
No of patients with leucopenia (WBC <4400×106/L)	3 (10.7%)	3 (15.7%)	0 (0%)	0.2154
PaO ₂ (mm Hg), median (min–max)	57 (36.2–67.1)	58.3 (36.2–67.1)	55.5 (39.9–61)	0.1224
PaCO ₂ (mm Hg), median (min–max)	32 (27–45)	31.9 (28–45)	32.9 (27–39)	0.9115
Arterial pH, median (min–max)	7.48 (7.39–7.54)	7.49 (7.39–7.52)	7.47 (7.40–7.54)	0.9357
SaO ₂ (%), median (min–max)	92 (79–97)	93 (79–97)	90 (79–94)	0.0293
FIO ₂ , median (min–max)	0.6 (0.4–1.0)	0.6 (0.4–1.0)	0.8 (0.6–1.0)	0.0085
PaO ₂ /FIO ₂ (mm Hg), median (min–max)	108 (52–296)	126 (52–296)	76 (53–190)	0.0194
No of patients with PaO ₂ /FIO ₂ ≤ 100	13 (46.4%)	6 (31.6%)	7 (77.8%)	0.0246
D-dimer (ng/mL), median (min–max)	444 (159–259)	327 (168–759)	727 (159–259)	0.1985
Serum CRP (μg/mL), median (min–max)	110 (29–270)	110 (29–180)	130.0 (110–270)	0.0277
Ferritin (ng/mL), median (min–max)	1465.5 (156–5292)	1399.5 (156–5292)	1465.5 (877–1999)	1.000
SOFA score, median (min–max)	2 (2–4)	2 (2–4)	3 (2–3)	0.4610

P values refer to differences between HFNC success and HFNC failure groups.

CRP, C reactive protein; HFNC, high-flow nasal cannula; PaO₂/FIO₂, arterial oxygen tension to inspired oxygen fraction ratio; SaO₂, arterial oxygen saturation; SOFA, sequential organ failure assessment.



Os cachimbos eletrônicos conduzem a pneumonia lipóide na Europa

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Received 29 November 2019

Revised 5 July 2020

Accepted 15 July 2020

Published Online First

29 September 2020



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ABSTRACT

Uma mulher de 53 anos, até à data saudável, foi admitida no serviço de urgência devido ao aumento de tosse e dispneia. Quatro dias antes da apresentação, o médico de clínica geral iniciou um tratamento ambulatorial com amoxicilina/ácido clavulânico devido à suspeita clínica e radiológica de uma pneumonia bilateral adquirida na comunidade. Para além de escitalopram e estrogénio contendo terapêutica de substituição hormonal, a doente não tomou qualquer medicação. Não tinha animais de estimação nem desumidificador e trabalhava como vendedora numa loja de recordações.

Três semanas antes do internamento, mudou de cigarros convencionais para cachimbo eletrônico disponível comercialmente (teor de nicotina 4 mg/ml, sabor a tabaco para cachimbo e depósito recarregável). Realizou inalações aproximadamente 4-5 vezes por dia. Negou usar líquidos contendo canabinoides e não era dupla utilizadora. Dez dias após ter começado a consumir cachimbo eletrônico, a doente sofreu de tosse seca e dispneia ao subir as escadas depressa.

Na admissão, a doente encontrava-se em bom estado de saúde, sem febre e com sinais vitais normais. A saturação de oxigénio era de 91% em ar ambiente. Os testes laboratoriais revelaram o seguinte: Proteína C reativa de 3,6 mg/l (referência <5 mg/l), hematógrama normal incluindo contagem diferencial, eletrólitos, enzimas hepáticas, peptídeo natriurético cerebral (BNP) e creatinina sérica. O teste para VIH, ANA/ANCA, parasitas e um esfregaço nasofaríngeo para bactérias atípicas e vírus respiratórios (PCR), incluindo a gripe, foi negativo. A tomografia computadorizada mostrou consolidações bilaterais com opacidades suaves de vidro moído (figura 1). O lavado broncoalveolar revelou uma alveolite linfocítica (contagem total de células 800/μl, 37% linfócitos (rácio CD4/8 5), 32% macrófagos, 18% eosinófilos e 12% neutrófilos). Os testes de *Pneumocystis jirovecii*, incluindo a PCR para o complexo *Mycobacterium tuberculosis* e as culturas bacterianas/fúngicas, foram negativos. As biópsias transbrônquicas do campo inferior direito demonstraram uma acumulação focal do espaço aéreo de gotículas lipídicas de diferentes tamanhos com macrófagos proliferados nos espaços alveolares adjacentes, infiltrados linfocíticos discretos e poucos focos de fibroblastos (figura 2A e B). Uma vez que o caso preenchia os critérios de lesão pulmonar associada a cigarro eletrônico ou a *vaping* (LPACEV) - ou seja, infiltrados pulmonares na ausência de infeção, *vaping* no período de 90 dias, sem evidências para um diagnóstico alternativo ou de agentes predisponentes à aspiração de lípidos como gotículas nasais - foi realizado um diagnóstico de pneumonia lipóide induzida por *vaping*. Sob um tratamento com prednisolona em regime de

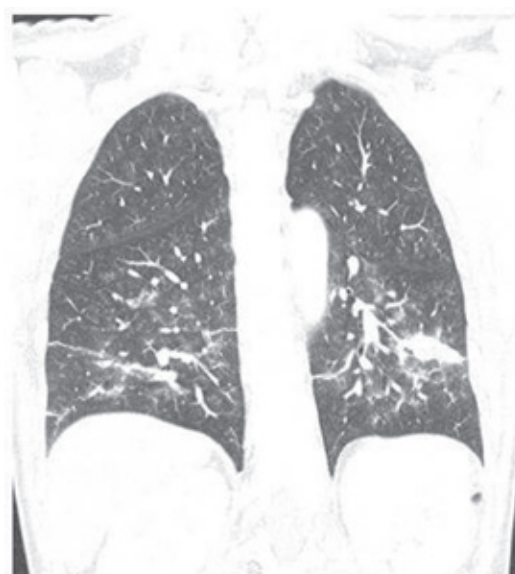


Figure 1 Chest CT scan revealing bilateral consolidations with diffuse ground glass opacities in all lung field.

tapering (0,5mg/kg de peso corporal) ao longo de 3 meses e abstinência de *vaping*, a doente recuperou totalmente com a eliminação das descobertas radiológicas. A capacidade de difusão melhorou de 88% inicialmente prevista para 104%.

Existem cada vez mais evidências sobre os malefícios dos cigarros ou cachimbos eletrônicos.¹ Os cigarros ou cachimbos eletrônicos são dispositivos que funcionam a pilhas e que aquecem um líquido, proporcionando um produto aerossolizado ao utilizador. Não foi identificado um único agente causal de LPACEV. O acetato de vitamina E surgiu como uma substância de interesse.² Na série de casos dos EUA, 94% referiram consumir tetra-hidrocanabinol (THC) por *vaping* nos dias anteriores, ou foram detetados THC ou seus metabólitos no fluido do lavado broncoalveolar. Este facto chamou a atenção para os produtos de *vaping* com THC nos EUA.¹ No nosso caso, o LPACEV ocorreu na ausência de uso de THC, que sublinha os problemas gerais de saúde em torno dos fluidos dos cigarros eletrônicos, que contêm diferentes compostos tóxicos (por exemplo, nicotina, compostos orgânicos voláteis e partículas). Uma explicação para a pneumonia lipóide aguda

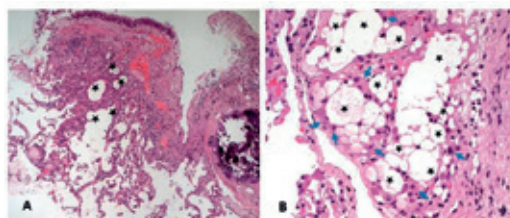


Figure 2 (A) Transbronchial lung biopsy showing intraalveolar optically empty vacuoles corresponding to lipid droplets (asterisk) adjacent to normal alveolar airspaces (H&E, 100 x). (B) Empty vacuoles (asterisk) surrounded by partly vacuolated macrophages (arrows) (H&E, 400 x).

Para citar: Kessler A-C, Dommann C, Nussbaumer-Ochsner Y. Thorax 2020;75:1026–1027.

poderia ser a inalação e depósito de gotículas de óleo aerossolizadas nas vias aéreas distais e nos alvéolos, levando a uma pneumonite química. Este caso ilustra melhor que a LPACEV pode ocorrer mesmo após apenas algumas semanas de *vaping*. Tanto quanto sabemos, trata-se do primeiro caso de um doente europeu nativo a desenvolver LPACEV após ter consumido um cachimbo eletrônico disponível comercialmente e após um curto período de *vaping*.³

Pneumonite por hipersensibilidade potencialmente fatal associada ao uso de cigarros eletrônicos

RESUMO

Relatamos um caso de pneumonite por hipersensibilidade (PH) num jovem indivíduo associada ao uso de produtos de *vaping*. Apresentou um diagnóstico putativo de asma e necessitou de oxigenação por membrana extracorpórea devido a insuficiência respiratória intratável. O doente desenvolveu uma doença crítica e miopatia esteroide, o que exigiu uma reabilitação prolongada. O nosso doente preenche os critérios de diagnóstico para PH associada ao uso de cigarros eletrônicos com um histórico de exposição positivo, deterioração após teste cutâneo de aler-

gia, anticorpos IgM específicos séricos contra o líquido implicado, aumentando a possibilidade de o antígeno relevante estar presente nesse líquido, e características radiológicas e histopatológicas compatíveis com PH aguda. Resultam duas aprendizagens. A primeira é considerar sempre uma reação aos cigarros eletrônicos em alguém que apresente uma doença respiratória atípica. A segunda é que consideramos os cigarros eletrônicos “muito mais seguros do que o tabaco” por nossa conta e risco.

Contributors A-CK collected the data; A-CK and YN-O wrote the article; CD made the Analysis of the lung biopsies.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed. Data availability statement All data relevant to the study are included in the article.

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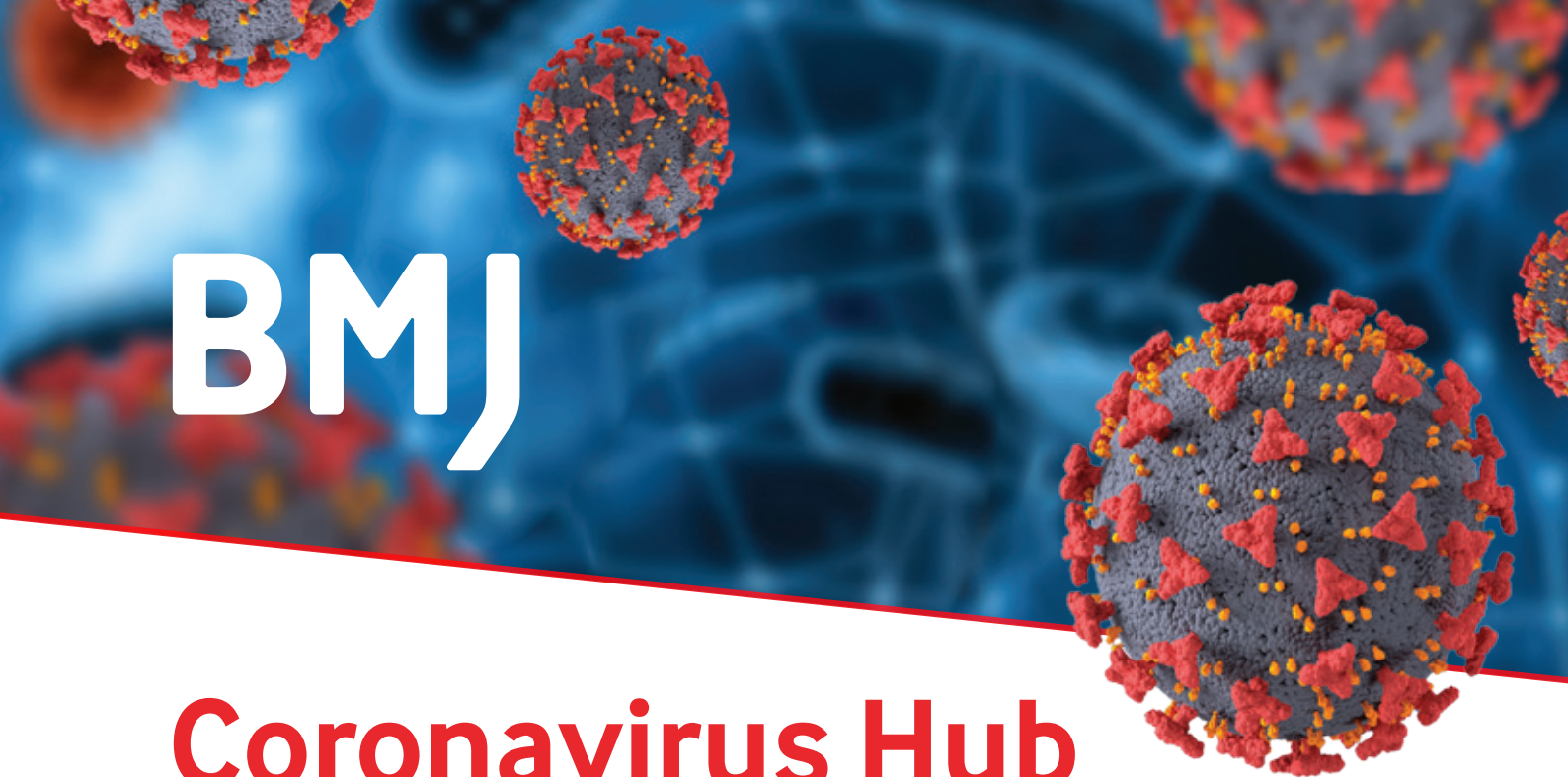
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1 INALAÇÃO



1 VEZ AO DIA



1 DISPOSITIVO

ELEBRATO
FUROATO DE FLUTICASONA | UMECLIDÍNIO | VILANTEROL | ELLIPTA
ELE RESPIRA

Referências: 1. Van der Palen J et al. NPJ Prim Care Respir Med 2016 26:16079 2. Lipson DA et al. N Engl J Med 2018 378:1671-1680 3. RCM Elebrato Ellipta março 2019
DPOC: Doença pulmonar obstrutiva crônica; ICS: Corticosteroide inalado; LABA: Agonista β_2 de longa ação; LAMA: Antagonista muscarínico de longa ação.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM

▼ Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas para <http://www.infarmed.pt/web/infarmed/submissaoam> e para o departamento médico da GlaxoSmithKline para HYPERLINK "mailto:lis.nucleo-farmacovigilancia@gsk.com" lis.nucleo-farmacovigilancia@gsk.com.

NOME DO MEDICAMENTO Elebrato Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada inalação disponibiliza uma dose administrada de 92 microgramas de furoato de fluticasona, 65 microgramas de brometo de umeclidínio equivalente a 55 microgramas de umeclidínio e 22 microgramas de vilanterol (como trifrenatato). Isto corresponde a um recipiente unidose de 100 microgramas de furoato de fluticasona, 74,2 microgramas de brometo de umeclidínio equivalente a 62,5 microgramas de umeclidínio e 25 microgramas de vilanterol (como trifrenatato). **FORMA FARMACÊUTICA** Pó para inalação em recipiente unidose. **Indicações terapêuticas** Tratamento de manutenção em doentes adultos com doença pulmonar obstrutiva crónica (DPOC) moderada a grave, que não estejam adequadamente tratados com uma associação de um corticosteroide para inalação e um agonista beta-2 de longa duração de ação ou uma associação de um agonista beta-2 de longa duração de ação e um antagonista muscarínico de longa duração de ação (ver RCM para informação sobre efeitos sobre o controlo dos sintomas e prevenção das exacerbações). **Posologia e modo de administração** **Adultos** A dose máxima recomendada é uma inalação 1x/dia, à mesma hora em cada dia. **Doentes idosos, Compromisso renal e Compromisso hepático** Não é necessário ajustar a posologia. Utilizar com precaução em doentes com compromisso hepático moderado a grave. **População pediátrica** A utilização não é relevante na população pediátrica (<18 anos) para a indicação de DPOC. **Modo de administração** Via inalatória. **Contraindicações** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Efeitos indesejáveis** As reações adversas mais frequentemente notificadas foram nasofaringite, cefaleia e infeção das vias respiratórias superiores. **Infeções e infestações** **Frequentes** Pneumonia, infeção das vias respiratórias superiores, bronquite, faringite, rinite, sinusite, gripe, nasofaringite, candidíase da boca e da garganta e infeção do trato urinário **Pouco frequentes** Infeção viral das vias respiratórias superiores **Doenças do sistema nervoso** **Frequentes** Cefaleia **Afeções oculares** **Desconhecido** Visão turva **Cardiopatias** **Pouco frequentes** Taquiarritmia supraventricular, taquicardia e fibrilhação auricular **Doenças respiratórias, torácicas e do mediastino** **Frequentes** Tosse e dor orofaríngea **Pouco frequentes** Disfonia **Doenças gastrointestinais** **Frequentes** Obstipação **Pouco frequentes** Boca seca **Afeções musculoesqueléticas e dos tecidos conjuntivos** **Frequentes** Artralgia e dorsalgia **Pouco frequentes** Fraturas **TITULAR DA AIM** GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** março 2020. **APRESENTAÇÃO:** Elebrato Ellipta 92 mcg+55 mcg+22mcg, 30 doses. **Comparticipação:** Escalão B; Regime Geral 69%; Regime Especial 84%. Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos HYPERLINK "http://www.ema.europa.eu" http://www.ema.europa.eu/. Consultar o RCM completo para informação detalhada. Medicamento sujeito a receita médica. 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 & Cª, S.A., -À Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. DMGMA_PT200330

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